CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206829Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Edward Cox, MD MPH
Subject	Office Director Decisional Memo
NDA/BLA #	NDA 206829
Applicant Name	Cubist Pharmaceuticals
Date of Submission (receipt)	April 21, 2014
PDUFA Goal Date	December 21, 2014
Proprietary Name **Established (USAN) Name**	Zerbaxa ceftolozane / tazobactam
Dosage Forms / Strength	fixed combination for intravenous infusion 1g ceftolozane / 0.5 g tazobactam
Indications	Complicated Intra-abdominal Infections ZERBAXA used in combination with metronidazole is indicated for the treatment of complicated intra-abdominal infections (cIAI) caused by the following Gram-negative and Gram-positive microorganisms: *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Bacteroides fragilis*, *Streptococcus anginosus*, *Streptococcus constellatus*, and *Streptococcus salivarius*. Complicated Urinary Tract Infections, including Pyelonephritis ZERBAXA is indicated for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis, caused by the following Gram-negative microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*.
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Maria Allende, Hala Shamsuddin, Thomas Smith
Product Quality	Shrikant Pagay, Dorota Matecka, Erika Pfeiler
Biopharmaceutics Review	Angelica Dorantes, Richard Lostritto
Statistical Review	Daniel Rubin, Christopher Kadoorie, Thamban Vallappil, Dionne Price
Pharmacology Toxicology Reviews	James Wild, Wendelyn Schmidt, Abigail Jacobs
Clinical Microbiology	Kerian Grande-Roche, Kerry Snow
Clinical Pharmacology Review	Ryan Owen, Kimberly Bergman, Jeffry Florian

OSI	Sharon Gershon, Susan Thompson, Kassa Ayalew
QT/IRT	Huifang Chen, Qianyu Dang, Dhananjay D Marathe, Jiang Liu, Michael Y Li, Norman Stockbridge
CDTL Review	Thomas Smith
Division Director's Review	Sumati Nambiar

OND=Office of New Drugs
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader

Zerbaxa is a combination of ceftolozane, a cephalosporin antibacterial drug, and tazobactam, a beta-lactamase inhibitor. Zerbaxa has been developed as a treatment for complicated intra-abdominal infections and complicated urinary tract infections caused by certain bacteria. The addition of tazobactam to ceftolozane is designed to inhibit some beta lactamases that would otherwise degrade ceftolozane.

Ceftolozane/tazobactam has been granted Qualified Infectious Disease Product (QIDP) designation. The application received a priority review based on its QIDP designation.

The development of antimicrobial resistance to existing antibacterial drugs creates a need for new antibacterial drug options, including antibacterial drugs that can treat patients with infections resistant to current therapies.

The review team has reviewed the issues in detail in their respective disciplines with regard to the safety and efficacy of ceftolozane/tazobactam. For a detailed discussion of NDA 206829, 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 CMC reviewer finds that the applicant has generally provided satisfactory information to assure the identity, strength, purity, and quality of the drug substance and drug product. The manufacturing facilities inspection summary of December 17, 2014 recommends approval. The biopharmaceutics review finds that there are no outstanding issues with NDA 206829 and recommends approval. The Product Quality Microbiology Reviewer identifies no product quality microbiology deficiencies and recommends approval.

The recommendation from the pharmacology/toxicology reviewers is for approval. The review of the toxicology studies finds the primary pathology associated with ceftolozane/tazobactam administration is increase in liver weights, and liver histopathology consistent with accumulation of liver glycogen and increase in smooth endoplasmic reticulum. The changes were generally of low magnitude and reversible so they were not considered adverse. At higher doses, alterations in blood counts were noted, but were generally mild, reversible, and did not extend to bone marrow. The pharmacology / toxicology team has discussed the pregnancy category for ceftolozane/tazobactam and ultimately has recommended Pregnancy Category B.

