DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021775/S-010

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT

Cubist Pharmaceuticals, Inc.
Attention: Jennifer Liscouski
Senior Manager, Regulatory Affairs
65 Hayden Avenue
Lexington, MA 02421

Please refer to your Supplemental New Drug Application (sNDA) dated and received December 21, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Entereg (alvimopan) Capsules, 12mg.

We acknowledge receipt of your amendments dated January 11, 2013; February 8 & 25, 2013; March 7, 11, 14 & 22, 2013; August 16, 2013; September 3, 2013; October 11 & 17, 2013 and your risk evaluation and mitigation strategy (REMS) assessment dated September 3, 2013.

This "Prior Approval" supplemental new drug application provides for revisions to the Indication and Usage, Warnings and Precautions and Clinical Studies sections of the package insert and proposed modifications to the approved risk evaluation and mitigation strategy (REMS).

APPROVAL & LABELING

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

In addition, we have found the REMS assessment, dated September 3, 2013, to be complete.

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 the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at

http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Matthew Scherer
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 5137
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

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.

Because none of these criteria apply to your application, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENT

We acknowledge that your submission dated December 21, 2012, includes the final report for the following postmarketing requirement listed in the May 20, 2008 approval.

918-3 A multi-center, double-blind, placebo-controlled, parallel group clinical trial of Entereg for the management or postoperative ileus in patients undergoing radical

cystectomy.

We have reviewed your submission and conclude that the above requirement was fulfilled.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for ENTEREG (alvimopan) was originally approved on May 20, 2008, and REMS modifications were approved on February 5, 2009 and September 25, 2012. The REMS consists of a communication plan, elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of the following:

- Ongoing activities related to prescriber and hospital pharmacist training and education have been modified and placed under the elements to assure safe use.
- Changes to the REMS document, the REMS Program Overview, the Dear Healthcare Provider (DHCP) letter, and the Prescriber and Pharmacist Information Brochure to align with the revised indication.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed modified REMS, submitted on October 11, 2013 (with minor modifications submitted on October 17, 2013) and appended to this letter, is approved.

The modified REMS consists of elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS will remain the same as that approved on May 20, 2008.

There are no changes to the REMS assessment plan described in our July 16, 2012 letter, described below.

REMS Assessments are to include the following:

1. An assessment of use data establishing the circumstances of use of Entereg (alvimopan):
    - the extent of outpatient use
    - the extent of inpatient use
    - the extent of use > 15 doses within hospitals
    - the extent of use in bowel resection procedures
    - the extent of use in non-bowel resection procedures
    - the extent of use for other reasons
    - the extent of use by specially certified hospitals
    - the extent of use by hospitals that are not specially certified

2. A description of the investigation of use deviations and corrective actions taken.

3. A narrative summary and analysis of myocardial infarctions reported with use of Entereg (alvimopan).

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 021775 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 021775 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021775
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)

FOR NDA 021775
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

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

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. 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.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

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

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, MD, MPH
Deputy Safety Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
REMS

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

/s/

JOYCE A KORVICK
10/18/2013