CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-897

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-897

Alkermes, Inc.
88 Sidney 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 (3), 27, and 29, July 6, 13, and 29(3), August 8, 12, 15, 16(2), 22, and 31, September 6, 7(2), 12(2), 14, 23, and 30, October 3, 5, 12, 14, and 27, November 3, 4, and 14, and December 14, 2005.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiencies.

1. You have not provided evidence of efficacy of Vivitrol in alcohol-dependent patients who are actively drinking at the time of treatment initiation.

   [redacted], propose labeling to restrict the use of the product to alcohol-dependent patients who have refrained from drinking [redacted] prior to treatment initiation.

   Note that if you elect this latter option, we would expect you to conduct a post-approval study to determine whether Vivitrol is effective in patients whose pre-treatment abstinence is enforced (i.e. via hospitalization) rather than spontaneous (as was the case with the population studied in your efficacy trial, ALK21-003).

2. Provide pharmacokinetic/toxicokinetic exposure data in the appropriate species necessary for interpreting the existing carcinogenicity and reproductive toxicology data in the product labeling. In the absence of adequate bridging data, the following nonclinical studies would have to be conducted:

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

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

c. a Segment III reproductive and developmental toxicology study including toxicokinetic data with the final drug product formulation; and

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

In addition, we have the following comments for your consideration, which are not approvability issues.

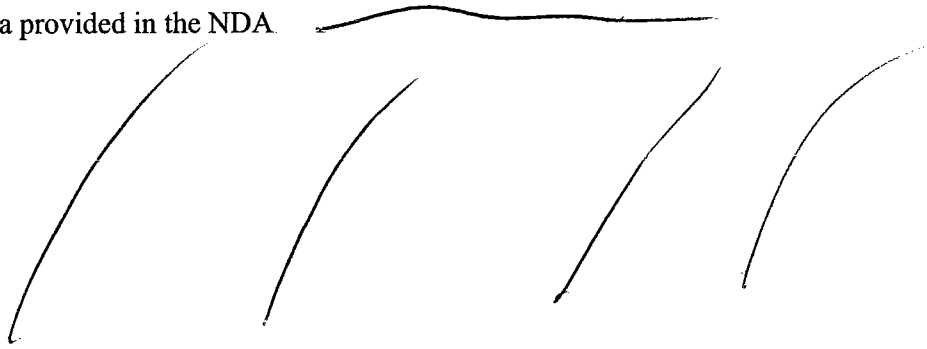
3. To further evaluate the allergenic potential of Vivitrol, conduct a trial to ascertain whether patients develop naltrexone-specific, naltrexone-carboxymethylcellulose-specific, and carboxymethylcellulose-specific antibodies (IgG, IgM, and IgG) following Vivitrol administration. Evaluate whether development of these specific antibodies is associated with adverse events of urticaria and angioedema.

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

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

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

7. The data provided in the NDA



. Therefore, provide additional data on percent crystallinity and *in vitro* drug release for all commercial scale batches of Vivitrol. Also, provide stability updates from the ongoing stability studies. Based these data, the need to revise the *in vitro* drug release specifications and to establish a specification to control the percent crystallinity in Vivitrol will be assessed.

In addition, it will be necessary for you to submit revised draft printed labeling as indicated in the attached, edited document. Note that these revisions are only preliminary draft comments. The labeling will be revised once the aforementioned deficiencies are addressed.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Lisa Basham-Cruz, Regulatory Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, MD
Director
Division of Anesthesia, Analgesia, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Bob Rappaport
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