CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206494Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 11, 2015
From	Hala Shamsuddin MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	206494
Applicant	Cerexa, a wholly-owned subsidiary of Forest Laboratories
Date of Submission	June 25, 2014
PDUFA Goal Date	February 25, 2015
Proprietary Name / Established (USAN) names	AVYCAZ®/ceftazidime-avibactam
Dosage forms / Strength	Injection/2.5 grams (2 grams ceftazidime and 0.5 grams avibactam) single-use vials
Proposed Indication(s)	1. Treatment of complicated intra-abdominal infections 2. Treatment of complicated urinary tract infections, including acute pyelonephritis 3. Treatment of gram-negative infections in patients with limited treatment options, including hospital-acquired/ventilator-associated bacterial pneumonia (HABP/VABP) and bacteremia.
Recommended:	• Approval for the following indications (when limited or no alternative treatments are available): 1. Treatment of complicated intra-abdominal infections 2. Treatment of complicated urinary tract infections, including pyelonephritis • Non-approval for the indication of treatment of gram-negative infections with limited treatment options including HABP/VABP and bacteremia

1. Introduction

NDA 206,494 was submitted by Cerexa Inc., seeking the following indications for ceftazidime-avibactam:

- Complicated intra-abdominal infections, in combination with metronidazole, caused by *Escherichia coli* (including cases with concurrent bacteremia), *Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Enterobacter cloacae, K. oxytoca, Pseudomonas aeruginosa,* and *P. stutzeri*; and polymicrobial infections caused by aerobic and anaerobic organisms including *Bacteroides* spp. (many strains of *Bacteroides fragilis* are resistant to ceftazidime-avibactam).

- Complicated urinary tract infections, including acute pyelonephritis, caused by *E. coli* (including cases with concurrent bacteremia), *K. pneumoniae, Citrobacter koseri, Enterobacter aerogenes, E. cloacae, Citrobacter freundii, Proteus spp*. (including *P. mirabilis* and indole-positive Proteus), and *P. aeruginosa*.

- Aerobic Gram-negative infections with limited treatment options: ceftazidime-avibactam may be used for hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP), and bacteremia where limited or no alternative therapies are available and the infection is caused by *E. coli, K. pneumoniae, K. oxytoca, P. aeruginosa, P. stutzeri, P. stuartii, C. freundii, C. koseri, Serratia spp., E. aerogenes, E. cloacae,* and *Proteus spp.,* including *P. mirabilis* and indole-positive *Proteus*. (b) (4) [redacted]

The proposed dose is 2.5 grams (2 gm ceftazidime and 0.5 grams avibactam) every 8 hours administered by intravenous infusion over 2 hours. The proposed duration is up to 14 days, depending on the site and severity of infection and the patient's clinical and microbiologic response. Dose adjustment is recommended in patients with renal impairment, maintaining a fixed ratio of ceftazidime:avibactam of 4:1.

2. Background

Ceftazidime-avibactam for injection is a fixed drug combination of ceftazidime, a third generation cephalosporin antibacterial drug, and avibactam, a beta-lactamase inhibitor, at a ratio of 4:1. Ceftazidime was initially FDA approved in July 1985 (FORTAZ®, NDA 50578). It is approved for the treatment of lower respiratory tract infections, skin and skin structure infections, urinary tract infections, intra-abdominal infections, gynecological infections, bacterial septicemia, and central nervous system infections. A mechanism of resistance to

ceftazidime is hydrolysis by bacterial beta-lactamase enzymes that enzymatically cleave the beta-lactam ring.

Avibactam is a new molecular entity that does not have a direct antibacterial activity at the proposed doses, but protects ceftazidime from degradation by some beta-lactamase enzymes thus potentially restoring its anti-bacterial activity.

The NDA is covered under the 505(b)(2) regulatory pathway. The Applicant is relying in part on the FDA's previous findings of efficacy and safety of ceftazidime as well as published literature on ceftazidime. Because confirmatory clinical trials comparing ceftazidime alone to ceftazidime-avibactam would not be feasible, the FDA agreed that the contribution of both components as required in 21 CFR § 300.50 can be demonstrated by in vitro studies and in animal models of infection, where the addition of avibactam restores the activity of ceftazidime against ceftazidime-nonsusceptible microorganisms. Limited clinical data from patients with ceftazidime-nonsusceptible pathogens who are treated with ceftazidime-avibactam could be used to describe the contribution of avibactam as well.

The non-clinical studies submitted in support of this application included toxicokinetic and embryofetal animal studies, PK modeling including hollow fiber simulations, in vitro antibacterial activity and activity in five animal models of infection (murine systemic infection, pneumonia immunocompromised mouse model, pyelonephritis immunocompromised mouse model, meningitis immunocompetent rabbit model, the neutropenic mouse thigh infection model), all evaluating avibactam alone and in combination with ceftazidime. Phase 1 studies to evaluate PK of avibactam alone or in combination with ceftazidime, a drug interaction study to evaluate drug interactions between ceftazidime and avibactam, and a drug interaction study to evaluate the interactions between ceftazidime and metronidazole were also submitted. The clinical efficacy and safety of ceftazidime-avibactam is supported by two randomized comparative Phase 2 clinical trials, one in complicated intraabdominal infections (cIAI, Study NXL104/2002) and one in complicated urinary tract infections (cUTI, Study NXL104/2001). Neither trial had a statistical hypothesis for inferential testing in the overall population or in the subset of patients who were infected with a ceftazidime non-susceptible organism. Interim results from an ongoing open-label Phase 3 trial in patients with cIAI or cUTI due to ceftazidime-resistant gram-negative bacteria (Resistant Pathogen Study D4280C00006) and a literature review to assess the historical efficacy of ceftazidime in cIAI and cUTI were also submitted.

Phase 3 trials in cIAI and cUTI have been recently completed, but efficacy data from these trials were not used to support this application. However, preliminary findings from the Phase 3 cIAI trial (RECLAIM study) indicated decreased efficacy of ceftazidime-avibactam in patients with creatinine clearance (CrCL) 30-50 mL/min. The reasons for this decreased efficacy have not been fully elucidated, but include inadequate dose/exposure and/or failure to adjust dosage in a timely fashion in patients with changing renal function. This information was included in the Warnings and Precautions section of labeling and was used to revise dosing recommendations in patients with renal impairment.

No clinical data were submitted to support approval for the limited use indication of treatment of aerobic gram-negative infections, including HABP/VABP and bacteremia, where limited or no alternative therapies are available. (b) (4)

Regulatory History

The initial Investigational New Drug (IND) application was submitted by Novexel in January 2008. Novexel transferred ownership to AstraZeneca in April 2010, who then transferred ownership to Cerexa, Inc., a wholly owned subsidiary of Forest Laboratories, Inc. in October 2011. On 11 March 2013, ceftazidime-avibactam was granted qualified infectious diseases product (QIDP) and Fast Track designations for the indications of cIAI, cUTI and HABP/VABP. At the time of the NDA submission, the applicant requested and received priority review.

In this NDA, Cerexa submitted a pediatric deferral request for the indications of cIAI and cUTI until after the ongoing Phase 3 trials for these indications have been completed. (See Pediatric section).

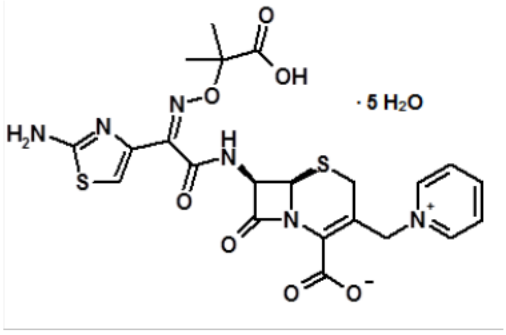
3. CMC/Device

The ONDQA reviewer was Zhengfang Ge, Ph.D, and the product quality microbiology reviewer was Robert Mello, Ph.D. Their findings are summarized.

Ceftazidime

Ceftazidime is a third generation cephalosporin. It is the pentahydrate of (6*R*,7*R*,*Z*)-7-(2-(2-aminothiazol-4-yl)-2-(2-carboxypropan-2-yloxyimino)acetamido)-8-oxo-3-(pyridinium-1-ylmethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate. Its molecular weight is 636.6. The empirical molecular formula: $C_{22}H_{32}N_6O_{12}S_2$. The chemical structure is

Figure 1: Chemical Structure of Ceftazidime

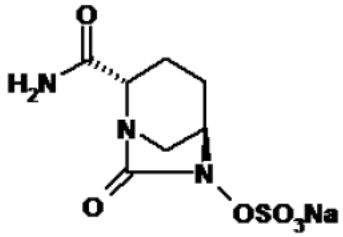


Ceftazidime is manufactured by (b) (4). This application cross referenced DMF # (b) (4) for the CMC information for ceftazidime. The DMF was previously reviewed on June 28, 2011 for NDA 50578 and found adequate.

Avibactam

Avibactam is sodium[(2S,5R)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl] sulfate. The molecular weight is 287.23, and the empirical molecular formula is $C_7H_{10}N_3O_6SNa$. The chemical structure is

Figure 2: Chemical Structure of Avibactam



Avibactam sodium has two chiral centers and is [redacted] (b) (4). Control strategy, critical quality attributes and the in-process parameters and controls for each of the intermediates were found to be properly established. Because avibactam is freely soluble in water, specification for particle size is not proposed. Two impurities [redacted] (b) (4) that are potentially genotoxic are below the threshold of toxicology concern.

Ceftazidime-Avibactam

The drug product, ceftazidime-avibactam, is a white to yellow sterile powder for injection supplied in type 1 single use glass vials. Each vial contains ceftazidime 2000 mg (equivalent to 2635 (b) (4) mg ceftazidime pentahydrate/sodium carbonate) and 500 mg avibactam (equivalent to (b) (4) mg avibactam sodium). The sodium carbonate content of the mixture is 239.6 mg/vial. The total sodium content of the mixture is approximately 146 mg (6.4 mEq)/vial. The drug product is manufactured [redacted] (b) (4) Specifications for the drug product including tests for identity, degradation products, vial content uniformity, reconstitution time, pH, [redacted] (b) (4), particulate matter, sterility and bacterial endotoxin were found adequate. The degradation product [redacted] (b) (4) was found to satisfy acceptance criteria at NMT (b) (4) % for the drug substance and (b) (4) % for the drug product. The degradation product [redacted] (b) (4) satisfied the acceptance criteria at (b) (4) % for the drug product.

