



NDA 021775/S-015

SUPPLEMENT APPROVAL

Cubist Pharmaceuticals, LLC
C/O Merck Sharp & Dohme Corp.,
Attention: Vamsidhara Dhulipala, Ph.D.
Regulatory Liaison, Global Regulatory Affairs
351 Sumneytown Pike
PO Box 1000, UG-2D68
North Wales, PA 19454

Dear Dr. Dhulipala:

Please refer to your supplemental new drug application (sNDA) dated October 31, 2018, received October 31, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ENTEREG (alvimopan) capsules. We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated May 15, 2019 and amendment dated October 18, 2019.

This Prior Approval Supplemental new drug application provides for proposed modifications to the approved Entereg risk evaluation and mitigation strategy (REMS).

We have completed our review of this supplemental application, as amended. It is approved effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for ENTEREG (alvimopan) was originally approved on May 20, 2008, and the most recent REMS modification was approved on May 18, 2016. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of a change in the REMS goal to remove the objective of informing healthcare providers about the potential risk of myocardial infarction observed with long-term use of alvimopan. Your proposed modification to the REMS also establishes a single shared system (SSS) REMS for the elements to assure safe use and the implementation system required for the reference listed drug (RLD) Entereg and ANDAs referencing Entereg, called the Alvimopan REMS Program.

Your proposed modified REMS, submitted on October 31, 2018, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS must be revised to 12 months from date of initial approval of the SSS REMS December 19, 2019 and annually thereafter.

The SSS REMS assessment plan must include, but is not limited to, the following:

Program Implementation and Operations

1. REMS Program Operations (per reporting period and cumulatively)

a. REMS Call Center

- i. Number of contacts by stakeholder type (patients, healthcare providers, pharmacies, healthcare settings, wholesaler/distributors, other)
- ii. Summary of reasons for calls (e.g., certification question) and by reporter (authorized representative, healthcare setting, patient/caregiver, other)
- iii. Summary of frequently asked questions (FAQ) by stakeholder type
- iv. Summary report of REMS-related problems identified and resulting corrective actions

b. REMS Enrollment Statistics

- i. Number of newly certified hospitals stratified by geographic regions
- ii. Number of certified wholesalers/distributors

2. REMS Compliance (per reporting period and cumulatively)

A summary report of non-compliance identified, including but not limited to:

- i. Provide a copy of the non-compliance plan, including the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each case, and which event lead to de-certification from the REMS.
- ii. Provide a copy of the audit plan for each stakeholder (including audit questionnaire).
- iii. Report of audit findings for each stakeholder (healthcare settings and wholesalers/distributors).
 1. The number of audits expected, and the number of audits performed.
 2. The number and types of deficiencies noted for each group of audited stakeholders. Include the corrective actions taken to address any non-compliance.
 3. For those with deficiencies noted, report the number that did not complete a corrective and preventive action (CAPA) plan within a month and the time it took to complete a CAPA plan.
 4. Include a unique identification (ID) for each stakeholder that had deviations to track deviations by stakeholder over time.

5. Documentation of completion of training for relevant staff.
 6. The existence of documented processes and procedures for complying with the REMS.
 7. A comparison of demographic representativeness of the audited healthcare settings and all certified healthcare settings.
- b. Healthcare Settings (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
- i. Number and type of healthcare settings for which non-compliance with the REMS is detected.
 - ii. Number of times alvimopan was administered for more than 15 doses.
 - iii. Number of times alvimopan was dispensed outpatient.
 - iv. Number of times non-certified healthcare settings administer alvimopan.
 - v. Number of healthcare settings deactivated for non-compliance, reasons for deactivation, and steps needed for re-certification (if applicable).
 - vi. Number of healthcare settings re-certified, and steps taken for re-certification (if applicable).
- c. Wholesalers/Distributors (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
- i. The number of certified wholesalers/distributors for which non-compliance with the REMS is detected.
 - ii. The number and type of non-certified wholesalers/distributors that shipped alvimopan.
 - iii. The number of times alvimopan was distributed to a non-certified healthcare setting.

Safe Use Behaviors

3. Alvimopan Utilization Data (per reporting period and cumulatively)
- a. Number of shipments distributed to wholesalers.
 - b. Number of shipments distributed to certified hospitals.
 - c. Number of certified hospitals stratified by low, medium or high use of alvimopan based on shipping data.
 - d. Number of active certified hospitals that have purchased alvimopan at least once during the reporting period.
 - e. An assessment of use data establishing the circumstances of use of alvimopan including the following:
 - i. A comparison of demographic representativeness of the certified hospitals in the dataset used and all certified hospitals.
 - ii. The extent of inpatient use.

- iii. The extent of use in bowel resection procedures, radical cystectomy or pelvic exenteration procedures.
- iv. The extent of use of alvimopan used in non-bowel resection procedures, radical cystectomy or pelvic exenteration procedures or other reasons.

Health Outcomes

4. Safety Surveillance (per reporting period and cumulatively)

- a. A summary of known and suspected adverse events related to myocardial infarctions associated with alvimopan. Include an overall summary and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication.

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.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) *If the new indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use: Provision of as many of the currently listed assessment plan items as is feasible.*

- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. If you are not proposing REMS modifications, provide a rationale for why the REMS does not need to be modified.*

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 21775 REMS 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.

We remind you that section 505-1(f)(8) of the FD&C Act prohibits holders of an approved covered application with element 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.

Prominently identify any submission containing a REMS assessment 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

or

**NEW SUPPLEMENT FOR NDA 021775/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 021775/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 021775/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING
CHANGES SUBMITTED IN SUPPLEMENT XXX**

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021775/ S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 021775

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no

later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

If you have any questions, contact Andrew Kelleher, Ph.D., Regulatory Project Manager, at (301) 796-9330 or email andrew.kelleher@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):

- REMS

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOYCE A KORVICK
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