CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206829Orig1s000

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:	September 19, 2014
Reviewer(s):	Joyce Weaver, Pharm.D., Risk Management Analyst Division of Risk Management (DRISK)
Team Leader:	Doris Auth, Pharm.D., Team Leader, DRISK
Division Director:	Cynthia LaCivita, Pharm.D., Acting Director, DRISK
Subject:	Review to determine if a REMS is necessary
Drug Name(s):	Zerbaxa (ceftolozane/tazobactam)
Therapeutic class & dosage form:	Antibacterial drug; intravenous injection
OND Review Division:	Division of Anti-infective Products
Application Type/Number:	NDA 206829
Application received:	April 21, 2014
PDUFA/Action Date:	December 24, 2014
Applicant/sponsor:	Cubist Pharmaceuticals
OSE RCM #:	2014-948

*** This document contains proprietary and confidential information that should not be released to the public. ***

1 INTRODUCTION

This review by the Division of Risk Management evaluates if a Risk Evaluation and Mitigation Strategy (REMS) is needed for the new molecular entity antibiotic, Zerbaxa (ceftolozane/tazobactam), a combination cephalosporin antibiotic and beta-lactamase inhibitor. The proposed indications for ceftolozane/tazobactam are treatment of complicated intra-abdominal infections, and treatment of complicated urinary tract infections including pyelonephritis, in adult patients.

Cubist Pharmaceuticals submitted the application April 21, 2014. Cubist Pharmaceuticals did not submit a Risk Evaluation and Mitigation Strategy (REMS) or risk management plan. The application was granted priority review status[1], with action to be taken on the application by December 21, 2014.

2 REGULATORY HISTORY

The following are regulatory milestones important for this application:

- End of Phase 2 meeting cancelled by the sponsor after receiving FDA comments to questions; March 11, 2011Pre-NDA CMC meeting January 14, 2014
- Pre-NDA meeting February 10, 2014
- Rolling review NDA, first piece received February 14, 2014 and final piece April 21, 2014, with both Fast Track and Qualified Infectious Disease Product designations.
- The NDA is a PDUFA V program submission with a due date of December 21, 2014

3 MATERIALS REVIEWED

We reviewed the following:

- Application submitted April 21, 2014.
- Discipline presentations at the mid-cycle meeting for NDA 206829, meeting held July 25, 2014.
- Draft FDA-edited labeling
- Draft clinical safety review by Maria Allende, M.D., Medical Officer for the application.

4 RESULTS OF REVIEW

4.1 OVERVIEW OF CLINICAL PROGRAM[2]

The data submitted in support of efficacy in the treatment of complicated intra-

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

[2] Efficacy summary presented here is adapted from the data submitted by the sponsor, and the draft FDA-edited labeling.

abdominal infections were derived from a randomized, multicenter, double-blind clinical trial enrolling 979 patients, half of whom were randomized to receive ceftolozane/tazobactam plus metronidazole, and the remaining patients were randomized to receive meropenem. Most of the patients were from Eastern Europe, with only about 6% of patients being treated in the United States. Ceftolozane/tazobactam plus metronidazole was non-inferior to meropenem, although a trend to better efficacy with meropenem was observed.

The data submitted in support of efficacy in the treatment of complicated urinary tract infection were derived from a randomized, multicenter, double-blind clinical trial enrolling 1,068 patients, half of whom were randomized to receive ceftolozane/tazobactam, and the remaining patients were randomized to receive levofloxacin. Most of the patients were from Eastern Europe, with fewer than 2% of patients being treated in the United States. Ceftolozane/tazobactam demonstrated efficacy, with clinical cure in 83% of the microbiologically evaluable patients treated with ceftolozane/tazobactam, compared to 75% of the microbiologically evaluable patients treated with levofloxacin.

4.2 SAFETY CONCERNS[3]

The most concerning issues with ceftolozane/tazobactam are hypersensitivity reactions, *Clostridium difficile*-associated diarrhea, and the development of drug resistant bacteria. Consistent with other cephalosporins, these issues are presented in the *Warnings and Precautions* section of the draft Zerbaxa labeling.

Overall, in testing for both proposed indications, the most frequently occurring adverse events in clinical testing were nausea, headache, and diarrhea. More patients receiving ceftolozane/tazobactam discontinued drug because of renal impairment compared to the comparator drugs. There were no cases of serious hypersensitivity reactions in ceftolozane/tazobactam-treated patients.

In the complicated urinary tract infection trial, three cases of *Clostridium difficile* infections occurred with ceftolozane/tazobactam, compared with no cases in patients treated with levofloxacin. Investigators were not required to test for *Clostridium difficile* in the event of diarrhea, so it is possible more cases of diarrhea represented *Clostridium difficile* infections in both treatment groups.

In the complicated intra-abdominal infection trial, more thromboembolic events occurred in the ceftolozane/tazobactam arm (1.4%) compared to the meropenem arm (0.6%). Thromboembolic events are known complications of intra-abdominal infections and surgery, and the higher incidence of thromboembolic events may reflect less efficacy in treating the complicated intra-abdominal infection with ceftolozane/tazobactam compared to meropenem.

In the complicated intra-abdominal infection trial, 2.5% of patients treated with ceftolozane/tazobactam died compared to 1.5% of patients receiving meropenem. The deaths were the result of treatment failures rather than adverse events. The difference in

[3] Safety summary presented here is adapted from the data submitted by the sponsor, the draft safety review by Dr. Allende, and the draft FDA-edited labeling.

mortality between the groups was not statistically significant, and, even in the ceftolozane/tazobactam group, was not beyond what might be expected in treatment of complicated intra-abdominal infections.

4.3 RISK MANAGEMENT PROPOSED BY THE SPONSOR

The sponsor did not propose risk management measures beyond labeling.

5 DISCUSSION OF A REMS FOR CEFTOLOZANE/TAZOBACTAM

REMS have not been required for cephalosporin antibiotics. No serious safety signals have emerged in the clinical testing of ceftolozane/tazobactam that would require a REMS to ensure the benefits out weight the risks. The risks placed in the *Warnings and Precautions* section of the labeling are class risks that are communicated with labeling alone for other cephalosporins. There are no data showing that these events are more concerning for ceftolozane/tazobactam compared with other cephalosporins.

6 CONCLUSION/RECOMMENDATION

DRISK believes that the risks of ceftolozane/tazobactam that have emerged to date can be communicated through labeling. We do not recommend a REMS at this time. Should any additional important risk information emerge during the review of the application, we ask that you include us in the discussion of appropriate risk management.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOYCE P WEAVER
09/19/2014

CYNTHIA L LACIVITA
09/19/2014
Concur