CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

RISK EVAULATION AND MITIGATION STRATEGY REVIEW

Date:	January 20, 2015
Reviewer(s):	Joyce Weaver, Pharm.D., Risk Management Analyst Division of Risk Management (DRISK)
Team Leader:	Naomi Redd, Pharm.D., Acting Team Leader, DRISK
Division Director:	Cynthia LaCivita, Pharm.D., Acting Director, DRISK
Subject:	Review to determine if a REMS is necessary
Drug Name(s):	Ceftazidime/avibactam
Therapeutic class & dosage form:	Antibacterial drug; intravenous injection
OND Review Division:	Division of Anti-infective Products (DAIP)
Application Type/Number:	NDA 206494
Application received:	June 25, 2014
PDUFA/Action Date:	February 25, 2015
Applicant/sponsor:	Cerexa, Inc
OSE RCM #:	2014-1285, 2014-1307

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1 INTRODUCTION

This review by the Division of Risk Management evaluates if a Risk Evaluation and Mitigation Strategy (REMS) is needed for the antibiotic, ceftazidime/avibactam, a combination cephalosporin antibiotic and beta-lactamase inhibitor. The proposed indications for ceftazidime/avibactam are treatment of complicated intra-abdominal infections, treatment of complicated urinary tract infections including pyelonephritis, and treatment of hospital-acquired and ventilator-associated bacterial pneumonia in adult patients.

Cerexa submitted the application June 25, 2014. Cerexa did not submit a REMS or risk management plan. The application was granted priority review status[1], with action to be taken on the application by February 25, 2015.

2 REGULATORY HISTORY

The following are regulatory milestones important for this application:

- Initial Investigational New Drug (IND) application submitted by Novexel January 2008
- Novexel transferred ownership to AstraZeneca April 2010
- AstraZeneca transferred ownership to Cerexa October 2011
- Ceftazidime/avibactam designated as a qualified infectious disease product with Fast Track Designation for complicated intra-abdominal infections, complicated urinary tract infections, and hospital-acquired and ventilator-associated bacterial pneumonia March 11, 2013
- Agency and sponsor agreed on the contents of a complete application under 505(b)(2) December 2013
- The NDA was submitted June 25, 2014; PDUFA date February 25, 2015

3 MATERIALS REVIEWED

We reviewed the following:

- Application submitted June 25, 2014
- Discipline presentations at the mid-cycle meeting for NDA 206494, meeting held October 7, 2014
- FDA background package for the December 5, 2014 meeting of the Anti-Infective Drugs Advisory Committee, convened to consider the application
- Cerexa background package for the December 5, 2014 advisory committee meeting

[1] Qualifies for priority review as a Qualified Infectious Disease Product under FDASIA

4 RESULTS OF REVIEW

4.1 OVERVIEW OF CLINICAL PROGRAM[2]

The data submitted in support of efficacy in the treatment of complicated intra-abdominal infections were derived from a randomized, multicenter, double-blind clinical trial enrolling 204 patients, half of whom were randomized to receive ceftazidime/avibactam (2000 mg ceftazidime/500 mg avibactam) every 8 hours plus metronidazole (500 mg) every 8 hours, and the remaining patients were randomized to receive meropenem (1000 mg every 8 hours). Most of the patients were white (60%) and younger than 65 years of age (88%). Clinical failures occurred in 18% of the microbiologically evaluable patients receiving ceftazidime/avibactam plus metronidazole compared to 11% of the microbiologically evaluable patients receiving meropenem.

In the subgroup of patients with complicated intra-abdominal infections who had creatinine clearance between 30 and 50 mL/min, a lower clinical cure rate was observed and a numerically higher mortality rate was observed in the patients receiving ceftazidime/avibactam compared to patients with creatinine clearance greater than 50 mL/min. Among patients with complicated intra-abdominal infections receiving ceftazidime/avibactam, clinical cure was 86% in patients with creatinine clearance over 80 mL/min, 83% in patients with creatinine clearance 50 to 80 mL/min, and 43% in patients with creatinine clearance 30 to 50 mL/min. Patients with creatinine clearance less than 30 mL/min were excluded from the trial. The lower cure rate was felt by the sponsor to be possibly attributable to the failure to adjust the dose upward in patients with improving renal function[3]. This has not been analyzed by the Agency.

The data submitted in support of efficacy in the treatment of complicated urinary tract infection were derived from a randomized, multicenter, investigator-blinded clinical trial enrolling 135 patients, half of whom were randomized to receive ceftazidime/avibactam 625 (500 mg ceftazidime/125 mg avibactam) every 8 hours, and the remaining patients were randomized to receive imipenem/cilastatin 500 mg every 6 hours. Most of the patients were white (60%) and younger than 65 years of age (84%). Ceftazidime/avibactam demonstrated efficacy, with clinical cure in 80% of the microbiologically evaluable patients treated with ceftazidime/avibactam, compared to 74% of the microbiologically evaluable patients treated with imipenem/cilastatin.

No clinical data were submitted in support of the hospital-acquired and ventilator-associated bacterial pneumonia indications. The Phase 3 study for this indication is ongoing. (b) (4)

[2] Efficacy summary presented here is adapted from the data submitted by the sponsor, and the FDA background document for the Dec 5, 2014 advisory committee meeting.

[3] From the FDA background document for the Dec 5, 2014 advisory committee meeting, Section 6, *Evaluation of Clinical Efficacy*

4.2 SAFETY CONCERNS[4]

The most concerning safety issues with ceftazidime, as reflected in the Fortaz labeling, are hypersensitivity reactions, *Clostridium difficile*-associated diarrhea, and seizures when used in patients with renal insufficiency. Consistent with Fortaz, these issues are presented in the *Warnings and Precautions* section of the draft labeling for ceftazidime/avibactam.

