DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021897/S-020, S-023

SUPPLEMENT APPROVAL

Alkermes Inc,
852 Winter Street
Waltham, MA 02451-1420

Attention: Renee Howard
Senior Director, Regulatory Affairs

Dear Ms. Howard:

Please refer to your Supplemental New Drug Applications (sNDAs) dated April 13, 2012 (S-020), and June 20, 2013 (S-023), received April 13, 2012, and June 20, 2013, respectively, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vivitrol (naltrexone for extended-release injectable suspension).

We also refer to our letter dated February 17, 2012, notifying you, under Section 505-1(g)(2)(C) of the FDCA, that your approved Risk Evaluation and Mitigations Strategy (REMS) must be modified based on the review of your REMS assessment that showed that patients are not adequately knowledgeable about the serious risks associated with Vivitrol (naltrexone for extended-release injectable suspension) that are described in the Medication Guide. The REMS modification notification letter indicated that the modified REMS must include a Medication Guide revised to improve patient comprehension of the risks, a communication plan, and a revised timetable for submission of REMS assessments.

We acknowledge receipt of your amendments dated August 20, 2012, May 17, June 11, and July 11, 2013.

Supplement S-020 proposed modifications to the approved REMS for Vivitrol (naltrexone for extended-release injectable suspension) consistent with our February 17, 2012, letter.

Supplement S-023 proposed revisions to the **BOXED WARNING, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTION, and PATIENT COUNSELING INFORMATION** sections of the Package Insert and revisions to the Medication Guide and carton labeling.

We have completed our review of these supplemental applications, as amended, and they are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revisions indicated in the enclosed labeling.

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, and Medication Guide, 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 include 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.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your June 20, 2013, submission containing the final printed carton label.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Vivitrol (naltrexone for extended-release injectable suspension) was originally approved on March 22, 2010, and a REMS modification was approved on October 12, 2010. The REMS consists of a Medication Guide, and a timetable for submission of assessments of the REMS. Your response to the REMS modification notification letter consists of a REMS with a revised Medication Guide, the addition of a communication plan to include information about the serious risks associated with Vivitrol (naltrexone for extended-release injectable suspension), and a revised timetable for submission of REMS assessments.

Your proposed modified REMS, submitted on July 11, 2013 and appended to this letter, is approved. The modified REMS consists of a Medication Guide, communication plan, and a revised timetable for submission of assessments of the REMS. The REMS assessments should

be submitted to the Agency 2 years, 4 years, and 7 years from the date of the approval of the modified REMS.

The revised REMS assessment plan should include, but is not limited to, the following:

1. Medication Guide

    a. An evaluation of patients' understanding of severe injection site reactions associated with VIVITROL

        i. Alkermes will submit the survey methodology and instrument(s) for review at least 90 days before the next assessment is conducted. Alkermes will submit both methods and instruments together, and clearly identify any changes from the previous protocols.

        ii. The protocols will include, at a minimum, the following:

            1. The expected sample size
            2. A description of the methodology for recruitment and selection of the patient sample
            3. The specific selection criteria for inclusion in each survey
            4. A description of how and when the surveys will be administered
            5. An explanation of the design features and controls that will be included to minimize bias and compensate for any limitations in the methodology

    b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24

    c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

2. Communication Plan

    a. An evaluation of the distribution of the communication materials

        i. The date(s) of mailing(s) and number of recipients of the DHCP Letters, which include the Patient Counseling Tool and the Key Techniques to Reduce Severe Injection Site Reactions Poster

            1. Number of DHCP Letters sent electronically or via US Postal service, and the number of letters returned undeliverable (electronically or US Postal Service)
            2. Number of DHCP Letters distributed by sales representatives or by Medical Information

ii. The number of Key Techniques to Reduce Severe Injection Site Reactions posters and Patient Counseling Tools distributed by the sales force

1. The number of face-to-face interactions with healthcare providers in which materials were provided
2. The number of calls on treatment centers during which materials were presented

iii. Metrics associated with the REMS website for VIVITROL

1. Date the communication information is posted to the REMS website for VIVITROL
2. Number of visits to the REMS website link for each reporting period

b. An evaluation of prescribers' understanding of severe injection site reactions associated with VIVITROL

i. The survey will be conducted among a representative sample of healthcare providers who are current or past prescribers or administrators of VIVITROL.

ii. Alkermes will submit the survey methodology and instrument(s) for review at least 90 days before the next assessment is conducted. Alkermes will submit both methods and instruments together, and clearly identify any changes from the previous protocols.

iii. The protocols will include, at a minimum, the following:

1. The expected sample size
2. A description of the methodology for recruitment and selection of the healthcare provider sample
3. The specific selection criteria for inclusion in each survey
4. A description of how and when the surveys will be administered
5. An explanation of the design features and controls that will be included to minimize bias and compensate for any limitations in the methodology

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.

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 021897 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 021897 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021897
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021897
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 Ayanna Augustus, Ph.D., Senior Regulatory Project Manager, at (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Judith A. Racoosin, M.D., M.P.H.
Deputy Director for Safety
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton 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/

JUDITH A RACOOSIN
07/29/2013