

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206494Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Edward Cox, MD MPH
Subject	Office Director Decisional Memo
NDA/BLA #	NDA 206494
Applicant Name	Forest Research Institute, Inc.
Date of Submission	June 25, 2014
PDUFA Goal Date	February 25, 2015
Proprietary Name	Avycaz
Established (USAN) Name	ceftazidime-avibactam
Dosage Forms / Strength	for injection (for intravenous use) / 2 grams ceftazidime and 0.5 grams avibactam in single-use vials
Indication	<ol style="list-style-type: none"> 1. Complicated urinary tract infection (cUTI), including pyelonephritis for patients who have limited or no alternative treatment options 2. Complicated intra-abdominal infections (cIAI), used in combination with metronidazole for patients who have limited or no alternative treatment options
Action:	Approval

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Benjamin Lorenz
Product Quality	Zhengfang Ge, Robert Mello
Statistical Review	Margaret Gamalo
Pharmacology Toxicology Reviews	Armand Balboni, Wendelyn Schmidt
Clinical Microbiology	Avery Goodwin
Clinical Pharmacology Review	Seong Jang
OSI	Janice Pohlman
Division of Medication Error Prevention and Analysis	Sevan Kolejian, Justine Harris
Risk Management	Joyce Weaver
Thorough QT Study	Interdisciplinary Review Team
CDTL Review	Hala Shamsuddin
Division Director's Review	Sumati Nambiar

OND=Office of New Drugs

OSI=Office of Scientific Investigations

CDTL=Cross-Discipline Team Leader

Avycaz (ceftazidime-avibactam) is a combination of a previously approved antibacterial drug, ceftazidime, with a new molecular entity beta-lactamase inhibitor, avibactam. The antibacterial drug component, ceftazidime, was initially approved in 1985. Ceftazidime is approved for the treatment of several different bacterial infections including complicated urinary tract infections (cUTI) and intra-abdominal infections (cIAI). Avibactam is a non-beta-lactam, beta-lactamase inhibitor. Its role is to protect ceftazidime from being degraded by certain types of beta-lactamases. Avibactam is not currently marketed in any country, either in combination or alone. The indications being sought in this application include cIAI and cUTI; in addition the applicant has also included a proposed indication for treatment of aerobic gram-negative infections with limited treatment options. The applicant has also further clarified that the data in the application are intended to support the cIAI and cUTI indications when limited or no alternative treatments are available.

NDA 206494 is a 505(b)(2) application that relies in part on the Agency's previous finding of safety and efficacy for ceftazidime (including the finding for the cUTI and cIAI indications), along with the data in the application that provide clinical data, data from animal models of infection, and in vitro data that support the role of the avibactam component and provide data on the combination product of ceftazidime-avibactam. The combination rule at 21CFR300.50 is addressed by the data from in vitro studies and the animal models of infection that demonstrate the role of avibactam in restoring the activity of ceftazidime in the setting of certain beta-lactams. The approach to this 505(b)(2) application was discussed at a Center Director briefing prior to submission of the NDA. The indications being sought are intended to address an unmet medical need, patients with cIAI and cUTI with limited or no alternative treatment options.

Avycaz received Qualified Infectious Disease Product designation for indications including cUTI and cIAI, and hence the application received a priority review.

The review team has reviewed the issues in detail in their respective disciplines with regard to the safety and efficacy of ceftazidime-avibactam for the proposed indications. For a detailed discussion of NDA 206494, the reader is referred to the individual discipline specific reviews. In addition, the Cross-Discipline Team Leader's review and the Division Director's review summarize key issues in the NDA submission. This memorandum will focus on select issues from the review.

The NDA is recommended for approval from the CMC perspective for the combination product of ceftazidime-avibactam (2/23/2015 addendum). Avycaz is a white to yellow powder of 500 mg of avibactam (b)(4) mg of avibactam sodium) and 2000 mg of ceftazidime (2635 (b)(4) mg ceftazidime pentahydrate/sodium carbonate) in a glass vial. The Product Quality Microbiology Review finds that adequate controls are in place for the (b)(4) process and identifies no product quality microbiology deficiencies and recommends approval. The manufacturing facilities inspection finds the facilities involved in the manufacturing of ceftazidime-avibactam to be acceptable.

The recommendation from the Pharmacology/Toxicology Reviewers is for approval. In toxicology studies of avibactam in rats and dogs findings included injection site reactions. In a

4-week combination study of ceftazidime-avibactam in dogs, injection site damage was noted and there was some evidence of liver toxicity. Avycaz is classified as pregnancy category B.