Overall, in clinical testing, the most frequently occurring adverse events in clinical testing were nausea and vomiting, headache, constipation, fever, abdominal pain, diarrhea, and hepatic transaminase elevations.

In the complicated urinary tract infection trial, more patients (18, 27%) receiving ceftazidime/avibactam discontinued treatment compared to patients (11, 16%) in the comparator group. Two of the discontinuations in the patients receiving ceftazidime/avibactam were attributed to treatment-emergent adverse events, accidental overdose and atrial fibrillation. None of the discontinuations in the comparator group were attributed to treatment-emergent adverse events.

In the complicated intra-abdominal infection trial, more deaths occurred in the ceftazidime/avibactam arm (6) compared to the meropenem arm (2). The deaths were attributed to underlying co-morbidities, treatment failure, or emergent infection. In the subgroup of patients with creatinine clearance between 30 and 50 mL/min, a lower clinical cure rate and a numerically higher mortality rate were observed in the patients receiving ceftazidime/avibactam compared to patients with creatinine clearance greater than 50 mL/min.

4.3 RESULTS OF ADVISORY COMMITTEE MEETING

The advisory committee voted on whether the applicant had demonstrated substantial evidence of safety and efficacy of ceftazidime/avibactam for the treatment of the following, when limited or no alternative treatments are available:

1. complicated intra-abdominal infections (vote 11 yes, 1 no)
2. complicated urinary tract infections (9 yes, 3 no)
3. aerobic gram-negative infections (including hospital-acquired bacterial pneumonia/ventilator associated bacterial pneumonia and bacteremia (0 yes, 12 no)

When the advisory committee voted on the third question changing "limited or no alternative treatments are available" to "no adequate treatment options are available" the vote was 1 yes, 11 no. Committee members cited the lack of human data as an important factor in the "no" votes for question 3, and revised question 3.

During the discussion of the application, one committee member expressed concern that, if used improperly, resistance might develop quickly to ceftazidime/avibactam. This committee member suggested that perhaps a REMS enforcing limited use should be put

[4] Safety summary presented here is adapted from the data submitted by the sponsor, and the FDA background document for the Dec 5, 2014 advisory committee meeting.

into place to prevent resistance from developing to ceftazidime/avibactam. This committee member also proposed a boxed warning to exclude use in patients with renal function impairment. Committee members expressed concern that underdosing of patients with improving renal function might lead to the development of resistance.

4.4 RISK MANAGEMENT PROPOSED BY THE SPONSOR

The sponsor did not propose risk management measures beyond labeling.

5 DISCUSSION OF A REMS FOR CEFTAZIDIME/AVIBACTAM

The most concerning safety signal that has emerged in the clinical testing of ceftazidime/avibactam is that there was decreased efficacy observed in patients with creatinine clearance 30 to 50 mL/min receiving ceftazidime/avibactam for complicated intra-abdominal infection. The applicant posited that the decreased efficacy in patients with creatinine clearance 30 to 50 mL/min is likely the result of failure to increase the dose of ceftazidime/avibactam when the patients' renal function improved. In addition to decreased efficacy, failure to respond to improving renal function with an increase in dose could lead to increased resistance to ceftazidime/avibactam.

The data regarding reduced efficacy by patients with reduced renal function has not been reviewed by the Agency, and likely will not be reviewed prior to the decision on this application. Therefore, the reason for decreased efficacy in patients with creatinine clearance 30 to 50 mL/min likely will not be known when a decision is made on the current application. Several advisory committee members advised that ceftazidime/avibactam should be labeled to exclude use in patients with creatinine clearance less than 50 mL/min until the data are analyzed and the reason for the disparity is understood. Until the risks are better characterized, the best advice about the use of ceftazidime/avibactam in patients with reduced renal function cannot be provided. Further analysis may assist in determining the effect that renal function and/or changing renal function has on efficacy.

The FDA-edited[5] labeling contains a warning in section 5.1 about the increased risk of treatment failure in patients with creatinine clearance 30 to 50 mL/min. The following is the entry in the *Highlights* section of the labeling: "Decreased efficacy in patients with baseline CrCL of 30 to 50 mL/ min. Monitor CrCL at least daily in patients with changing renal function and adjust the dose of [ceftazidime-avibactam] accordingly (5.1)."

REMS have not been required for cephalosporin antibiotics. The following risks placed in the *Warnings and Precautions* section of the labeling for cephalosporins, including Fortaz, are class risks that are communicated with labeling alone for other cephalosporins: hypersensitivity reactions, *Clostridium difficile*- associated diarrhea, serious neurologic adverse reactions, including encephalopathy, myoclonus, and seizures. There are no data showing that these events are more concerning for ceftazidime/avibactam compared with other cephalosporins. These issues can be

[5] Final labeling is still being negotiated with the sponsor.

communicated in labeling for ceftazidime/avibactam, as is the case for other cephalosporins.

Development of resistance is a problem common to all antibiotics. To date, REMS have not been used to address the development of antibiotic resistance, and it is not apparent that it would be useful to use REMS to address this issue.

6 CONCLUSION/RECOMMENDATION

DRISK and DAIP believe that the risks of ceftazidime/avibactam that have emerged to date are similar to Fortaz and can be communicated through labeling alone. 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.

There might be a need for a safety initiative regarding the overall issue of the development of resistance to antibiotics, an issue for all antibiotics. However, we do not believe that a product-specific REMS would be helpful in dealing with the larger safety issue.

We do not recommend a REMS at this time. Should any additional important risk information emerge for ceftazidime/avibactam, we ask that you include us in the discussion of appropriate risk management.

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/s/

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01/21/2015

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