Stability data at 25°C/60% RH for 18 months and 6 months at 40°C/75% RH were provided for 3 primary drug product batches and support 24 months expiration when stored at USP controlled room temperature and protected from light and were acceptable.

The contents of the drug product vial is reconstituted with 10 mL of sterile water or 0.9% sodium chloride for injection or 5% dextrose injection or lactated ringer's solution. The constituted solution is further diluted to achieve a total volume between 50 and 250 mL for infusion to patients. The in-use stability data with the above various diluents supported the recommendation that the constituted solution may be stored in the refrigerator for 24 hours but should be used within 12 hours at room temperature as described in the drug product labeling.

Inspection of the manufacturers/facilities is pending recommendation from the Office of Compliance.

The DMF files referenced in this application are DMF# (b) (4) for the drug substance ceftazidime held by (b) (4) All DMF files were found adequate.

Dr. Ge concluded that the NDA provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product, and did not recommend any post-marketing commitments or requirements. At the time Dr. Ge filed her review, the recommendation from the microbiology quality reviewer, Dr. Mello, was pending and the Office of Compliance had not issued an overall "Acceptable" recommendation. Dr. Ge's recommendation was not to approve until all the pending issues are resolved. In an addendum, Dr. Ge recommended approval of this NDA.

I agree with Dr. Ge's recommendation.

Dr. Mello notes that the Applicant has demonstrated adequate controls over the (b) (4) manufacture of the two drug substances and the (b) (4) filling process. The primary container closure integrity study data supporting the sterility maintenance of the final packaged drug substances as well as the drug product was found to be adequate. Post-constitution microbial challenge studies support the preparation and use hold times listed in the product labeling. Dr. Mello recommends approval of the NDA from a product quality microbiology perspective. I agree with his recommendations.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewers for this NDA were Armand Balboni, MD/Ph.D., and Wendelyn Schmidt, Ph.D. Their findings are summarized.

Ceftazidime
The nonclinical toxicities of ceftazidime are described in the package insert label[1]. Ceftazidime was negative in genotoxicity assays, and had no teratogenic effects in mice or rabbits at doses of 6.5 g/kg/day and 0.2 mg/kg/day respectively.

Avibactam
The toxicity of avibactam was investigated in mice, rats, and dogs. In single dose studies, the NOAEL in rats and mice was 2000 mg/kg administered by intravenous administration or by oral gavage. Avibactam administered in doses up to 1000 mg/kg/day to rats or dogs for 4 or 13 weeks primarily caused damage to the injection site with minimal systemic toxicities, although the13-week rat study was difficult to interpret due to presumed *P. aeruginosa* catheter infection with resultant multiple organ abscesses. Other toxicity studies including, local

[1] http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/050578s055,050634s023lbledt.pdf

tolerance in the rabbit, human blood hemolysis, immunotoxicology in the rat, and phototoxicity in 3T3 cells. All were negative.

Avibactam had no effects on fertility in male or female rats at the highest dose tested (1000 mg/kg or approximately 20 fold greater than the proposed human dose based on body surface area). However, pre and post implantation loss was increased in females administered avibactam beginning two weeks prior to mating at doses greater than or equal to 500 mg/kg. Avibactam was not teratogenic in rats or rabbits. In rats, IV doses up to 1000 mg/kg/day (approximately 9 times the human dose based on AUC) resulted in no embryofetal toxicities. In the rabbit fetal development study, avibactam had no effects on embryofetal development at doses of 100 mg/kg (twice the human exposure based on AUC). Higher doses resulted in an increase in late resorptions and decrement in fetal body weights.

In the rat peri and post-natal toxicity study, dose related increase in the incidence of renal pelvis and ureter dilatation was noted in weanling pups without pathologic changes in renal parenchyma or function was noted at the high dose of 825 mg/kg/day. The renal pelvic dilatation persisted into adulthood.

The potential for avibactam genetic toxicity was investigated in the Ames bacterial mutation, unscheduled DNA synthesis, mouse lymphoma clastogenicity, human lymphocyte chromosomal aberrations, and rat micronucleus assays. All were negative.

Ceftazidime-Avibactam
In the 4 week studies of ceftazidime-avibactam combination at 4:1 ratio, no new toxicities were noted compared to either drug alone.

Drs. Balboni and Schmidt recommend approval of this Application. I agree with their recommendation.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology reviewer for this application was Seong Jang, Ph.D. His findings and recommendations are summarized.

The pharmacokinetic parameters for ceftazidime and avibactam in healthy adult male subjects with normal renal function after single and multiple 2-hour intravenous infusions of ceftazidime-avibactam 2.5 grams (2 grams ceftazidime and 0.5 grams avibactam) administered every 8 hours are presented in table 1.

Table 1: PK parameters (geometric mean [%CV]) of ceftazidime and avibactam following administration of ceftazidime-avibactam 2.5 g (2 g ceftazidime and 0.5 g avibactam) in healthy adult males

	Ceftazidime		Avibactam	
Parameter	Single CAZ-AVI 2.5 g[a] (n = 16)	CAZ-AVI 2.5 g[a] q8h for 11 Days (n = 16)	Single CAZ-AVI 2.5 g[a] (n = 16)	CAZ-AVI 2.5 g q8h[a] for 11 Days (n = 16)
Cmax (mg/L)	88.1 (14)	90.4 (16)	15.2 (14)	14.6 (17)

AUC (mg·h/L)[b]	289 (15)[c]	291 (15)	42.1 (16)[d]	38.2 (19)
T1/2 (h)	3.27 (33)[c]	2.76 (7)	2.22 (31)[d]	2.71 (25)
CL (L/h)	6.93 (15)[c]	6.86 (15)	11.9 (16)[d]	13.1 (19)
Vss (L)	18.1 (20)[c]	17.0 (16)	23.2 (23)[d]	22.2 (18)

Source: Table 18, Dr. Jang's review
CAZ-AVI = ceftazidime-avibactam
a: 2 g ceftazidime + 0.5g avibactam, administered as infusion over 2 hours.
b: AUC0-inf reported for single dose administration; AUC0-tau reported for multiple dose administration.
c: n = 15.
d: n = 13.

The PK of ceftazidime and avibactam are linear, with Cmax and AUC increasing in proportion to dose and with no appreciable accumulation. The protein binding of both ceftazidime and avibactam is independent of concentration and is less than 10%. The steady-state volumes of distribution of ceftazidime and avibactam are 17 L and 22.2 L respectively.

Both avibactam and ceftazidime undergo limited metabolism and both are primarily eliminated unchanged by the kidney (80-90% for ceftazidime and 85% for avibactam). The mean renal clearance of ceftazidime is approximately 100 mL/min. Renal clearance of avibactam is 158 mL/min, suggesting active tubular secretion. The terminal elimination half-life (t½) of both ceftazidime and of avibactam is approximately 2 hours in patients with normal renal function and is prolonged in patients with renal impairment.

Ceftazidime and avibactam do not inhibit or induce cytochrome P450 enzymes in vitro and do not inhibit any major renal or hepatic transporters in vitro in the clinically relevant exposure range. Avibactam is a substrate of human organic anion transporter (OAT)1 and OAT3 in vitro. In vitro uptake of avibactam by OAT1 and OAT3 was not inhibited by ceftazidime but was inhibited (by 56% to 70%) by probenecid, a potent OAT inhibitor. The clinical impact of potent OAT inhibitors on the PK of avibactam is not known. There is no evidence of a drug-drug interaction between ceftazidime and avibactam. There is no drug interaction between ceftazidime-avibactam and metronidazole.

Because of the predominant renal clearance of both ceftazidime and avibactam, dosage adjustment is required in patients with creatinine clearance (CrCL) less than 50 mL/min. No dosage adjustments for ceftazidime-avibactam based on gender or hepatic impairment are required. Dose adjustment in the geriatric population should be based on renal function. Ceftazidime-avibactam PK has not been evaluated in the pediatric population.

Population PK analyses for both avibactam and ceftazidime from a pooled plasma concentrations obtained in the Phase 2 cIAI study and five Phase 1 clinical pharmacology studies in healthy volunteers demonstrated that the main predictors of clearance for avibactam and ceftazidime were body surface-normalized creatinine clearance (nCrCl) and CrCL, respectively, consistent with the predominant renal excretion of both compounds. In addition, cIAI was identified as a significant covariate impacting clearance and central volume of distribution of both avibactam and ceftazidime. The clearance and central volume of distribution were higher for both ceftazidime and avibactam in the cIAI population compared to healthy volunteers. The population PK model predicted a 34% and 59% decrease in the mean steady state AUC and Cmax for avibactam, respectively, for Phase 2 cIAI subjects with

normal renal function compared to Phase 1 subjects with normal renal function. Similarly, the population PK model predicted a 20% and 38% decrease in the mean steady state AUC and Cmax for ceftazidime, respectively, for Phase 2 cIAI subjects with normal renal function compared to Phase 1 subjects with normal renal function.

Patients with CrCL of less than 50 mL/min were excluded from the Phase 2 cIAI trial and patients with CrCL less than 70 mL/min were excluded from the Phase 2 cUTI trial. The dosing regimen that was originally proposed by the Applicant and that was used in the recently completed Phase 3 cIAI trial and the predicted exposure resulting from this dosing regimen are shown in tables 2 and 3 respectively.