Zerbaxa is a combination of ceftolozane and tazobactam. Ceftolozane is a cephalosporin antibacterial drug that acts by inhibition of cell wall biosynthesis by binding to penicillin-binding proteins (PBPs). Tazobactam is an inhibitor of some beta-lactamases. The tazobactam component of Zerbaxa has been previously approved as part of the combination product Zosyn (piperacillin/tazobactam). The Clinical Microbiology Reviewer has worked with the review team to develop product labeling describing the mechanism of action, mechanisms of resistance, and susceptibility test interpretive criteria for ceftolozane/tazobactam.

During the review there was considerable discussion of how to describe the activity of ceftolozane/tazobactam in product labeling. The challenges faced in accurately describing this activity include, the imprecision of the definition of extended spectrum beta-lactamases, the limits of the available data in studying the many different beta-lactamases, that new ones will likely continue to be discovered in the future, that some bacteria may carry multiple beta-lactamases, and that ceftolozane/tazobactam is active against only certain beta-lactamases. The complex and heterogeneous biology of the many different beta-lactamases also has made providing a succinct description of the activity of ceftolozane/tazobactam challenging. The labeling provides information describing the mechanism of action and mechanisms of resistance to ceftolozane/tazobactam. Most important is that whenever possible, culture and susceptibility information, local epidemiology, and appropriate antimicrobial drug use practices should be considered by healthcare providers in selecting whether or not to use ceftolozane/tazobactam or another antibacterial drug.

The Clinical Pharmacology reviewers find the clinical pharmacology information presented in NDA 206829 acceptable. Ceftolozane is not metabolized; it is excreted unchanged in the urine. Less than 20% of tazobactam is metabolized to the inactive metabolite tazobactam M-1. Both tazobactam and tazobactam M-1 are excreted in the urine. Dose adjustments for moderate and severe renal impairment and for patients with end-stage renal disease on hemodialysis are described in the product labeling. Ceftolozane/tazobactam does not undergo hepatic metabolism and hence, no dose adjustment is recommend for patients based on degree of hepatic impairment. No dose adjustment is recommended based on age, gender, or race. Zerbaxa is not a substrate for CYPs. A clinical drug interaction study found that interactions involving CYP1A2 and CYP3A4 are not anticipated. Tazobactam is a substrate for OAT1 and OAT3 and therefore co-administration of Zerbaxa with OAT1 and/or OAT3 inhibitors may increase plasma tazobactam levels.

Zerbaxa's efficacy was evaluated in a phase 3 clinical trial in complicated intra-abdominal infections (cIAI) and a phase 3 clinical trial in complicated urinary tract infection (cUTI). Both trials were randomized, double-blind, active controlled trials. The cIAI trial compared Zerbaxa plus metronidazole to meropenem. The results for the primary efficacy endpoint of clinical response in the primary analysis population, the microbiological intent-to-treat (MITT) population, demonstrated the efficacy of Zerbaxa by showing non-inferiority to meropenem (Table 1). Table 1 also shows the results for the microbiologically evaluable population (ME) which includes patients in the MITT population whose clinical course and management adhered to the protocol.

Table 1. Clinical Response Rates in a Phase 3 Trial of Complicated Intra-Abdominal Infections

Analysis Population	**ZERBAXA plus metronidazole[a] n/N (%)**	**Meropenem[b] n/N (%)**	**Treatment Difference (95% CI)[c]**
MITT	323/389 (83)	364/417 (87.3)	-4.3 (-9.2, 0.7)
ME	259/275 (94.2)	304/321 (94.7)	-0.5 (-4.5, 3.2)

[a] ZERBAXA 1 g/0.5 g intravenously every 8 hours + metronidazole 500 mg intravenously every 8 hours
[b] 1 gram intravenously every 8 hours
[c] The 95% confidence interval (CI) was calculated as an unstratified Wilson Score CI.

