DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-897

Alkermes, Inc.
88 Sydney Street
Cambridge, MA 02139-4136

Attention: Priya Jambhekar
Global Vice President, Regulatory and Government Affairs

Dear Ms. Jambhekar:

Please refer to your new drug application (NDA) dated March 31, 2005, received March 31, 2005, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Vivitrol (naltrexone for extended-release injectable suspension).

We acknowledge receipt of your submissions dated May 6, 9, 12, 16, and 19, June 17, 24, 27, and 29, July 6, 13, and 29, August 8, 12, 15, 16, 22, and 31, September 6, 7, 12, 14, 23, and 30, October 3, 5, 12, 14, and 27, November 3, 4, and 14, December 14, and 28, 2005, January 10, and 31, February 7, and 14, March 10, and 13, and April 10, 2006.

The February 14, 2006, submission constituted a complete response to our December 23, 2005, action letter.

This new drug application provides for the use of Vivitrol (naltrexone for extended-release injectable suspension) for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with Vivitrol.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions listed below.

1. Tray Lid
   a. Remove the term “kit” from the tray lid.
   b. Revise “380 mg/vial dose kit” to “380 mg/vial” and move this statement underneath the established name.
   c. Reorient the trade name and established name, marketing information, company logos, and bar code to the left side of the tray lid.
   d. Reorient the carton contents to the right side of the tray lid and revise the language as follows:

Each Carton Contains:

1) One vial of 380 mg of Vivitrol (naltrexone for extended-release injectable suspension)*
2) One vial containing 4 mL of diluent†
3) One 5-mL prepackaged syringe
4) One 20-guage ½-inch needle
5) Two 20-guage 1½-inch safety needles

2. Carton Label
   a. Remove the term "kit" from the carton labels.
   b. Revise "380 mg/vial dose kit" to 380 mg/vial" and move this statement underneath the established name.
   c. Revise the carton contents as above.

3. Remove all references to the term "kit" in any other labeling and replace with "carton."

The final printed labeling (FPL) must be identical to, except for including the agreed-upon revisions listed, the enclosed labeling (text for the package insert, text for the patient package insert, directions for use, and immediate container and carton labels). Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission(s) "**FPL for approved NDA 21-873**." Approval of this submission by FDA is not required

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages 0 through 11 years and deferring pediatric studies for ages 12 through 16 years for this application.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The statues of these postmarketing studies shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Conduct a pediatric study under PREA for the treatment of alcohol dependence in patients ages 12 through 16 who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with Vivitrol.

   Protocol Submission: April, 2007
   Study Start: October, 2007
   Final Report Submission: April, 2011

Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment(s) must be clearly designated "**Required Pediatric Study Commitments**."

We remind you of your postmarketing study commitments in your email dated April 11, 2006. These commitments are listed below.

2. Conduct a clinical study to determine whether Vivitrol is effective in patients who are abstinent by virtue of hospitalization or other mechanism to limit access to alcohol, rather than patients who are abstinent in spite of access to alcohol. As these populations are likely to differ with respect to level of motivation and/or alcoholism severity, this is a relevant question important to clinicians deciding whether or not patients being discharged from alcohol-free settings would benefit from treatment with Vivitrol upon discharge.

   Protocol Submission October 2006
   Study Start: April 2007
   Study Report Submission October 2009

3. Perform a Segment I reproductive and developmental toxicology study including toxicokinetic data in a single species with the final drug product formulation,

   Protocol Submission: October 2006
   Study Start: January 2007
   Final Report Submission: January 2008

4. Conduct Segment II reproductive and developmental toxicology studies in two species including toxicokinetic data with the final drug product formulation,

   Protocol Submission: October 2006
   Study Start: January 2007
   Final Report Submission: January 2008

5. Conduct a Segment III reproductive and developmental toxicology study including toxicokinetic data with the final drug product formulation, and

   Protocol Submission: October 2006
   Study Start: January 2007
   Final Report Submission: January 2008

6. Conduct carcinogenicity assessment in two species using the final drug product formulation.

   Protocol Submission: April 2007
   Study Start: August 2007
   Final Report Submission: August 2010

7. In lieu of the animal studies listed in commitments 3 through 6 above, you may be able to obtain adequate pharmacokinetic/toxicokinetic exposure data in the appropriate species necessary for interpreting the existing carcinogenicity and reproductive toxicology data on oral naltrexone in the product labeling. Bridging data will be needed for the mouse, rat, pregnant rat and pregnant rabbit. The following timelines should be followed for this option:

   Protocol Submission: October 2006
   Study Start: January 2007
   Final Report Submission: January 2008

8. Conduct *in vitro* CYP inhibition studies using conventional CYP substrates and validated analytical methodology.

   Protocol Submission: July 2006
   Study Start: August 2006
   Final Report Submission: May 2007

9. Conduct *in vitro* studies in human hepatocytes to evaluate the potential of naltrexone to induce CYP3A4 and CYP1A2.

   Protocol Submission: July 2006
   Study Start: August 2006
   Final Report Submission: May 2007

10. Develop an immediate hypersensitivity skin test to Vivitrol drug product, naltrexone drug substance, and carboxymethylcellulose (CMC). Perform a study with this test to detect immediate hypersensitivity in patients who have been exposed to Vivitrol. Include appropriate controls to assess whether there is a direct, non-immune, histamine releasing effect of Vivitrol drug product, naltrexone drug substance, and CMC.

    Protocol Submission: October 2006
    Study Start: March 2007
    Final Study Report Submission: October 2007

11. Develop in vitro tests for drug-specific IgE, IgG, and IgM to Vivitrol drug product, naltrexone drug substance, and CMC. Perform a study using these tests to detect drug specific IgE, IgG, and IgM to Vivitrol drug product, naltrexone drug substance, and CMC.

    Protocol Submission: October 2006
    Study Start: March 2007
    Final Study Report Submission: October 2007

12. Develop an in-vivo test for delayed hypersensitivity testing or patch testing to detect Type IV or delayed hypersensitivity reactions to Vivitrol and its components (naltrexone, CMC).

    Protocol Submission: October 2006
    Study Start: March 2007
    Final Study Report Submission: October 2007

In addition, we remind you of the following agreements.

1. Revise the drug release specifications to include Day 14 and Day 28 drug release information.

2. Tighten the in-vitro drug release acceptance criteria to an acceptable range and assess the need to establish a specification to control percent crystallinity of naltrexone in the microspheres based on the manufacturing experience with five consecutive commercial scale batches or on one-year manufacturing experience from the date of approval of the NDA, whichever comes first, and submit the results of this evaluation in a CBE-30 supplement.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

This product is approved with an expiration dating period of 18 months.

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

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