Table 2: Initially Proposed Dosage Regimen and Used in Phase 3 Trial

Estimated CrCL (mL/min)	Proposed Dosage Regimen
> 50	2.5 g IV (over 2 hours) every 8 hours
≥ 31 to ≤ 50	1.25 g IV (over 2 hours) every 12 hours
≥ 16 to ≤ 30	1.25 g IV (over 2 hours) every 24 hours
≥ 6 to ≤ 15	0.625 g IV (over 2 hours) every 24 hours
≤ 5	0.625 g IV (over 2 hours) every 48 hours

Table 3: Predicted Exposure in Simulated cIAI Patients with Varying Degree of Renal Function Resulting Using the Initially Proposed Dosing Regimen

		Ceftazidime		Avibactam	
Renal Function	Proposed Dose Regimen	Cmax,ss (µg/mL)	AUC0-24,ss (µg·h/mL)	Cmax,ss (µg/mL)	AUC0-24,ss (µg·h/mL)
NORM	2000 mg CAZ + 500 mg AVI q8h	47.2±13.4	542±161	9.31±1.87	93.5±21.3
MILD	2000 mg CAZ + 500 mg AVI q8h	59.9±17.1	828±260	11.2±2.37	131±36.4
MOD	1000 mg CAZ + 250 mg AVI q12h	33.5±9.6	448±142	6.84±1.48	80.3±22.8
SEV1	1000 mg CAZ + 250 mg AVI, q24h	33.9±10.2	400±136	7.61±1.85	82.8±26.7
SEV2	500 mg CAZ + 125 mg AVI q24h	27.0±9.03	455±180	6.79±2.07	116±47.6
ESRD	500 mg CAZ + 125 mg AVI q48h	45.7±22.9	898±527	5.26±1.04	75.6±16.8

NORM (CrCL > 80 mL/min); MILD (CrCL 51 mL/min to ≤ 80 mL/min); MOD (CrCL 31 mL/min to ≤ 50 mL/min); SEV1 (CrCL 16 mL/min to ≤ 30mL/min); SEV2 (CrCL 6 mL/min to ≤ 15 mL/min); ESRD End-stage renal disease (CrCL 0 mL/min to ≤ 5 mL/min).
Source: Table 27, Dr. Jang's review

Predicted exposure was higher in patients with mild renal impairment or end stage renal disease compared to patients with other degrees of renal impairment or patients with normal renal function. Predicted exposure in patients with moderate or severe renal impairment was lower compared to the exposure in patients with normal renal function.

Although the predicted Cmax and AUC of ceftazidime and avibactam in the simulated patients with moderate and severe renal impairments receiving the initially proposed dosing regimen were substantially lower compared with the simulated patients with normal renal function, target attainment analysis suggested that this dosing adjustment still provides ~100% probability of achieving the PK/PD target (i.e., 50%fT > MIC for ceftazidime and 50%fT > 1.0 mg/L for avibactam) for MIC up to 8 µg/mL (table 4). The originally proposed dosing regimens for patients with renal impairment were therefore initially deemed acceptable.

Table 4: Percentage of Simulated Patients with cIAI Achieving PK/PD* Target Ceftazidime-Avibactam (5000 Simulated Subjects per Group)**

Renal Function	Proposed Dosing Regimen	% of Simulated Patients Achieving PK/PD Target
CAZ-AVI MIC=4 µg/mL		
NORM	2000 mg CAZ + 500 mg AVI, q8h	98.9
MILD	2000 mg CAZ + 500 mg AVI, q8h	99.9
MOD	1000 mg CAZ + 250 mg AVI, q12h	98.9
SEV1	1000 mg CAZ + 250 mg AVI, q24h	97.8
SEV2	500 mg CAZ + 125 mg AVI, q24h	100
ESRD	500 mg CAZ + 125 mg AVI, q48h	100
CAZ-AVI MIC=8 µg/mL		
NORM	2000 mg CAZ + 500 mg AVI, q8h	98.1
MILD	2000 mg CAZ + 500 mg AVI, q8h	99.9
MOD	1000 mg CAZ + 250 mg AVI, q12h	95.7
SEV1	1000 mg CAZ + 250 mg AVI, q24h	85.9
SEV2	500 mg CAZ + 125 mg AVI, q24h	94.4
ESRD	500 mg CAZ + 125 mg AVI, q48h	99.9
CAZ-AVI MIC=16 µg/mL		
NORM	2000 mg CAZ + 500 mg AVI, q8h	50.8
MILD	2000 mg CAZ + 500 mg AVI, q8h	93.8
MOD	1000 mg CAZ + 250 mg AVI, q12h	35.2
SEV1	1000 mg CAZ + 250 mg AVI, q24h	21.8
SEV2	500 mg CAZ + 125 mg AVI, q24h	40.8
ESRD	500 mg CAZ + 125 mg AVI, q48h	84.7
CAZ-AVI MIC=32 µg/mL		
NORM	2000 mg CAZ + 500 mg AVI, q8h	1.3
MILD	2000 mg CAZ + 500 mg AVI, q8h	27.5
MOD	1000 mg CAZ + 250 mg AVI, q12h	0.4
SEV1	1000 mg CAZ + 250 mg AVI, q24h	0.3
SEV2	500 mg CAZ + 125 mg AVI, q24h	2.3
ESRD	500 mg CAZ + 125 mg AVI, q48h	36.8

CAZ = ceftazidime; AVI = avibactam; NORM (CrCL > 80 mL/min); MILD (CrCL 51 mL/min to ≤ 80 mL/min); MOD (CrCL 31 mL/min to ≤ 50 mL/min); SEV1 (CrCL 16 mL/min to ≤ 30mL/min); SEV2 (CrCL 6 mL/min to ≤ 15 mL/min); ESRD End-stage renal disease (CrCL 0 mL/min to ≤ 5 mL/min).
**ceftazidime 2 grams and avibactam 500 mg, every 8 hours intravenously over 2 hours
PK/PD target for ceftazidime is 50% fT > ceftazidime-avibactam MIC and for avibactam is 50% fT > 1 mg/L.
Source: Table 15 in Dr. Jang's review and Table 143 Dr. Goodwin review

In October 2014, the Applicant informed the FDA that analysis of a recently completed Phase 3 study in patients with cIAI showed that patients with baseline moderate renal impairment (CrCL ≤ 50 mL/min) who were treated with ceftazidime-avibactam had a lower clinical cure rate compared with patients with normal renal function/mild impairment treated with ceftazidime-avibactam or patients with moderate renal impairment treated with meropenem (Table 5). In addition, mortality was higher in this subgroup of ceftazidime-avibactam patients with moderate renal impairment compared to ceftazidime-avibactam patients with normal

renal function/mild impairment or meropenem patients with moderate renal impairment. (See safety section)

Table 5: Clinical Cure Rate at Test-of-Cure Visit by Baseline Renal Function Group – Phase 3 cIAI Study - mMITT Analysis Set

	Ceftazidime-avibactam + Metronidazole	Meropenem
CrCL > 50 mL/min	322/379 (85%)	321/373 (86%)
CrCL > 30 to ≤ 50 mL/min	14/31 (45%)	26/35 (74%)

mMITT = microbiologically Modified Intent-to-Treat
Source: Applicant's Communication October 9, 2014

The reasons for the worse outcomes in patients with moderate renal impairment treated with ceftazidime-avibactam are not currently clear, as patient level data was not submitted for review. Possible explanations included inadequate exposure in patients with moderate renal impairment and/or failure to increase the dose in patients with improving renal function. Additional analyses were therefore performed to assess if the originally proposed dosing regimen in patients with renal impairment needs to be modified taking into account that FORTAZ labeling allows for 50% increase in ceftazidime dosing in renally impaired patients with severe infections.

The revised/newly proposed dosing regimen and the resulting predicted exposures are shown in tables 6 and 7.

Table 6: Revised/Newly Proposed Dosing Regimen for Ceftazidime-Avibactam

Estimated CrCL (mL/min)[a]	Recommended Dosage Regimen for Ceftazidime/Avibactam
Greater than 50	2.5 grams (2 grams/0.5 grams) intravenously (over 2 hours) every 8 hours
31 to 50	1.25 grams (1 grams/0.25 grams) intravenously (over 2 hours) every 8 hours
16 to 30	0.94 grams (0.75 grams/0.19 grams) intravenously (over 2 hours) every 12 hours
6 to 15[b]	0.94 grams (0.75 grams/0.19 grams) intravenously (over 2 hours) every 24 hours
Less than or equal to 5[b]	0.94 grams (0.75 grams/0.19 grams) intravenously (over 2 hours) every 48 hours

[a]As calculated using the Cockcroft-Gault formula; [b]Both ceftazidime and avibactam are hemodialyzable; thus, ceftazidime-avibactam should be administered after hemodialysis on hemodialysis days.

Table 7: Predicted Exposures for the Revised Dosing Regimen in Patients with Varying Degrees of Renal Function

Renal Function	Revised Dosing Regimen	Ceftazidime		Avibactam	
		Cmax,ss (µg/mL)	AUC0-24,ss	Cmax,ss (µg/mL)	AUC0-24,ss (µg·h/mL)
NORM	2000 mg CAZ + 500 mg AVI, q8h	45.5 (63)	518 (63)	9.17 (62)	91.2 (62)
MILD	2000 mg CAZ + 500 mg AVI, q8h	57.6 (63)	783 (64)	11.0 (62)	126 (63)
MODE	1250 mg CAZ + 250 mg AVI, q8h	39.5 (63)	643 (64)	7.87 (62)	116 (63)
SEV1	750 mg CAZ + 188 mg AVI, q12h	34.6 (63)	571 (64)	7.61 (62)	118 (64)
SEV2	750 mg CAZ + 188 mg AVI, q24h	38.6 (64)	628 (65)	9.70 (63)	158 (66)
ESRD	750 mg CAZ + 188 mg AVI, q48h	59.6 (67)	1120 (69)	7.78 (62)	111 (62)

NORM (CrCL > 80 mL/min); MILD (CrCL 51 mL/min to ≤ 80 mL/min); MODE (CrCL 31 mL/min to ≤ 50 mL/min); SEV1 (CrCL 16 mL/min to ≤ 30mL/min); SEV2 (CrCL 6 mL/min to ≤ 15 mL/min); ESRD End-stage renal disease (CrCL 0 mL/min to ≤ 5 mL/min).
Source: Table 29, Dr. Jang's review

As the revised dosing regimen has not been studied in patients, Dr. Jang recommends that the Applicant conduct a postmarketing study to evaluate the pharmacokinetics, efficacy and safety of this revised dosing regimen in patients with complicated intra-abdominal infections with CrCL ≤ 50 mL/min.