The Clinical Microbiology Reviewer recommends that the data in NDA 206494 support approval. Avycaz is comprised of ceftazidime, a cephalosporin antibacterial drug that acts through binding to bacterial penicillin-binding proteins, and avibactam, a non-beta-lactamase, beta-lactamase inhibitor that inactivates some beta-lactamases thereby preventing the degradation of ceftazidime. The contribution of avibactam to the efficacy of the combination product of ceftazidime-avibactam was shown both in in vitro studies and a variety of animal models of infection where it was demonstrated that avibactam restored the activity of ceftazidime against certain beta-lactamase producing gram-negative bacteria. These data demonstrate the contribution of avibactam to this combination product in accordance with 21CFR300.50. In other previously approved beta-lactam / beta-lactamase inhibitor combinations, these same types of data were the key types of information that demonstrated the contribution of the beta-lactamase inhibitor. The product labeling describes for which types of beta-lactamases, ceftazidime-avibactam has shown activity in in vitro studies and animal models of infection. The labeling also notes some types of beta-lactamases for which ceftazidime-avibactam is not active. The data support that ceftazidime-avibactam will retain activity against certain types of beta-lactamase producing gram-negative bacteria for which there are currently limited or no alternative treatment options. In vitro susceptibility testing will be important in guiding the selection of an appropriate antibacterial drug to treat a patient's infection. Susceptibility test interpretive criteria for ceftazidime-avibactam have been established.

The Clinical Pharmacology Reviewers find there is sufficient clinical pharmacology information to support approval of NDA 206494. Both ceftazidime and avibactam are primarily excreted by the kidney. Hence, dose adjustment is needed in patients with creatinine clearance less than 50 mL/min. The correct dose adjustment for patients with reduced creatinine clearance was carefully evaluated. Considering the lower clinical cure rates observed in patients with moderate renal impairment in the phase 3 cIAI trial with the originally proposed dosage adjustment and the lower ceftazidime-avibactam exposures in patients with moderate or severe renal impairment, the dosage adjustment in the setting of reduced creatinine clearance was revised. The product labeling includes the recommended dosage adjustment for patients with renal impairment. Additional data from the phase 3 trial in cIAI, including pharmacokinetic data, will be provided as a postmarketing requirement which will further inform dosage adjustment in patients with renal impairment.

NDA 206494 is a 505(b)(2) application that relies in part upon the Agency's previous finding of safety and efficacy for ceftazidime, including the indications for cUTI and cIAI. The data from in vitro studies and animal models of infection demonstrate the role of avibactam in this combination product in restoring the activity of ceftazidime in the presence of certain beta-lactamases. The application also includes data from phase 2 studies in patients with complicated intra-abdominal infection and complicated urinary tract infection. The phase 2 trials did not include pre-specified hypothesis for inferential testing; descriptive statistics are provided describing the results of the trials.

The phase 2 trial in cUTI randomized patients to either ceftazidime-avibactam 625 mg IV q8h or imipenem-cilastatin 500 mg IV q6h with a treatment duration of 7 to 14 days. The trial allowed for a switch to oral levofloxacin after 4 days of therapy. A total of 135 patients were randomized. The microbiological modified intent-to-treat (mMITT) population was considered the primary analysis population. In the mMITT population, the combined clinical and microbiological response rates at the test of cure visit were 29/46 (63.0%) in the ceftazidime-avibactam arm and 25/49 (51.0%) in the imipenem-cilastatin arm with a difference and 95% confidence interval around the difference of 12.0% (-9.1%, 31.7%). In the mMITT population, the eradication rates at the test of cure visit were 31/46 (67.4%) in the ceftazidime-avibactam arm and 31/49 (63.3%) in the imipenem-cilastatin arm with a difference and 95% confidence interval around the difference of 4.1% (-16.1%, 23.8%). No formal hypotheses were pre-specified for this trial. A post-hoc comparison with the expected natural history of disease supports that ceftazidime-avibactam is active in treating complicated urinary tract infections. The dose studied in the trial is lower than the dose in product labeling. The efficacy shown at the lower dose studied supports activity at a higher dose; in addition, there is adequate safety data at the higher dose to support the use of the higher dose for this antibacterial drug combination product intended for use for patients with cUTI with limited or no alternative treatment options.

The phase 2 trial in cIAI randomized patients to ceftazidime-avibactam 2.5 grams IV q8 plus metronidazole 500 mg IV q8 hours or meropenem 1 gram IV q8 hours for a duration of 5 to 14 days. A total of 204 patients were randomized. The microbiological modified intent-to-treat (mMITT) population was considered the primary analysis population. In the mMITT population the clinical response rates at the test of cure visit were 70/85 (82.4%) in the ceftazidime-avibactam arm and 79/89 (88.8%) in the meropenem arm with a difference and 95% confidence interval around the difference of -6.4% (-18.0%, 5.2%). No formal hypotheses were pre-specified for this trial. A post-hoc comparison with the expected natural history of disease supports that ceftazidime-avibactam is active in treating cIAI.

The applicant also provided descriptive results from a study enrolling patients with ceftazidime-resistant organisms. During the review cycle the applicant also submitted topline results from a recently completed phase 3 trial in cIAI. The trial was a randomized, multi-center, double-blind, non-inferiority trial comparing ceftazidime-avibactam 2.5 g IV q8 hours plus metronidazole 500 mg IV q8h to meropenem 1g IV q8h. The clinical cure rates at the test of cure visit were 81.6% in the ceftazidime-avibactam arm and 85.1% in the meropenem arm with a treatment difference of -3.5%, 95% CI (-8.6%, to 1.6%). The topline results from this trial support that ceftazidime is effective for treatment of cIAI as the results are within a non-inferiority margin of -10%. (b) (4)

Of note within a subgroup of patients with reduced renal function (CrCl 30 to 50 mL/min), a numerically lower cure rate was observed in the ceftazidime-avibactam arm that appears more marked than what was noted for the comparator arm. Because this represents a potential safety issue, a description of these events is provided in the Warnings and Precautions section of the product labeling.

