DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205436

**NDA APPROVAL**

Cubist Pharmaceuticals, Inc.
Attention: Mary Celine Scott, PhD, MBA
Senior Director, Regulatory Affairs
6310 Nancy Ridge Dr., Suite 105
San Diego, CA 92121

Dear Dr. Scott:

Please refer to your New Drug Application (NDA) dated October 18, 2013, received October 21, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for SIVEXTRO (tedizolid phosphate) Injection.

We acknowledge receipt of your amendments dated November 7, 18, 20 and 22; December 4 (2), 12, 13 and 18, 2013; January 14, 17, 28 and 30; February 5, 10, 11, 12, 19, 21, 25 and 26; March 4, 5, 6, 20(2), 21and 25(2); April 4(2), 9, 10, 18 and 21; May 2 (2), 8 (3), 13, 19 and 22; June 12 13, 17, 19 and 20 (2), 2014.

This new drug application provides for the use of SIVEXTRO (tedizolid phosphate) Injection for the treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We note that your June 20, 2014, submission includes final printed labeling (FPL) for your package insert. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for package insert. Information on submitting SPL files using eLIST may be found in the guidance for industry SPL Standard for Content of Labeling Technical Qs and As, available at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

We acknowledge your May 13, 2014, submission containing final printed carton and container labels.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

**REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric studies until February 20, 2020, because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Please note that these deferred studies are the same as those required in the approval letter for NDA 205435 SIVEXTRO (tedizolid phosphate) Tablets.

Your deferred pediatric studies required under section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

**2159-1:** Conduct a randomized Single-Blind, Multicenter Safety and Efficacy Study of Intravenous to Oral SIVEXTRO (tedizolid phosphate) and Intravenous to Oral Comparator for the Treatment of Acute Bacterial Skin and Skin Structure Infections in Pediatric Patients Aged 12 to <18 Years.

The timetable you submitted on June 12, 2014, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | 11/14 |
| Study Completion: | 03/17 |
| Final Report Submission: | 06/17 |

**2159-2**:Conduct a randomized, Single-Blind, Multicenter Safety and Efficacy Study of Intravenous to Oral SIVEXTRO (tedizolid phosphate) and Intravenous to Oral

Comparator for the Treatment of Acute Bacterial Skin and Skin Structure Infections in Pediatric Patients Aged >3 Months to < 12 years.

The timetable you submitted on June 12, 2014, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | 01/16 |
| Study Completion: | 02/19 |
| Final Report Submission: | 05/19 |

**2159-3**: Conduct an open-Label, Multicenter Study of 10-14 days IV SIVEXTRO (tedizolid phosphate) for hospital-acquired late onset sepsis in full term and preterm neonates and infants aged 5 days to ≤ 3months.

The timetable you submitted on June 12, 2014, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | 07/18 |
| Study Completion: | 11/19 |
| Final Report Submission: | 02/20 |

**2159-4:** Conduct a Phase 1 Single-Dose Safety and Pharmacokinetic Study of Oral and IV SIVEXTRO (tedizolid phosphate) in Patients 2 years to < 12 years of age.

The timetable you submitted on June 12, 2014, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | 12/14 |
| Study Completion: | 01/17 |
| Final Report Submission: | 04/17 |

**2159-5**: Conduct a Phase 1 Single-Dose Safety and Pharmacokinetic Study of Oral and Intravenous SIVEXTRO (tedizolid phosphate) in Inpatients Under 2 Years Old.

The timetable you submitted on June 12, 2014, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | 04/16 |
| Study Completion: | 04/19 |
| Final Report Submission: | 07/19 |

Submit the protocol(s) to your IND 106307, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When

submitting the reports, please clearly mark your submission **"SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS"** in large font, bolded type at the beginning of the cover letter of the submission.

**POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the serious risk of development of resistance to SIVEXTRO (tedizolid phosphate) in organisms specific to the ABSSSI indication in the label. Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

**2159-6**: Conduct US surveillance studies for five years from the date of marketing SIVEXTRO to determine if resistance to tedizolid has developed in those organisms specific to the indication in the label for ABSSSI.

The timetable you submitted on June 12, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 07/14
First interim report: 06/15
Second interim report: 06/16
Third interim report: 06/17
Fourth interim report: 06/18
Fifth interim report: 06/19
Sixth interim report: 06/20
Study completion: 02/20
Final report submission: 08/20

Submit the protocols to your IND 106307, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:
**"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a

safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii).We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

## PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

## REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

## MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment

instructions and program description details at
http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

**POST APPROVAL FEEDBACK MEETING**

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

**PDUFA V APPLICANT INTERVIEW**

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Carmen DeBellas, Regulatory Project Manager, at (301) 796-1203.

Sincerely,

*{See appended electronic signature page}*

Edward Cox, MD, MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and Container Labeling

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

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/s/

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EDWARD M COX
06/20/2014