Ceftazidime-Avibactam PK/PD Target

The percent time that free-drug concentrations are above the minimum inhibitory concentration (MIC) over a dose interval (% fT > MIC) has been established as the PK/PD index associated with the efficacy of ceftazidime. The % fT > MIC index for ceftazidime for infections due to Enterobacteriaceae and *Pseudomonas aeruginosa* is approximately 40% to 50%.

The PK/PD target for avibactam was determined in hollow fiber model and in neutropenic thigh and lung infection animal models to be the percent time of free-drug concentrations that are above a threshold concentration (CT) over a dose interval (% fT > CT). These models collectively suggested that 50% fT > 1.0 mg/L was the PK/PD target for avibactam that was associated with restoring the activity of ceftazidime against ceftazidime-nonsusceptible *P. aeruginosa* (MIC > 4 mcg/mL).

Dr. Jang recommend approval of this NDA with the previously mentioned recommendation for a postmarketing study to study to evaluate the pharmacokinetics, efficacy and safety of this revised dosing regimen in patients with cIAI with CrCL ≤ 50 mL/min. I agree with his recommendations.

6. Clinical Microbiology

Avery Goodwin Ph.D. was the clinical microbiology reviewer for this application. His findings are summarized.

Ceftazidime binds to bacterial penicillin binding proteins (PBPs), mainly PBP3 and to a lesser extent, PBPs 1a and 1b, leading to inhibition of cell wall synthesis and bacterial cell death. Resistance to ceftazidime occurs primarily through hydrolysis by beta-lactamases, alteration of PBPs and decreased bacterial cell wall permeability.

The Ambler classification system divides beta-lactamases into four classes: A, B, C and D based on amino acid sequences. Class A beta-lactamases include CTX-M, SHV, and TEM extended spectrum beta-lactamase enzymes (ESBLs) as well as *K. pneumoniae* carbapenemases (KPC). Class B enzymes require zinc, and hence are referred to as metallo-beta-lactamases. These include New Delhi metallo-beta-lactamase (NDM-1). Class C enzymes include AmpC enzymes and Class D enzymes cephalosporinases (such as OXA-10, OXA-48) and carbapenemases (such as OXA-23).

Avibactam is a diazabicyclooctanone, non-beta-lactam beta-lactamase inhibitor that has no appreciable antibacterial activity at the proposed doses, but employs a reactive urea to inhibit serine beta-lactamases, including Class A beta-lactamases, some Class C, and some Class D enzymes. Avibactam inhibits these beta-lactamase enzymes by binding to the serine residue of the active site of the enzyme, resulting in a highly stable carbmoyl linkage. Avibactam does not inhibit Class B metallo-B-lactamases (NDM-1, IMP and VIM).

In vitro Activity

The in vitro activity of ceftazidime-avibactam was evaluated against more than 5700 clinical isolates of Enterobacteriaecae collected in the United States in 2012, including 701 isolates that met the CLSI criteria for ESBL phenotype. CTX-M, SHV and KPC enzymes were the most commonly expressed. The MIC of ceftazidime-susceptible organisms was not altered by the addition of avibactam. The MIC_{90} of ceftazidime alone against the ESBL expressing isolates ranged from 16->32 mg/L. The MIC_{90} of ceftazidime-avibactam against these same isolates ranged from 0.25-2 mg/L.

The in vitro activity of ceftazidime-avibactam was evaluated against 7400 *P. aeruginosa* isolates collected globally. Approximately 90% of all the isolates tested had ceftazidime-avibactam MIC values of ≤ 8 mg/L, including those highly resistant to ceftazidime.

Ceftazidime-avibactam did not demonstrate meaningful activity against the majority of *Acinetobacter baumannii* isolates, with MIC ranging from 8 to >128 mg/L. The in vitro activity of ceftazidime-avibactam against *S. aureus, S. pneumoniae, S. pyogenes* and *S. agalactiae* was similar to that of ceftazidime. Ceftazidime-avibactam had poor in vitro activity against anaerobes, including *B. fragilis*.

Among clinical isolates, avibactam restored the in vitro activity of ceftazidime against clinical isolates of *P. aeruginosa* and Enterobacteriaceae that expressed TEM, SHV, CTX-M type and KPC beta-lactamases. All were inhibited by ≤4 mg/L. Avibactam did not alter the activity of ceftazidime against ceftazidime susceptible organisms.

No synergy or antagonism was observed when ceftazidime-avibactam was tested with metronidazole under anaerobic conditions. No synergy or antagonism was observed when between ceftazidime-avibactam and other antibacterial agents against individual representative bacterial strains of Enterobacteriaceae using the checkerboard method.

Similar to other beta-lactams, there was an inoculum effect in MIC testing, and bacterial killing was time dependent. The maximal rates of killing occurred at greater than or equal to twice the MIC. There was a low propensity for the development of ceftazidime-avibactam resistance following in vitro serial passage at 4 x MIC. The ceftazidime-avibactam mutation frequencies ranged from 10^{-7} to 10^{-9}. The highest mutation frequency (10^{-7}) was observed against a KPC producing *K. pneumoniae* strain.

Activity in Animal Models

The activity of ceftazidime-avibactam (4/1 w/w) was evaluated in five animal models: murine systemic infection, pneumonia immunocompromised mouse model, pyelonephritis

immunocompromised mouse model, meningitis immunocompetent rabbit model, the neutropenic mouse thigh infection model

In the murine systemic infection model, the addition of avibactam to ceftazidime restored the activity of ceftazidime against Enterobacteriaceae strains that expressed Class A or Class C beta-lactamases as demonstrated by significant decrease in ED50 from >50 mg/kg for ceftazidime alone to 5-29 mg/kg for the combination.

In the pneumonia immunocompromised mouse model, ceftazidime-avibactam restored the activity of ceftazidime against two *Klebsiella pneumoniae* strains, one that expressed AmpC DHA-2 and one that expressed AmpC Lat-4 + SHY-11 as demonstrated by significant decrease in bacterial burden (lung CFU/gram).

In the pyelonephritis immunocompromised mouse model, ceftazidime-avibactam restored the activity of ceftazidime against *K. pneumoniae* strain that expressed Class A and AmpC, two *E. coli* strains that expressed either Class A or Class C enzymes, *E. cloacae* strain that expressed AmpC, *M. morganii* strain that expressed AmpC, and *C. freundii* strain that expressed AmpC. Restoration of ceftazidime activity was demonstrated by significant decrease in bacterial burden (kidney CFU/gram).

In the meningitis immunocompetent rabbit model, ceftazidime-avibactam restored the activity of ceftazidime against *K. pneumoniae* that expressed AmpC and DHA-2 as demonstrated by significant decrease in CSF bacterial load.

In the neutropenic mouse thigh infection model, avibactam restored the activity of ceftazidime against KPC-producing *K. pneumoniae* strain as demonstrated by decrease in bacterial burden.

In the mouse neutropenic model, simulated human doses resulted in reduction of bacterial load in 16 of 17 *P. aeruginosa* isolates with ceftazidime-avibactam MIC ≤ 8mcg/mL and 5 of 8 isolates with ceftazidime-avibactam MIC ≤16 mcg/mL.

Susceptibility Test Interpretive Criteria (Susceptibility Breakpoints)
PK/PD relationships could not be identified from clinical data due to the limited data available from the Phase 2 cIAI and cUTI studies. The PK/PD targets that were determined from in vitro and animal studies were used to determine the probability of target attainment for ceftazidime-avibactam. Population PK analyses were used to evaluate the probability of PK/PD target attainment (PTA) for ceftazidime and avibactam (See Clinical Pharmacology Section).

The probability of target attainment analyses were used to support the susceptibility test interpretive criteria. Because cIAI was identified as a significant factor that resulting in lower ceftazidime-avibactam exposure, PTA analyses was performed in simulated cIAI patients. The PTA analyses demonstrated > 90% joint target attainment with the proposed dose (2.5 g ceftazidime-avibactam; 2.0 g ceftazidime plus 0.5 g avibactam q8h infused over 2 hours) for MICs up to 8 mcg/mL (Table 4, Clinical Pharmacology section).

Surveillance data obtained from 8,640 US isolates of Enterobacteriaceae collected in 2012 showed the MIC values for ceftazidime-avibactam ranged from ≤ 0.03 to > 32 mcg/mL. The MIC_{90} value for ceftazidime-avibactam was reported as 0.25 mg/L. Therefore, at the proposed PK/PD breakpoint of 8 mg/L 99.9 % of all US Enterobacteriaceae isolates would be considered susceptible to ceftazidime-avibactam. Among the 925 isolates that were non-susceptible (intermediate and resistant) to ceftazidime, the ceftazidime-avibactam MIC values ranged from ≤ 0.03 to 16 mcg/mL (MIC_{90} value of 1 mcg/mL). At the proposed breakpoint of 8 mg/L, 99.4% of US isolates of ceftazidime-non-susceptible Enterobacteriaceae would be reported as susceptible to ceftazidime-avibactam.

The MIC_{90} for Enterobacteriaceae isolated from the two Phase 2 trials was 0.25 mcg/mL. Very limited clinical data are available at ceftazidime-avibactam MICs > 0.5 mcg/mL. Table 8 summarizes clinical outcomes by MIC for baseline Enterobacteriaceae isolates in the two Phase 2 trials.

Table 8: Clinical Outcome by MIC for Enterobacteriaceae – Pooled Phase 2 Data

Ceftazidime-avibactam MIC (mcg/mL)	mMITT Population Favorable Microbiological Response n/N (%)		ME population Favorable Microbiological Response n/N (%)	
	cUTI	cIAI	cUTI	cIAI
≤ 0.03	4/6 (66.7)	10/12 (83.3)	2/2 (100)	9/11 (81.8)
0.06	12/14 (85.7)	18/21 (85.7)	7/9 (77.8)	18/18 (100)
0.12	8/15 (53.3)	15/20 (75.0)	6/10 (60)	15/17 (88.2)
0.25	6/6 (100)	8/9 (88.9)	4/4 (100)	8/8 (100)
0.5		2/2 (100)		1/1 (100)
1		1/1 (100)		1/1 (100)
2		2/3 (66.7)		2/3 (66.7)
8		1/1 (100)		
>32		0/1 (0.0)		

In the two Phase 2 trials, the number of isolates of *P. aeruginosa* was very small.