NDA 206494 also included a third indication for the treatment of patients with gram-negative infections with limited treatment options. Other than the data described above that supports

the efficacy of ceftazidime-avibactam for treatment of cUTI and cIAI, there are no specific clinical trial data for the wide range of infections that such a claim would represent. Hence the focus of the efficacy review is on the indications for which some clinical trial data have been provided. This indication was also discussed at the December 5th, 2014 Anti-Infective Drugs Advisory Committee meeting. (Please also see the section of this memo describing the Advisory Committee votes on this proposed indication.)

The safety of ceftazidime-avibactam is supported in part by the Agency's previous finding of safety for ceftazidime. The application includes safety data for avibactam and the combination of ceftazidime-avibactam from the clinical studies reported in the NDA. The Warnings and Precautions section describes the decreased clinical response observed in patients with baseline creatinine clearance of 30 to 50 mL/min. Class labeling for beta-lactam drugs and hypersensitivity reactions and class labeling for antibacterial drugs on *Clostridium difficile*-associated diarrhea are also included in Warnings and Precautions. A review of literature and the FDA Adverse Events Reporting System (FAERS) identified nonconvulsive status epilepticus (NCSE) reports in patients receiving ceftazidime. The Avycaz product labeling includes NCSE among the Warnings and Precautions. A thorough QT (TQT) study was done and found no significant effects on the QT interval when supratherapeutic doses of ceftazidime-avibactam were administered. The labeling also lists adverse drug reactions occurring in 5% or more of the patients in phase 2 trials which includes vomiting, nausea, constipation, abdominal pain, upper abdominal pain, increased blood alkaline phosphatase, increased alanine aminotransferase, dizziness, and anxiety.

The Office of Scientific Investigations summarizes inspections of four clinical trial sites and Actavis and (b) (4). OSI also reviewed the issue with the IVRS (interactive voice response system) that led to problems with assignment of study drug and the drug reconciliation report. While some deficiencies were identified at some of the sites involved with the application, overall, OSI finds that the data submitted in the application appear to be acceptable for use in support of the application.

NDA 206494 was presented before the Anti-Infective Drugs Advisory Committee (AIDAC) on December 5th 2014. The following questions were asked of the Committee.

Question to the Committee:

1. VOTE: 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?

Vote: Yes: 11 No: 1 Abstain: 0

- a. If yes, please provide any recommendations concerning labeling.
- b. If no, what additional studies/analyses are needed?

2. VOTE: Has the applicant demonstrated substantial evidence of safety and efficacy of ceftazidime-avibactam for the proposed indication of complicated urinary tract infections, including pyelonephritis, when limited or no alternative treatments are available?

Vote: Yes: 9 No: 3 Abstain: 0

- a. If yes, please provide any recommendations concerning labeling.
- b. If no, what additional studies/analyses are needed?

3. VOTE: 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 or no alternative treatments are available?

Vote: Yes: 0 No: 12 Abstain: 0

- a. If yes, please provide any recommendations concerning labeling.
- b. If no, what additional studies/analyses are needed?

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

Vote: Yes: 1 No: 11 Abstain: 0

- a. If yes, please provide any recommendations concerning labeling.
- b. If no, what additional studies/analyses are needed?

Additional details are available in the minutes for the AIDAC meeting¹ and the transcript.²

The submission of pediatric studies has been deferred, because this product is ready for approval for use in adults and pediatric studies have not been completed. The approval letter contains a listing of the required pediatric studies and milestone dates for each of the studies.

In summary, I agree with the review team, CDTL, and the Division Director, that the overall benefits and risks support the approval of NDA 206494 for Avycaz (ceftazidime-avibactam) for the treatment of patients with cUTI, including pyelonephritis for patients who have limited or no alternative treatment options and for treatment of cIAI, used in combination with metronidazole for patients who have limited or no alternative treatment options. This approval action is also consistent with the advice of the AIDAC. The data support a positive benefit-risk ratio for the aforementioned limited indications. Based on the limited clinical safety and efficacy data for Avycaz that are currently available, Avycaz should be reserved for use in patients who have limited or no alternative treatment options. (b) (4)

¹ <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM432232.pdf>

² <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM432233.pdf>

(b) (4)

The product labeling adequately describes the safety and efficacy findings based on the currently available data. Postmarketing requirements include studies that will provide additional information on resistance, data in patients with renal impairment and data from pediatric studies.

Edward Cox, MD, MPH
Director, Office of Antimicrobial Products
OND/CDER/FDA

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/s/

EDWARD M COX
02/25/2015