CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205435Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Edward Cox, MD MPH
Subject	Office Director Decisional Memo
NDA/BLA #	NDA 205435 and NDA 205436
Applicant Name	Cubist Pharmaceuticals, Inc.
Date of Submission (receipt)	October 21, 2013
PDUFA Goal Date	June 21, 2014
Proprietary Name / Established (USAN) Name	Sivextro tedizolid phosphate
Dosage Forms / Strength	tablet, 200mg sterile lyophilized powder for injection, 200 mg/vial
Indication	for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae, Streptococcus anginosus* Group (including *Streptococcus anginosus*, *Streptococcus intermedius* and *Streptococcus constellatus*), and *Enterococcus faecalis*
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Sheral Patel, Shrimant Mishra
Product Quality	Rajiv Agarwal, Rapti Madurawe, Robert J. Mello
Biopharmaceutics Review	Minerva Hughes, Angelica Dorantes
Statistical Review	Margaret Gamalo-Siebers, Thamban Valappil, Dionne Price
Pharmacology Toxicology Reviews	James Wild, Wendelyn Schmidt, Abigail Jacobs
Clinical Microbiology	Avery Goodwin, Kerry Snow
Clinical Pharmacology Review	Zhixia (Grace) Yan, Kim Bergman, Fang Li, Jeffry Florian
OSI	Anthony Orencia, Kassa Ayalew, Janice Pohlman, Susan Thompson, Ni Khin
DMEPA & OMEPRM	Aleksander Winiarski, Morgan Walker, Tingting Gao, Julie Neshiewat, Azeem Chaudhry, Todd Bridges, Kellie Taylor
CDTL Review	Shrimant Mishra
Deputy Division Director's Review	Katie Laessig

OND=Office of New Drugs
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OMEPRM=Office of Medication Error Prevention and Risk Management

Sivextro (tedizolid phosphate) is an oxazolidinone class antibacterial drug that has been developed for the treatment of patients with acute bacterial skin and skin structure infections. Sivextro received Qualifying Infectious Disease Product Designation (QIDP) for the treatment of patients with acute bacterial skin and skin structure infection. As a QIDP, the NDAs 205435 and 205436 for tedizolid also 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 tedizolid. For a detailed discussion of NDAs 205435 and 205436, the reader is referred to the individual discipline specific reviews. In addition, the Cross-Discipline Team Leader's review and the Deputy Division Director's Summary Review discuss key issues in the NDA submission. This memorandum will focus on select issues from the review.

The Office of New Drug Quality Assessment (ONDQA) finds that the Chemistry, Manufacturing, and Controls (CMC) information in the NDA as amended is adequate and recommends approval of Sivextro (tedizolid phosphate) lyophilized powder for injection, 200 mg, and also for Sivextro (tedizolid phosphate) tablets, 200 mg. The applicant provided stability data to support 36 month expiration dating when the product is stored at the labeled conditions of 20°C to 25°C with excursions permitted to 15°C to 30°C (USP Controlled Room Temperature) (both for the lyophilized powder for injection and the tablets). The Office of Compliance has made an "acceptable" recommendation for the manufacturing facilities involved in these applications. The Product Quality Microbiology Review recommends approval. The Product Quality Biopharmaceutics Reviewer (tablet) recommends approval. Overall from the Product Quality standpoint, the applications are recommended for approval.

The recommendation from the pharmacology/toxicology reviewer is for approval. Tedizolid phosphate is a pro-drug that is converted to tedizolid. In nonclinical studies in rats and dogs the major toxicities were hematopoietic, gastrointestinal, and injection site reactions (dog only). The hematopoietic findings included decreased red blood cells, white blood cells, platelets and bone marrow hypocellularity; these toxicities were dose and duration dependent, reversible, and occurred at exposures 4 and 10 times higher than the human exposure using the recommended dosing regimen. In a 1-month immunotoxicology study in rats, repeated oral dosing of tedizolid phosphate was shown to reduce splenic B-cells and T-cells and plasma IgG titers. Tedizolid is labeled as Pregnancy Category C.

The Clinical Microbiology Reviewer recommends that the data in NDA 205435 and 205436 support approval. Tedizolid is an oxazolidinone-class antibacterial drug. Zyvox, (linezolid) was the first member of the oxazolidinone class to be approved (approved in 1999). Tedizolid's antibacterial activity is mediated through binding to the 50S subunit of the bacterial ribosome resulting in inhibition of protein synthesis. Tedizolid was bacteriostatic against enterococci, staphylococci, and streptococci in *in vitro* time-kill studies.