Drs. Jang and Goodwin propose the susceptibility test interpretive criteria shown in table 9:

Table 9: Susceptibility Interpretative Criteria for Ceftazidime-Avibactam

	Ceftazidime-avibactam MIC mg/L		Disk Diffusion Zone Diameter (mm)	
	S	R	S	R
Enterobacteriaceae	≤ 8/4	≥ 16/4	≥ 21	≤ 20
Pseudomonas aeruginosa	≤ 8/4	≥ 16/4	≥ 18	≤ 17

Source: Clinical Microbiology Review page 6

The error rates generated for ceftazidime-avibactam at PK/PD breakpoint of 8 mcg/mL were similar to those generated using the PK/PD breakpoint of (b) (4) for ceftazidime.

Dr. Goodwin concluded that in vitro, ceftazidime-avibactam demonstrated bactericidal activity against *P. aeruginosa* and Enterobacteriaceae isolates, including isolates that produced Class

A, Class C and some Class D β-lactamases and restored the activity of ceftazidime against ceftazidime nonsusceptible *P. aeruginosa* and Enterobacteriaceae isolates expressing Class A, Class C and some Class D beta-lactamases.
Dr. Goodwin recommends approval of ceftazidime-avibactam for the treatment of cIAI and UTI caused by susceptible gram-negative isolates. I agree with his recommendations.

I also agree with Dr. Goodwin and Dr. Jang's recommendation for the susceptibility interpretative criteria. Although clinical data are very limited at the higher MICs, the proposed criteria are supported by PK/PD data and microbiology surveillance data. The interpretive criteria for *P. aeruginosa* are consistent with those of ceftazidime. For ceftazidime, the susceptible breakpoint of (b) (4) for Enterobacteriaceae is based on a dose of 1 gram every 8 hours and the intermediate category (MIC 8 mcg/mL) is based on a dosing regimen of 2 gram every 8 hours. As the highest dose of ceftazidime-avibactam is 2 grams every 8 hours and the PTA at an MIC of 16 is 50.8%, an MIC value for the intermediate category cannot be supported.

7. Clinical/Statistical- Efficacy

The clinical reviewer for this NDA was Benjamin Lorenz MD and the statistical reviewer was Margaret Gamalo-Siebers, Ph.D. Their findings are summarized.

The clinical data supporting this NDA included the results of two Phase 2 trials, one in cUTI including pyelonephritis and one in cIAI. Neither trial was designed for formal statistical inferential testing. Preliminary interim efficacy results from an ongoing Phase 3 trial in patients with cIAI or cUTI caused by ceftazidime-resistant Gram-negative bacteria (Resistant Pathogen Study D4280C00006) were also provided, as well as literature review to assess the historical efficacy of ceftazidime in these infections.

Complicated Urinary Tract Infections Trial (NXL104/2001)
The trial was conducted between November 2008 and June 2010 at 26 centers in five countries.

This was a Phase 2 multicenter, randomized, investigator-blind trial comparing ceftazidime-avibactam 625 mg (500 mg ceftazidime plus 125 mg avibactam) IV over 30 minutes every 8 hours to imipenem-cilastatin 500 mg IV over 30 minutes every 6 hours in adults with cUTI. Of note, the ceftazidime-avibactam dose used in this trial is 25% of the proposed dose for approval (2.5 grams). If clinically acceptable, switch to oral ciprofloxacin (500 mg every 12 hours) was allowed after at least 4 days of IV study therapy. Total duration of therapy ranged from 7 to 14 days. Patients were stratified by absence or presence of pyelonephritis. Patients with an estimated CrCL < 70 mL/min were excluded. Patients who received more than 1 dose of a potentially effective systemic antibacterial therapy within 48 hours prior to obtaining baseline urine culture were also excluded.

Urine cultures were obtained at baseline, during therapy (Days 3, 4 or 5), at end of IV therapy, at the test-of-cure (TOC visit, 5 to 9 days post-therapy and at late follow up visit (LFU, 4-6 weeks after EOT).

The protocol-specified primary endpoint was microbiologic response in the microbiologically evaluable (ME) population at the TOC Visit. However, the FDA draft guidance for industry (Complicated Urinary Tract Infections: Developing Drugs for Treatment[2]) recommends resolution of clinical symptoms of cUTI and microbiological success (urine culture demonstrating a reduction in the baseline pathogen to less than 10^4 colony forming units (CFU) per mL) at approximately 7 days after completion of therapy as the primary endpoint and recommends the microbiologic modified intent-to-treat population (mMITT, defined as patients who have a qualifying pre-treatment urine culture containing $>10^5$ CFU/mL of at least one pathogen and received at least one dose of study therapy) as the primary analysis population.

Sixty-eight (68) patients received ceftazidime-avibactam and 67 received imipenem-cilastatin. Approximately 65% of randomized patients in the ceftazidime-avibactam arm and 61% in the imipenem arm had pyelonephritis. Approximately 75% of patients were female and 80% were less than 65 years of age.

The mMITT population included 46 patients who received ceftazidime-avibactam and 49 patients who received imipenem-cilastatin. Less than 10% in each arm had concurrent baseline bacteremia. *E. coli* was the most common organism isolated (40 patients in the ceftazidime-avibactam arm and 41 in the imipenem-cilastatin arm). All14 isolates that were ceftazidime non-susceptible in the ceftazidime-avibactam arm were *E. coli*.

In the mMITT population, 29/46 (63.0%) of the patients in the ceftazidime-avibactam group and 25/49 (51.0%) of the patients in the impinem-cilastatin group achieved clinical and microbiologic cure.

Table 10: Clinical and Microbiological Response at TOC—mMITT Population – Phase 2 cUTI Trial

	Ceftazidime-Avibactam N = 46 n (%)	Imipenem-Cilastatin N = 49 n (%)	Difference (95% CI) *
Microbiological Response			
Eradication	31 (67.4)	31 (63.3)	4.1 (-16.1, 23.8)
Persistence	10 (21.7)	14 (28.6)	
Indeterminate	5 (10.9)	4 (8.2)	
Clinical Response			
Cure	37 (80.4)	36 (73.5)	7.0 (-11.6, 24.7)
Failure	5 (10.9)	9 (18.4)	
Indeterminate	4 (8.7)	4 (8.2)	
Clinical & Microbiological Response			
Cure + Eradication	29 (63.0)	25 (51.0)	12.0 (-9.1, 31.7)

[2] http://www.fda.gov/downloads/Drugs/Guidances/ucm070981.pdf

Failure + Persistence or Indeterminate	17 (37.0)	24 (49.0)	

*Exact 95% Clopper-Pearson confidence intervals
Source: Table 3-13 Statistics Review

In the subpopulation with ceftazidime non-susceptible organisms (MIC ≥ 8 mcg/mL for Enterobacteriaceae and ≥ 16 mcg/mL for *P. aeruginosa*), clinical and microbiologic cure was achieved in 8/14 (57.1%) of ceftazidime-avibactam recipients and in 7/18 (38.9%) imipenem-cilastatin recipients. Characterization of specific mechanisms of resistance for the ceftazidime-resistant isolates was not provided in the study report.

Table 11: Clinical Response and Microbiologic Outcome at TOC - mMITT Population - Ceftazidime-nonsusceptible Isolates – Phase 2 cUTI Trial

	Ceftazidime-Avibactam N=14 n (%)	Imipenem-Cilastatin N=18 n (%)	Difference (95% CI)*
Microbiological Outcome			
Eradication	9 (64.3)	10 (55.6)	8.7 (-27.4, 41.3)
Persistence	3 (21.4)	6 (33.3)	
Indeterminate	2 (14.3)	2 (11.1)	
Clinical Response			
Cure	11 (78.6)	10 (55.6)	23.0 (-14.0, 51.2)
Failure	2 (14.3)	5 (27.8)	
Indeterminate	1 (7.1)	3 (16.7)	
Clinical & Microbiological Outcome			
Cure + Eradication	8 (57.1)	7 (38.9)	18.3 (-22.4, 58.9)
Failure + Persistence or Indeterminate	6 (42.9)	11 (61.1)	

*Exact 95% Clopper-Pearson confidence intervals
Source: Table 3-17, Statistics Review

The combined clinical and microbiologic cure rates were numerically higher in the ceftazidime-avibactam arm in the overall population and the subpopulation with ceftazidime-nonsusceptible organisms. However, the 95% confidence interval for the difference is wide, and no statistical conclusions can be drawn. Although the ceftazidime-avibactam dose used in this trial (625 mg) is lower than the proposed dose for labeling (2.5 grams), this lower dose does not explain the cure rates that are lower in both arms than the cure rates seen in more recent cUTI trials.

Complicated Intra-abdominal Infections (NXL104/2002)
This trial was conducted between March 2009 and December 2009 at 33 centers in eight countries.

This was a Phase 2 multicenter, randomized, double-blind trial comparing ceftazidime-avibactam 2.5 grams (2 grams ceftazidime and 500 mg avibactam) IV over 30 minutes every 8 hours plus metronidazole 500 mg IV over 1 hour every 8 hours to meropenem 1000 mg IV over 30 minutes every 8 hours in adults with cIAI. For enrollment, patients should have

evidence of systemic inflammatory response, physical findings consistent with intra-abdominal infection, supportive radiologic imaging and requirement for surgical intervention. Patients with an estimated CrCL < 50mL/min were excluded. Patients who had received more than one dose of potentially effective systemic antibacterial therapy within the 72 hours prior to study entry were excluded. Treatment duration was 5 to 14 days. Randomization was stratified by baseline severity of disease (APACHE II score < 10, and > 10 to ≤ 25). Clinical assessments were performed at baseline, daily during study therapy, at the discontinuation of study therapy, at the TOC visit (2 weeks post-therapy), and at the late follow-up visit (4 to 6 weeks post-therapy).

