ANDA 217753/S-001

PRIOR APPROVAL SUPPLEMENT APPROVAL

Hikma Pharmaceuticals USA Inc.
1809 Wilson Road
Columbus, OH 43228
Attention: James Connell
Associate Director, Regulatory Affairs

Dear Sir:

This is in reference to your supplemental abbreviated new drug application (sANDA) received for review on April 4, 2025, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Alvimopan Capsules.

Reference is also made to any amendments to the sANDA submitted prior to the issuance of this letter.

The sANDA, submitted as "Prior Approval Supplement," provides for modifications to the approved Alvimopan Risk Evaluation and Mitigation Strategy (REMS). This supplement is in response to our September 16, 2024, REMS Modification Notification letter.

We have completed the review of this sANDA, as amended. It is **approved** effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

In order to ensure the benefits of alvimopan outweigh the risks, we determined that you were required to make the REMS modifications outlined in our REMS Modification Notification letter dated September 16, 2024.

In addition to the required REMS modifications, you proposed the addition of maintaining records of staff training as part of the requirements for healthcare settings that dispense alvimopan and updated the description of the enrollment process for hospital pharmacies.

In addition, the following modifications were communicated during the course of the review: a revised REMS Document which includes removal of references to the *Alvimopan REMS Kit*, revision of audit language, and revised REMS materials to update their formatting and usability.

Your REMS, received on August 26, 2025, referenced in Drug Master File (DMF) 038233, is approved and will be posted on the FDA REMS website: http://www.fda.gov/rems.

The modified REMS for Alvimopan Shared System REMS consists of elements to assure safe use and an implementation system.

Other products may be added in the future if additional NDAs or ANDAs are approved.

Under section 505-1(g)(2)(C) of the FD&C Act, FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS.

FDA has determined that assessments are needed for the Alvimopan Shared System REMS.

Additionally, the details for what should be included in your REMS assessments and the dates of the REMS assessments are listed in Appendix 1.

If the information provided in an assessment is insufficient to allow FDA to determine whether the REMS is meeting its goals or whether the REMS must be modified, FDA may require the submission of a new assessment plan that contains the metrics and/or methods necessary to make such a determination. Therefore, FDA strongly recommends obtaining FDA feedback on the details of your proposed assessment plan to ensure its success. To that end, we recommend that methodological approaches, other analysis plans and assessment approaches used to assess a REMS be submitted for FDA review as follows:

i. Submit your proposed audit plan **and** non-compliance plan for FDA review within 60 days of this letter.

We remind you that 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 FD&C Act.

We remind you that section 505-1(f)(8) of the FD&C Act 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) of the FD&C Act. A violation of this provision in 505-1(f) of the FD&C Act could result in enforcement action.

Prominently identify any 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:

ANDA XXXXXX REMS ASSESSMENT
CROSS REFERENCE TO THE REMS DMF

or

NEW SUPPLEMENT FOR ANDA XXXXXX/S-000/
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION
CROSS REFERENCE TO THE REMS DMF

or

NEW SUPPLEMENT FOR ANDA XXXXXX/S-000/
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION
CROSS REFERENCE TO THE REMS DMF

or

NEW SUPPLEMENT FOR ANDA XXXXXX/S-000/
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX
CROSS REFERENCE TO THE REMS DMF

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 ANDA XXXXXX
CROSS REFERENCE TO THE REMS DMF

The Alvimopan Shared System REMS uses a Type V DMF for shared system REMS submissions. Please refer to the draft guidance for industry *Use of a Drug Master File for Shared System REMS Submissions*,[1] for instructions on how to submit and reference the shared system REMS DMF.

[1] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903
www.fda.gov

REQUIREMENTS AND RECOMMENDATIONS POST-APPROVAL

Under applicable statutes, regulations, and guidances, your ANDA may be subject to certain requirements and recommendations post-approval, including requirements regarding changes to approved ANDAs, postmarketing reporting, promotional materials, and annual facility fees, among others. For information on post-approval requirements and recommendations for ANDAs and a list of resources for ANDA holders, we refer you to https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/requirements-and-resources-approved-andas.

If you have any questions, call James Barlow, REMS Coordinator, at (240) 402-8587.

Sincerely,

{See appended electronic signature page}

Debra M. Catterson, RPh
Deputy Director
Division of Clinical Safety and Surveillance
Office of Safety and Clinical Evaluation
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosed: See REMS Assessment Plan

U.S. Food & Drug Administration
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Appendix 1

REMS Assessment Plan

REMS Assessments are due to be submitted to the FDA every 2 years following the approval of the REMS modification. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. The Alvimopan Shared System REMS Applicant(s) will submit each REMS assessment so that it will be received by the FDA on or before the due date.

The Alvimopan REMS Assessment Plan must include, but is not limited to, the following:

For each metric, provide the two previous, current, and cumulative reporting periods (where applicable) unless otherwise noted.

Program Implementation and Operations

1. REMS Operations

    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

    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 decertified for non-compliance, reasons for decertification, 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.

iv. Disposition of alvimopan (e.g., drug returned, drug administered, drug lost/stolen) for any shipping deviations identified.

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.

Overall Assessment of REMS Effectiveness

5. 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 one or more such goals or such elements should be modified.

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/

DEBRA M CATTERSON
09/23/2025 01:27:16 PM