The cUTI trial compared Zerbaxa to levofloxacin. The primary efficacy endpoint was complete resolution or marked improvement of the clinical symptoms and microbiological eradication (all uropathogens found at baseline at $\geq 10^5$ were reduced to $<10^4$ CFU/mL) at the test-of-cure (TOC) visit 7 (± 2) days after the last dose of study drug in the modified microbiological intent-to-treat (MITT) population. The results demonstrated the efficacy of Zerbaxa in the treatment of cUTI (Table 2). In order to attribute a treatment effect to (and hence derive a non-inferiority margin for) the comparator antibacterial drug (in this case levofloxacin), it is essential that the comparator drug is effective in the condition under study. As is shown in the table a subgroup of significant size had baseline pathogens that were resistant to levofloxacin and this same subgroup had reduced response rates when treated with levofloxacin. Table 2 also shows the results for the microbiologically evaluable population (ME) which includes patients in the mMITT population whose clinical course and management adhered to the protocol.

Table 11: Composite Microbiological and Clinical Response Rates in a Phase 3 Trial of Complicated Urinary Tract Infections

Analysis Population	**ZERBAXA[a] n/N (%)**	**Levofloxacin[b] n/N (%)**	**Treatment Difference (95% CI)[c]**
mMITT	306/398 (76.9)	275/402 (68.4)	8.5 (2.3, 14.6)
Levofloxacin resistant baseline pathogen(s)	60/100 (60)	44/112 (39.3)	
No levofloxacin resistant baseline pathogen(s)	246/298 (82.6)	231/290 (79.7)	
ME	284/341 (83.3)	266/353 (75.4)	8.0 (2.0, 14.0)

[a] 1 g/0.5 g (ceftolozane/tazobactam) intravenously every 8 hours
[b] 750 mg intravenously once daily
[c] The 95% confidence interval was based on the stratified Newcombe method.

The results from the phase 3 clinical trials collectively demonstrate the efficacy of Zerbaxa in the treatment of cIAI and cUTI.

The safety database for Zerbaxa includes 1015 patients treated with Zerbaxa in Phase 3 comparator-controlled clinical trials of cIAI and cUTI. In clinical trials, the most common adverse reactions reported in clinical study participants treated with Zerbaxa were nausea, headache, diarrhea, and pyrexia. The product labeling includes a statement in the Warnings and Precautions section that describes decreased efficacy in patients with baseline creatinine clearance of 30 to $\leq$ 50 mL/min. In addition, the Warnings and Precautions section includes information on hypersensitivity reactions, *Clostridium difficile*-associated diarrhea, and development of drug-resistant bacteria.

The Interdisciplinary Review Team for QT studies' review of the thorough QT study notes no significant QTc prolongation effect of ceftolozane/tazobactam.

NDA 206829 was not presented before the Anti-Infective Drugs Advisory Committee. There were no particular issues with safety, efficacy, or trial design that warranted presenting the application to an Advisory Committee.

The Office of Scientific Investigations Clinical Inspection Summary notes that the data in the application may be considered reliable.

We are deferring submission of pediatric studies for ages 0-17 years until December 2020 because this product is ready for approval for use in adults and pediatric studies have not been completed. The required pediatric assessments are enumerated in the approval letter.

In summary, I agree with the review team, the CDTL, and the Division Director, that the overall benefits and risks support the approval of NDA 206829 for Zerbaxa (ceftolozane/tazobactam) for the treatment of patients with cIAI and cUTI as described in the product labeling. The benefits of Zerbaxa for the treatment of cIAI and cUTI outweigh the risk of treatment with Zerbaxa. The approval of Zerbaxa provides a therapeutic option that can be considered for patients with cIAI and cUTI. The product labeling adequately describes the safety and efficacy findings. Postmarketing requirements include studies that will provide additional information on resistance and required pediatric assessments.

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Director, Office of Antimicrobial Products
OND/CDER/FDA

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EDWARD M COX
12/19/2014