The protocol-defined primary endpoint was the clinical outcome (clinical cure was defined as complete resolution or significant improvement of signs and symptoms without requirement for further antimicrobial therapy or surgical or radiologic intervention) at TOC visit (2 weeks post-therapy in the ME population. However, the FDA guidance for industry "Complicated Intra-abdominal Infections: Developing Drugs for Treatment" recommends the mMITT population, defined as all randomized patients who have baseline pathogens that cause cIAI, to be the primary analysis population.[3]

One hundred and one (101) patients with cIAI received ceftazidime-avibactam/metronidazole and 102 received meropenem. Approximately 75% were male and 90% were less than 65 years of age. The mMITT population included 85 patients in the ceftazidime-avibactam plus metronidazole group and 89 patients in the meropenem group. In the mMITT population, the site of infection was the appendix in approximately 48% and the stomach/duodenum in approximately 23% of patients. Approximately 90% underwent open laparotomy and 45% had generalized peritonitis. Approximately 83% had an APACHE II score ≤ 10 and approximately one third had polymicrobial infection The most common pathogens identified from intra-abdominal sites were *E. coli* (70% of patients), *K. pneumoniae, S. aureus, P. aeruginosa, B. fragilis* and *E. faecium.*

In the mMITT population, clinical cure was achieved at TOC in 70/85 (82.4%) of ceftazidime-avibactam recipients and 79/89 (88.8%) in meropenem recipients.

Table 12: Clinical Response at TOC in the mMITT population – Phase 2 cIAI

Clinical Outcome	Ceftazidime-avibactam plus metronidazole N=68; n (%)	Meropenem N=76; n (%)	Difference (95% CI)
Clinical Response	70 (82.4)	79 (88.8)	-6.4 (-18.0, 5.2)
Clinical Failure + Indeterminate	15 (17.7)	10 (11.2)	

Source: Table 3-24 Statistics Review

In the subpopulation of patients with ceftazidime non-susceptible organisms at baseline (MIC ≥ 8 mcg/mL for Enterobacteriaceae and ≥ 16 mcg/mL for *P. aeruginosa*), cure was achieved in

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

27/90 (90%) and 19/23 (82.6%) in the ceftazidime-avibactam and meropenem arms respectively. The specific mechanism(s) of resistance in these isolates was not reported.

Table 13: Clinical Response at TOC in the ceftazidime nonsusceptible subgroup - mMITT population – Phase 2 cIAI Trial

Clinical Outcome	Ceftazidime-avibactam plus metronidazole N=30; n (%)	Meropenem N=76; n (%)	Difference (95% CI)
Clinical Response	27 (90.0)	19 (82.6)	7.4 (-15.3, 30.0)
Clinical Failure + Indeterminate	3 (10.0)	4 (17.4)	

Source: Table 3-29 Statistics Review

The cure rate was higher in ceftazidime-avibactam recipients compared with meropenem recipients in the subgroup of patients with ceftazidime nonsusceptible organism.

The cure rates were lower among ceftazidime-avibactam recipients compared to meropenem in the overall population and in the subpopulation with ceftazidime susceptible organism (76.2% ceftazidime-avibactam and 88.7% meropenem respectively). Because avibactam does not interfere with the activity of ceftazidime in ceftazidime susceptible organism, this is likely a chance finding in a small trial without inferential statistical testing.

Resistant Pathogen Study (Study D4280C00006)
This was a multicenter, randomized, open-label study in adult patients with cIAI or cUTI caused by ceftazidime non-susceptible organisms. Patients were stratified by disease (cIAI or cUTI), region of enrollment (North America and Western Europe, Eastern Europe, and rest of the world). Ceftazidime-avibactam was compared to best available therapy (BAI), which was carbapenem based. Ceftazidime-avibactam dose was 2.5 g (2.0 g ceftazidime + avibactam 0.5 g) infused over 2 hours every 8 hours. As of the 09 Dec 2013 interim data cutoff, the mMITT population included only 4 subjects diagnosed with cIAI and 44 subjects with cUTI.
The Applicant only reported clinical outcomes for the cUTI patients. Clinical cure in the mMITT population at TOC in the cUTI subset was 19/21 (90.5%) in the ceftazidime-avibactam arm and 18/23 (78.3%) in the comparator arm.

Historical Efficacy of Ceftazidime in cUTI and cIAI
The Applicant performed a meta-analysis of published articles assessing treatment of cUTI/cIAI with ceftazidime. Based on the 15 articles included in the meta-analysis in which ceftazidime was used to treat cUTI, microbiological response rates at TOC was 89.1% (95% CI: 85.0, 93.2%) and clinical outcome rates were 90.4% (95% CI: 85.5, 95.4%) at TOC. The populations in these studies were similar to a ME population. Two studies were identified in cIAI. In neither study, the duration of therapy or the timing of assessment was specified. The clinical response rate post-therapy was 86% (95% CI: 74.1, 98.0%). the publications had several limitations with respect to trial design, treatment duration, timing of assessment, and analysis populations.

Preliminary Results from Recently Completed Phase 3 cIAI Trial (D4280C00001/5)

The data from this trial was not submitted for review, but topline results were communicated in October 2014. This trial was randomized, multi-center, double-blind, non-inferiority trial comparing ceftazidime-avibactam (2000 mg/500 mg over 2 h, q8h) plus metronidazole (0.5 g IV q8h) to meropenem (1 g IV q8h) in the treatment of cIAI, using a 10% NI margin. Per the protocol, patients with CrCL of 31-50 mL/min at baseline were to have their dose adjusted to 1.25 g q12h for ceftazidime-avibactam or 1 g q12h for meropenem. Patients with severe renal impairment (CrCL ≤ 30 mL/min) were excluded.

The primary endpoint was the clinical cure at TOC (28 to 35 days after randomization) in subjects who had at least one identified pathogen (mMITT population). Clinical cure was 81.6% in the ceftazidime-avibactam plus metronidazole arm and 85.1% in the meropenem arm [treatment difference -3.5% (95% CI -8.6% to 1.6%)]. Cure rate was lower in each treatment arm in patients with moderate renal impairment (CrCL 30-50 mL/min) compared to patients with normal renal function or mild renal impairment (CrCL >50 mL/min). However, the decrease in clinical cure was more marked in ceftazidime-avibactam recipients.

Table 14: Clinical Cure Rate at TOC by Baseline Renal Function (mMITT Population) – Phase 3 cIAI Trial

Baseline Renal Function	Ceftazidime-avibactam + Metronidazole	Meropenem
CrCL >50 mL/min	322/379 (85%)	321/373 (86%)
CrCL > 30 to ≤ 50 mL/min	14/31 (45%)	26/35 (74%)

Source: Applicant's Correspondence, October 9, 2014

Reasons for the decreased efficacy in patients with renal impairment are not clear, as patient-level data is not yet available to the FDA for review. These results led to revising the proposed dosage adjustment in patients with moderate renal impairment (See Clinical Pharmacology).

In addition to decreased efficacy in the subpopulation of ceftazidime-avibactam recipients with moderate renal impairment at baseline, there was also a mortality imbalance in this subpopulation (See Safety Section).

Dr. Gamalo concludes that, absent reliance on the 505(b)(2) pathway, the evidence of efficacy for ceftazidime-avibactam in the treatment of cUTI or cIAI is scant and uncertain, with wide confidence interval around point estimates for cures in both studies. In addition, although cure rates in the cUTI study were numerically higher in ceftazidime-avibactam recipients compared to imipenem-cilastatin recipients, they are lower than cure rates that are historically reported for ceftazidime. The higher cure rates seen in the Resistant Pathogens trial may reflect the higher dose of ceftazidime-avibactam used.. Dr. Gamalo notes that cure rates were numerically higher than the comparator in patients with baseline ceftazidime non-susceptible pathogens in both trials, however the numbers are small. Dr. Gamalo also expresses concern regarding the lower efficacy noted in patients with moderate renal impairment compared to patients without, or with mild renal impairment. Despite these concerns, Dr. Gamalo recommends approval for limited use, given the effectiveness in the ceftazidime non-susceptible patients that is comparable to the historically reported efficacy for ceftazidime, the in vitro activity and activity of ceftazidime-avibactam in animal models and the unmet medical need.

Dr. Lorenz concludes that adequate evidence has been provided to support the approval of ceftazidime-avibactam for the treatment of adults with cUTI and cIAI when alternative treatments are not suitable. Dr. Lorenz also notes that there is insufficient data to support approval for the following "Limited Use" indication: treatment of aerobic gram-negative infections, including hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP) and bacteremia, where limited or no alternative therapies are available.

I agree with the recommendations of Dr. Gamalo and Dr. Lorenz that the clinical data, although limited, support approval of ceftazidime-avibactam in patients with cIAI and cUTI who have limited or no alternative treatment options. I also agree with Dr. Lorenz that due to the lack of clinical data, approval is not recommended for the indication of treatment of aerobic gram-negative infections, including HABP/VABP and bacteremia, where limited or no alternative therapies are available.

8. Safety

The clinical reviewer for this NDA was Benjamin Lorenz MD. His assessment is summarized.

The Applicant is relying on previous findings of safety for ceftazidime. The Applicant also conducted a literature search and search of the FDA Adverse Event Reporting System (FAERS) database for adverse events associated with ceftazidime exposure.

Serious reactions included in ceftazidime or other cephalosporin class antibacterial drugs labeling include urticaria, anaphylaxis, angioedema, hyperbilirubinemia, jaundice, myoclonus and status epilepticus, colitis, hepatic dysfunction (including cholestasis), aplastic anemia, hemorrhage, toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Nephrotoxicity has been reported following concomitant administration of cephalosporins with aminoglycosides or potent diuretics such as furosemide. Abnormal laboratory tests include prolonged prothrombin time, false-positive test for urinary glucose, and pancytopenia. The literature search identified non-convulsive status epilepticus, a prolonged seizure diagnosed by electroencephalogram (EEG) that manifests primarily as altered consciousness or encephalopathy, as an additional safety concern that was not previously described in the product labeling for ceftazidime.

Extent of Exposure

The safety database included 11 Phase 1 studies, two Phase 2 trials, and data from ongoing/recently completed Phase 3 trials.

In the completed Phase 1 and Phase 2 studies, 521 subjects received any dose of ceftazidime-avibactam (360 subjects) or avibactam alone (204 subjects). A total of 286 subjects received either single or multiple doses of 2000/500 mg of ceftazidime-avibactam (217 subjects) or 500 mg of avibactam alone (96 subjects). The median duration of ceftazidime-avibactam therapy was 5 days.