The Clinical Pharmacology reviewers recommend approval for tedizolid, 200 mg intravenous or oral dosing regimen for 6 days. Tedizolid phosphate is a pro-drug that is converted to tedizolid by phosphatases. Tedizolid is the microbiologically active moiety. Following oral administration, the time to peak plasma concentration is approximately 3 hours after oral dosing. For intravenous administration peak plasma concentrations are achieved at the end of the one-hour infusion. Oral tedizolid phosphate may be administered without regard to food as systemic exposure was not different in the fed or fasted state. The oral bioavailability is 91% and therefore no dosage adjustment is needed between the intravenous and oral forms for tedizolid. Tedizolid is 70-90% bound to human plasma proteins. Tedizolid is unlikely to be a substrate for hepatic CYP450 enzymes based on studies utilizing human microsomes that showed no degradation of tedizolid. The major elimination pathway is through the liver with 82% of a radioactive dose excreted in the feces and 18% in the urine. The excreted form is predominantly a microbiologically inactive sulfate form of tedizolid. No dosage adjustment is required in elderly patients, patients with renal impairment, on hemodialysis, or with hepatic impairment.

The parameter of AUC/MIC (minimal inhibitory concentration) is the parameter in animal models of infection that was shown to best correlate with tedizolid antibacterial activity. In an animal model of infection, the degree of Staphylococcal killing was impacted by the presence of neutrophils. Exposures 16-20 times higher were required for granulocytopenic animals to achieve comparable levels of Staphylococcal killing compared to animals that were not granulocytopenic. Given the degree of the difference in exposure required for granulocytopenic and non-granulocytopenic animals to achieve comparable levels of staphylococcal killing, the lack of clinical data that can address this concern, and the potential consequences of less effective or ineffective antibacterial drug treatment in a neutropenic patient, a statement has been added to the Warnings and Precautions section of labeling citing this finding and recommending that alternative therapy be considered when treating patients with neutropenia and acute bacterial skin and skin structure infections. This finding is also further described in the Clinical Pharmacology section.

The Medical Officer and Statistical Reviewer recommend approval for Sivextro (tedizolid phosphate). The efficacy of tedizolid was evaluated in two randomized, double-blind, active-controlled, non-inferiority clinical trials in patients with acute bacterial skin and skin structure infections. Patients were randomized to either tedizolid or linezolid. In the first trial patients received oral tedizolid or linezolid. In the second trial patients received at least one day of intravenous tedizolid or linezolid prior to being transitioned to oral tedizolid or linezolid to complete therapy. The duration of therapy in these trials was 6 days for tedizolid and 10 days for linezolid. In each of the two trials tedizolid was found to be non-inferior to its comparator, linezolid, for the treatment of patients with acute bacterial skin and skin structure infections. The trial results are shown in Table 1.

Table 1 Early Clinical Response in the ITT Patient Population

	SIVEXTRO (200 mg)	Linezolid (1200 mg)	Treatment Difference (2-sided 95% CI)
No increase in lesion surface area from baseline and oral temperature of ≤37.6°C, confirmed by a second temperature measurement within 24 hours at 48-72 Hours*			
Trial 1, N	323	326	
Responder, n (%)	256 (79.3)	258 (79.1)	0.2 (-6.2, 6.3)
Trial 2, N	332	334	
Responder, n (%)	286 (86.1)	281 (84.1)	2.0 (-3.5, 7.3)
At least a 20% decrease from baseline in lesion area at 48-72 Hours **			
Trial 1, N	323	326	
Responder, n (%)	252 (78.0)	246 (75.5)	2.5 (-4.0, 9.1)
Trial 2, N	332	334	
Responder, n (%)	283 (85.2)	276 (82.6)	2.6 (-3.0, 8.2)

CI=confidence interval
* Primary endpoint for Trial 1; sensitivity analysis for Trial 2
** Primary endpoint for Trial 2; sensitivity analysis for Trial 1

The trial designs were consistent with the recommendations on trials for acute bacterial skin and skin structure infections at the time that the trials were conducted. In the first trial, clinical success at the primary endpoint was defined as absence of fever as well as cessation of spread (i.e., no increase in lesion surface area) at the 48-72 hour visit. In the second trial, a 20% or more reduction in lesion area at the 48-72 hours visit was the definition of clinical success at the primary endpoint. The results for both of these endpoints for both trials are shown above and are supportive of the finding of non-inferiority for the primary endpoint in each of the two trials.