Adverse Events

Table 16 summarizes the incidence of treatment emergent adverse events (TEAEs) noted in Phase 2 and 3 clinical trials evaluating ceftazidime-avibactam. Of note, the dose used in the Phase 2 cUTI study was 625 mg (500 mg ceftazidime and 125 mg avibactam), while the dose used in the Phase 2 cIAI and the Phase 3 studies was 2.5 grams (2 grams ceftazidime and 0.5 grams avibactam.

Table 15: Overall Summary of Treatment-Emergent Adverse Events—Safety Population

	Trial 2001 (cUTI)		Trial 2002 (cIAI)		Phase 3
Subjects with	CAZ-AVI (N = 68) n (%)	IMI-CS (N = 67) n (%)	CAZ-AVI + MTZ (N = 101) n (%)	Meropenem (N = 102) n (%)	Overall (N = 2649) n (%)
Any TEAE	46 (67.6)	51 (76.1)	65 (64.4)	59 (57.8)	n/a
Any SAE	6 (8.8)	2 (3.0)	9 (8.9)	11 (10.8)	180 (6.8)
Discontinuation due to AE	2 (2.9)	0 (0.0)	6 (5.9)	4 (3.9)	46 (1.7)
TEAE resulting in Death	0	1 (1.5)	3 (3.0)	2 (2.0)	54 (2.0)

CAZ-AVI = ceftazidime-avibactam; IMI-CS = imipenem-cilastatin; MTZ = metronidazole
Source: Table 74 – Clinical Review

Deaths

Table 17 summarizes the deaths that have been reported in the ceftazidime-avibactam clinical program. Review of the 12 unblinded narratives that were provided indicated that deaths were attributable to underlying comorbidities, treatment failure and/or emergent infection.

Table 16: Overview of Deaths Reported during the Ceftazidime-Avibactam Clinical Program as of June 25, 2014

	Ceftazidime-avibactam	Comparator	Total
All Phase 1 (completed/ongoing)	0	-	0
Trial 2001 (cUTI)	0/68	1/67	1
Trial 2002 (cIAI)	4/101	2/102	6
Phase 3 cIAI (D4280C00001/5)*	13/532	8/532	22
Phase 3 cUTI (D4280C00002/4)	-	-	0
cIAI and cUTI (D4280C00006)	3	3	6
cIAI in Asia (D4280C00018)	-	-	3 (1.2%)£
HABP/VABP (D4281C00001)	-	-	23 (10.6%)£
Total Subjects	20	14	61

*deaths in each treatment arm reported in the mMITT population, one additional ceftazidime-avibactam-treated subject who died after LFU due to a myocardial infarction is not included here.
£Blinded
Source (Modified): Table 75 Clinical Review

In the Phase 3 cIAI Trial (D4280C00001/5), there was an imbalance in mortality among patients with moderate renal impairment. In the overall population, death occurred in 2.4% (13/532) ceftazidime-avibactam recipients compared to 1.5% (8/534) meropenem recipients. In the subgroup of patients with moderate renal impairment, death occurred in 25.8% (8/31) ceftazidime-avibactam recipients compared to 8.6% (3/35) meropenem recipients. Patient level

data is not available to the FDA for review. Analysis conducted by the Applicant suggests that the etiology of the deaths was multifactorial.

Serious Adverse Events

There were no SAEs in the Phase 1 studies. The incidence of SAEs reported in Phase 2 cUTI and cIAI studies and in the Phase 3 study is shown in table 16. In the cUTI study, none of the SAEs was experienced by more than one subject. In the cIAI study, no SAE occurred in > 2 subjects in either treatment group. Diarrhea, accidental overdose and acute renal failure were assessed by the Investigator as likely related to the study drug in the ceftazidime-avibactam group. None of the SAEs in the Resistant Pathogen Study (D4280C00006) were considered by the investigator to be related to study drug. In the blinded ongoing Phase 3 studies, 6 SAEs were considered related to study drug including: transaminases increased, drug eruption, hypersensitivity, pyrexia, increased ALT, and increased AST.

Discontinuation Due to Treatment Emergent AE

In phase 1 studies, one subject discontinued study drug due to AE (urticaria). The incidence of SAEs reported in Phase 2 cUTI and cIAI studies and in the Phase 3 study is shown in table 16. Most of the discontinuations in the Phase 2 cUTI trial were due to screening failures.
In the Phase 2 cIAI trial, hepatic enzymes increase and rash led to discontinuation of ceftazidime-avibactam plus metronidazole arm. In the Resistant Pathogen study, one subject in the ceftazidime-avibactam group discontinued study drug due to cardio-respiratory arrest, which was also a fatal SAE

Common AEs

In the Phase 1 studies, the most frequent adverse events in all subjects receiving avibactam alone were headache, diarrhea, and application site bruise. Mild and reversible elevations in serum transaminases and alkaline phosphatase were noted.

In the Phase 2 cUTI trial, the most common TEAEs where incidence was greater in the ceftazidime-avibactam group than imipenem-cilastatin group were constipation (10.3%), anxiety (10.3%) and abdominal pain (8.8%). In the Phase 2 cIAI trial, the most common TEAEs where incidence was greater in the ceftazidime-avibactam plus metronidazole group than the meropenem group were vomiting (13.9%), nausea (9.9%) and anxiety (5.0%).

Laboratory Changes

Positive Coombs' test was reported in 7.3% and 1.9% of ceftazidime-avibactam recipients in the cIAI and cUTI trials respectively. No patient had evidence of hemolysis. Mean and maximum changes in QTcF were similar between ceftazidime-avibactam and comparator groups. One in the ceftazidime group in the cUTI trial had QTcF values > 500 msec and changes from baseline > 60 msec based on the centrally read ECG values, but no associated cardiac TEAEs were reported. There were no hepatic enzyme changes that satisfied Hy's law.

Adverse Events of Interest

The Applicant investigated five adverse events of special interest in the ceftazidime-avibactam safety database: liver disorders, diarrhea, hypersensitivity, hematologic disorders, and renal disorders.

Liver disorders: One subject receiving avibactam in Phase 1 studies experienced a TEAE of transient increase in transaminases that was considered mild in severity and related to study drug. One ceftazidime-avibactam plus metronidazole recipient was reported to have SAE of hepatic enzyme elevation n the Phase 2 cIAI trial that resulted in prolonged hospitalization. No patient met Hy's Law.
Diarrhea: No patient discontinued treatment due to diarrhea. No cases of *Clostridium difficile* associated diarrhea (CDAD) were reported in the Phase 2 trials. One case of CDAD was reported in the comparator arm in the resistant pathogen study.
Hypersensitivity: No cases of hypersensitivity/anaphylaxis were reported in the Phase 2 trials. One subject in a Phase 1 study discontinued high-dose ceftazidime-avibactam (5 g) due to a TEAE of urticaria.
Hematologic: Positive Coombs' test was reported in <10% of ceftazidime-avibactam recipients and was not associated with hemolysis or other TEAEs representing hematologic disorders.
Renal: In the cUTI trial, two patients in the ceftazidime-avibactam group had SAEs representing renal disorders (acute renal failure, renal impairment); both had renal comorbidities and the SAEs resolved without sequelae. In the cIAI trial, an SAE of acute renal failure occurred in one subject in the meropenem group that led to premature discontinuation of study drug.

Overall, the safety profile of ceftazidime-avibactam is similar to the safety profile of ceftazidime and to other cephalosporins. The most concerning safety signal is the mortality imbalance in Phase 3 cIAI trial in the subgroup of patients with moderate renal impairment treated with ceftazidime-avibactam compared to patients treated with meropenem. As noted in the efficacy section, efficacy of ceftazidime-avibactam was lower in this subgroup compared to ceftazidime-avibactam subgroup with normal renal function or mild impairment. Mortality in patients with normal renal function or mild impairment was similar among ceftazidime-avibactam and meropenem recipients. Reasons for this imbalance are not yet clear, as patient-level data from this Phase 3 trial are not yet available for review. The possibility that this may be related to inadequate exposure in this renally impaired group led to revised dosage adjustments as noted in the clinical pharmacology section.

Dr. Lorenz concludes that there is sufficient evidence to recommend approval of ceftazidime-avibactam for the treatment of adults with cIAI and cUTI when alternative treatments are not suitable. He concludes that due to lack of clinical data, there is insufficient evidence to recommend approval for the treatment of aerobic gram-negative infections, including HABP/VABP where limited or no alternative therapies are available. I agree with his recommendations.

9. Advisory Committee Meeting

The Anti-Infective Drugs Advisory Committee met on December 5, 2014 to discuss this NDA for CAZ-AVI for the proposed indications of cIAI, cUTI including pyelonephritis, and aerobic Gram-negative infections in patients with limited treatment options. Findings from the Phase 2 trial were presented, as well as preliminary findings of decreased efficacy in the subgroup of

patients with moderate renal impairment that was noted in the Phase 3 CIAI study. Minutes of the meeting are available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM432232.pdf.

Four questions were posed to the committee.
Q. 1 Has the applicant demonstrated substantial evidence of safety and efficacy of ceftazidime-avibactam for the proposed indication of complicated intra-abdominal infections, when limited or no alternative treatments are available?

Eleven committee members voted in favor of approval, one member voted against, with no members abstaining. Some members were concerned regarding the mortality imbalance and the decreased efficacy in patients with baseline moderate renal impairment that were noted in the Phase 3 clinical trials, and recommended several possible approaches that ranged from including this information in labeling, restricting use in patients with moderate renal impairment, recommending therapeutic dose monitoring, REMS to restrict use to patients with resistant pathogens. The one member who voted against approval cited the concern regarding decreased efficacy in patients with moderate renal impairment and noted that there is no regulatory mechanism to enforce limited use post-marketing.

Q. 2 Has the applicant demonstrated substantial evidence of safety and efficacy of ceftazidime-avibactam for the proposed indication of UTI, including pyelonephritis, when limited or no alternative treatments are available?

Nine committee members voted in favor of approval, three voted against with no member abstaining. Two committee members who voted “No” noted that they were concerned about the high (40%) failure rate.

Q. 3 Has the applicant demonstrated substantial evidence of safety and efficacy of ceftazidime-avibactam for the proposed indication of aerobic gram-negative infections (including hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia and bacteremia) when limited treatments are available?

Twelve members voted no, with no member voting yes and none abstaining. The members agreed that further clinical trials are needed.

Q. 4 Has the applicant demonstrated substantial evidence of safety and efficacy of ceftazidime-avibactam for the proposed indication of aerobic gram-negative infections (including hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia and bacteremia) when no treatments are available?

Eleven members voted no, one member voted yes with none abstaining. The committee members noted that more clinical data is needed, but that it would also be helpful to include non-clinical data regarding CAZ-AVI lung penetration (epithelial fluid lining concentrations) in labeling because non-approval for HABP/VABP does not preclude off-label use.

10. 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.

An initial Pediatric Study Plan (iPSP) was not submitted prior to the NDA submission. A pediatric plan was submitted at the time of the NDA submission.

The proposed Pediatric Study Plan includes one non-clinical toxicology study in weanling rats, and the following four pediatric clinical studies:

Study 1: A single dose, (b) (4), PK, safety and tolerability study in children 3 months to < 18 years of age (b) (4) (estimated CSR submission December 2104)

Study 2: A (b) (4), multicenter, active controlled trial employing therapeutic dose(s) identified in the single dose PK study to evaluate safety and efficacy of ceftazidime-avibactam in children from 3 months to <18 years of age (b) (4) (estimated complete study report (CSR) submission December 2018)

Study 3: A single-blind, randomized, multicenter, active controlled trial employing therapeutic dose(s) identified in the single dose PK study to evaluate safety and efficacy of ceftazidime-avibactam in children from 3 months to <18 years of age (b) (4) (estimated CSR submission December 2017)

Study 4: An open-label trial to evaluate PK, safety and tolerability of ceftazidime-avibactam in children from birth to less than 3 months of age, (b) (4) onset sepsis (estimated CSR submission December 2019).

The applicant requested deferral of pediatric studies. The PSP and deferral requests were discussed with the Pediatric Review Committee (PeRC) on January 14, 2015. The pediatric studies will be postmarketing requirements.

11. Other Relevant Regulatory Issues

Clinical Site Inspections
Dr. Janice Pohlman filed the Clinical Inspection Summary.

In the Phase 2 cUTI trial, the sites with the highest enrollment were in Lebanon, Guatemala, Jordan, USA and India (in decreasing frequency).The Office of Scientific Investigations conducted inspections at two sites, one domestic (Modesta, CA) and one foreign (Guatemala The preliminary classification for each site was Voluntary Action Indicated (VAI). At both

sites, there were protocol violations such as timing of repeat urine culture and use of nonstudy antibacterial drugs, but there were no issues with data integrity at either site.

In the Phase 2 cIAI trial, the sites with the highest enrollment were in India, Romania and USA (in decreasing order). Two inspections were requested, one domestic (Somers Point, NJ) and one foreign (India). The preliminary classification for the domestic site was No Action Indicated (NAI). Inspection of the foreign site has not yet been completed.

An inspection of the sponsor, Actavis P.L.C. (formerly Forest Laboratories, Inc./Cerexa, Inc. subsidiary) was also conducted. The preliminary classification is VAI, primarily related to monitoring practices during the course of the study. Problems with the IVRS randomization and assignment of study drug vials were not acted upon promptly. Dr. Pohlman notes that the Applicant performed an extensive drug reconciliation process and appears to have ensured that subjects received appropriate study drug treatment. (b) (4) the Contract Research organization (CRO) responsible for the malfunctioning IVRS was also inspected and preliminary classification for that inspection is NAI. Inspection classifications will be finalized when the inspection correspondence is issued to the inspected entity.

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 Risk Evaluation and Mitigation Strategy (REMS) is not required at this time. Dr. Weaver also noted that the risk related to decreased efficacy in patients with creatinine clearance 30 to 50 mL/min is not understood at this time, and cannot be characterized until the data for these patients are analyzed. I agree with Dr. Weaver's assessment that safety findings with ceftazidime-avibactam have been adequately addressed in labeling and that a REMS is not required at this time.

Facilities Inspection
The report is pending at this time.

Financial disclosures
Financial disclosures for the clinical investigators who enrolled subjects in the cUTI (NXL104/2001) or cIAI (NXL104/2002) studies were provided. The Applicant certifies that the financial information described meets requirements in 21 CFR § 54.4.

12. Labeling

Labeling recommendation from Sevan Kolejian, 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.

The Division of Medication Error Prevention and Risk Management of the Office of Surveillance and Epidemiology determined that the proprietary name, AVYCAZ®, was acceptable. The previously proposed proprietary name, Cazavi, was found unacceptable due to orthographic similarities and shared product characteristics with the proprietary name Cozaar.

The main issues addressed in labeling are:
Indications and Usage: The Indications and Usage section will include a statement that, due to limited clinical data, AVYCAZ should be reserved for use when limited or no alternative therapies are available.
Dosage and Administration: The revised dosing adjustment in patients with renal impairment will be recommended instead of the proposed dosing regimen that was used in the Phase 3 cIAI trial.
Warnings and Precautions: The decreased efficacy noted in the Phase 3 trial in cIAI patients with moderate renal impairment will be addressed in the Warnings and Precautions section with a recommendation to monitor Cr at least daily in these patients and to adjust ceftazidime-avibactam dosage accordingly.
Adverse Reactions: The increased mortality noted in ceftazidime-avibactam patients with moderate renal impairment will be described under a separate subheading in the Adverse Events section.
Clinical Studies: This section will not include a detailed description of the Phase 2 cIAI and cUTI studies, as neither study is considered adequate and well controlled, mainly due to the lack of statistical inferential testing. This section will include the following statement: "The determination of efficacy of AVYCAZ was supported by the previous findings of the efficacy of ceftazidime for the treatment of cIAI and cUTI. The contribution of avibactam to AVYCAZ was established *in vitro* and in animal models of infection". It is anticipated that this section will be updated once the Phase 3 study results are reviewed.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I agree with the recommendation of the review team that there is adequate evidence to support approval of ceftazidime-avibactam for the indications of treatment of complicated intra-abdominal infections and treatment of complicated urinary tract infections, including pyelonephritis, caused by susceptible designated organisms, in patients with limited or no available alternative treatments.

The above indications are supported by in vitro and animal model data that indicate that avibactam restores the activity of ceftazidime in ceftazidime non-susceptible gram-negative organisms expressing some Class A, some Class C and some Class D (but not Class B) beta-lactamases. The clinical data supporting the indications of cIAI and cUTI are obtained from small Phase 2 studies that were not designed for statistical inferential testing. Despite the small size and limitations of these trials, efficacy of ceftazidime-avibactam in the subpopulation with ceftazidime non-susceptible organisms was numerically similar to the efficacy in the overall population.

For the indication of treatment of aerobic gram-negative infections (including hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia and bacteremia), no clinical data were submitted. I agree with the clinical reviewer and with the Advisory Committee and recommend non-approval for this indication.

- Risk Benefit Assessment

Evaluation of the risk benefit of ceftazidime-avibactam is in the context of unmet need and antibacterial drug development for resistant organisms. The efficacy of ceftazidime-avibactam is supported by in vitro and animal model data that indicate that avibactam restores the activity of ceftazidime against ceftazidime resistant gram-negative bacteria and by limited clinical data in Phase 2 studies in patients with cIAI and cUTI. The Phase 2 studies were not designed for inferential testing. However, efficacy of ceftazidime-avibactam in the subpopulation with ceftazidime-nonsusceptible infections was similar to the efficacy in the overall population.

The overall safety profile of ceftazidime-avibactam is similar to that of ceftazidime and other cephalosporins. The major concern is decreased efficacy and increased mortality noted in the Phase 3 cIAI trial among the ceftazidime-avibactam subgroup with moderate renal impairment compared to the ceftazidime-avibactam subgroup with normal renal function or mild impairment. The reasons for this imbalance are not clear. The possibility that this may be related to inadequate exposure led to revision of dosage adjustment recommendations in labeling.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Routine postmarketing pharmacovigilance is sufficient.

- Recommendation for other Postmarketing Requirements and Commitments

The following PMRs are required under PREA

1. Conduct a randomized, multicenter, active-controlled trial to evaluate the safety and tolerability of AVYCAZ (ceftazidime-avibactam) in children from 3 months to less than 18 years of age with (cUTI). The dose for this study will be determined upon review of the data to be submitted by June 2015 from a single-dose, multicenter, non-comparative study assessing the pharmacokinetics (PK) of ceftazidime-avibactam in pediatric patients from 3 months to less than 18 years of age.

Final Protocol Submission:	06/30/2015
Study/Trial Completion:	09/30/2017
Final Report Submission:	09/30/2018

2. Conduct a randomized, multicenter, active-controlled trial to evaluate the safety and tolerability profile of AVYCAZ ceftazidime-avibactam in children from3 months to less than 18 years of age with (cIAI). The dose for this study will be determined upon review of the data to be submitted by June 2015 from a single-dose, multicenter, non-comparative study assessing the (PK) of AVYCAZ (ceftazidime-avibactam) in pediatric patients from birth to less than 18 years of age.

Final Protocol Submission:	06/30/2015
Study/Trial Completion:	09/30/2017

Final Report Submission: 09/30/2018

3. Conduct a trial to evaluate the pharmacokinetics, safety and efficacy of AVYCAZ (ceftazidime-avibactam) in children from birth to less than 3 months of age with late-onset sepsis.

Final Protocol Submission:	10/31/2017
Study/Trial Completion:	06/30/2019
Final Report Submission:	06/30/2020

The following PMRs are required under 505(o):

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

Final protocol submission:	09/30/2015
First interim report:	05/31/2016
Second interim report:	05/31/2017
Third interim report:	05/31/2018
Fourth interim report:	05/31/2019
Fifth interim report:	05/31/2020
Study Completion	02/25/2020
Study completion:	12/31/2020

2. Conduct a trial or submit data from the Phase 3 trial in cIAI to evaluate the PK, safety, and clinical outcomes in adult patients with baseline renal impairment (creatinine clearance of 50 mL/min or less) receiving AVYCAZ (ceftazidime-avibactam) dosing regimens adjusted for renal function.

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/s/

HALA H SHAMSUDDIN
02/19/2015