The safety database included 1050 patients in phase 2 and phase 3 trials that received Sivextro. In phase 3 trials, serious adverse events occurred in 12/662 (1.8%) Sivextro-treated patients and 13/662 (2.0%) of linezolid-treated patients. The most common adverse events in patients treated with Sivextro were nausea 8%, headache 6%, diarrhea 4%, vomiting 3%, and dizziness 2%. The product labeling includes a statement in the Warnings and Precautions section describing reduced antibacterial activity of Sivextro in animal models of infection in the absence of granulocytes and recommends that alternative therapies be considered for treating patients with neutropenia. The Adverse Reactions section of the product labeling also provides information on myelosuppression, and peripheral and optic neuropathy. A phase 1 study in healthy adults exposed to Sivextro for 21 days showed a possible dose and duration effect on hematologic parameters. In the phase 3 trials, peripheral neuropathy was reported for 1.2% of tedizolid-treated patients and 0.6% of linezolid-treated patients and optic nerve disorders were reported for 0.3% of tedizolid-treated patients and 0.2% of linezolid-treated

patients. The statement in Adverse Reactions regarding peripheral and optic neuropathy also notes the lack of data available for patients exposed to Sivextro for longer than 6 days.

The tedizolid NDAs 205435 and 205436 were presented before the Anti-Infective Drugs Advisory Committee. On the question of whether the applicant has provided substantial evidence of the safety and effectiveness of tedizolid phosphate for the treatment of acute bacterial skin and skin structure infections caused by susceptible isolates of the designated microorganisms, the Committee voted Yes= 14, No= 0, Abstain= 0. Some of the points discussed by Committee members were that efficacy has not been shown in immunocompromised patients, cross-resistance with linezolid, and that safety data were only available for 6 days of treatment. The product labeling includes a statement in Warnings and Precautions that recommends alternative therapy be considered for granulocytopenic patients. The mechanism of cross-resistance between linezolid and tedizolid is described in the Microbiology subsection in the product labeling. The approved dosing regimen for Sivextro is a regimen of 6 days duration as described in Dosage and Administration. The product labeling also notes in the statement on Peripheral and Optic Neuropathy in the Adverse Reactions section the lack of data for exposures greater than 6 days in duration.

The trade name of Sivextro has been reviewed and found to be acceptable by the Office of Medication Error Prevention and Risk Management.

With regard to the required pediatric studies, the applicant has proposed to conduct PK studies to span the pediatric age range; ABSSSI studies in patients aged 3 months to less than 18 years (two separate studies to cover the age range), and a hospital-acquired late onset sepsis study in full term and preterm neonates and infants aged 5 days to ≤ 3 months. The applicant's proposed pediatric program was discussed at the Pediatric Review Committee and found to be acceptable. The approval letter lists the required pediatric assessments.

The Office of Scientific Investigations (OSI) inspected three domestic clinical trial sites and the applicant. OSI found that the data from these three domestic sites were generally reliable. A fourth clinical trial site inspection in Russia was not able to be performed because of recent events in Russia and Ukraine. The inspection of the applicant is preliminarily classified as NAI (No Action Indicated). The applicant submitted an amendment to their NDAs on January 14, 2014 identifying three Good Clinical Practice non-compliant sites. Data from these sites were not included in the analyses of efficacy in the product labeling. OSI evaluation of these sites is ongoing.

In summary, I agree with the review team, CDTL, and the Deputy Division Director, that the overall benefits and risks support the approval of NDAs 205435 and 205436 for Sivextro (tedizolid phosphate) 200 mg tablets and sterile powder for intravenous infusion for the treatment of acute bacterial skin and skin structure infections. The product labeling adequately

describes the safety and efficacy findings. Postmarketing requirements include studies to monitor for the development of resistance and required pediatric studies.

Addendum:
Based on a June 20, 2014 addendum, the Office of Scientific Investigations (OSI) has determined that the data from study sites 120 and 121 can be used in support of the indication. With the inclusion of these data, there is sufficient data to warrant inclusion of the bacteria *Enterococcus faecalis* and *Streptococcus agalactiae* within the listed organisms in the Indications and Usage section of the product labeling. These changes and other corresponding changes to the product labeling for these bacterial species will be made. The results from inspections of site 122 are currently ongoing. Additional changes to other sections of the product labeling that are impacted upon by the inclusion of patients from sites 120 and 121 will be addressed in a labeling supplement as will any additional revisions based upon the outcome of the evaluation of site 122.

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

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

/s/

EDWARD M COX
06/20/2014