WARNING LETTER

Alkermes, Inc.

MARCS-CMS 597260 — DECEMBER 02, 2019

Product:

Drugs

Recipient:

Richard F. Pops

Chairman and Chief Executive Officer

Alkermes, Inc.

852 Winter Street
Waltham, MA 02451
United States

Issuing Office:

Center for Drug Evaluation and Research | CDER

10903 New Hampshire Avenue
Silver Spring, MD 20993
United States

RE: **NDA 021897**

VIVITROL (naltrexone for extended-release injectable suspension), for intramuscular use

MA 864

WARNING LETTER

Dear Mr. Pops:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a print advertisement (print ad) (VIV-003460-v2) for VIVITROL (naltrexone for extended-release injectable suspension) for intramuscular use (Vivitrol) submitted by Alkermes, Inc. (Alkermes) under cover of Form FDA 2253. The print ad is false or misleading because it omits important risk information associated with the use of Vivitrol. Thus, the print ad misbrands Vivitrol within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act) and makes its distribution violative. 21 U.S.C. 352(n); 321(n); 331(a). See 21 CFR 202.1(e)(5). This violation is concerning from a public health perspective because it creates a misleading impression regarding the overall safety of Vivitrol. Opioid dependence and misuse is a significant public health concern and a national crisis that impacts millions of lives in the United States. When used as provided

in the FDA- approved product labeling, Vivitrol is safe and effective for the prevention of relapse to opioid dependence, following opioid detoxification. However, those utilizing Vivitrol for the treatment of opioid dependence should be made aware of the vulnerability to potentially fatal overdose at the end of a dosing interval, after missing a dose, or after discontinuing Vivitrol treatment. Attempts to overcome blockade may also lead to fatal overdose.

Background

Below is the indication and the summary of the most serious and most common risks associated with the use of Vivitrol.*1* According to the INDICATIONS AND USAGE section of the FDA-approved product labeling (PI) for Vivitrol:

Treatment with VIVITROL should be part of a comprehensive management program that includes psychosocial support.

VIVITROL is indicated 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. Patients should not be actively drinking at the time of initial VIVITROL administration.

VIVITROL is indicated for the prevention of relapse to opioid dependence, following opioid detoxification.

Vivitrol is contraindicated in patients receiving opioid analgesics, patients with current physiologic opioid dependence, patients in acute opioid withdrawal, any individual who has failed the naloxone challenge test or has a positive urine screen for opioids, and patients who have previously exhibited hypersensitivity to naltrexone, polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other components of the diluent. The PI for Vivitrol includes warnings and precautions regarding vulnerability to opioid overdose, injection site reactions, precipitation of opioid withdrawal, hepatotoxicity, depression and suicidality, when reversal of Vivitrol blockade is required for pain management, eosinophilic pneumonia, hypersensitivity reactions including anaphylaxis, intramuscular injections, alcohol withdrawal, and interference with laboratory tests. The most common adverse reactions observed with Vivitrol therapy in opioid-dependent patients were hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache.

False or Misleading Risk Presentation

Promotional materials misbrand a drug if they are false or misleading with respect to risk. The determination of whether promotional materials are misleading includes, among other things, not only representations made or suggested in promotional materials, but also failure to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials.

The print ad contains claims and representations about the benefits of Vivitrol. However, the print ad fails to communicate information from the WARNINGS AND PRECAUTIONS section of the PI concerning vulnerability to opioid overdose, a potentially fatal risk. Specifically, the PI states that after opioid detoxification, patients are likely to have reduced tolerance to opioids. Vivitrol blocks the effects of exogenous opioids for approximately 28 days after administration. However, as the blockade wanes and eventually dissipates completely, patients who have been treated with Vivitrol may respond to lower doses of opioids than previously used, just as they would have shortly after completing detoxification. This could result in potentially life-threatening opioid intoxication (respiratory compromise or arrest, circulatory collapse, etc.) if the patient uses previously tolerated doses of opioids. Cases of opioid overdose with fatal outcomes have been reported in

patients who used opioids at the end of a dosing interval, after missing a scheduled dose, or after discontinuing treatment. Furthermore, there is also the possibility that a patient who is treated with Vivitrol could overcome the opioid blockade effect of Vivitrol. Patients should be told of the serious consequences of trying to overcome the opioid blockade.

By omitting this serious and potentially fatal risk, the print ad fails to provide material information about the consequences that may result from the use of the drug and creates a misleading impression about the drug's safety. This is extremely concerning from a public health perspective because of the potential for fatal overdose in this vulnerable patient population.

In addition, the print ad omits other important warnings and precautions, including the risk of injection site reactions (one of the risks addressed by the Vivitrol Risk Evaluation and Mitigation Strategy (REMS)), and the most common adverse reactions associated with the use of drug.

We note the statement, "**For additional Important Safety Information, please see the Brief Summary of Prescribing Information on adjacent pages**" (emphasis in original) in small print at the bottom of the print ad; however, this statement and the inclusion of the brief summary on adjacent pages do not mitigate the misleading omissions of material risk information from the main body of the print ad.

Prior Communications

OPDP

OPDP refers Alkermes to OPDP's advisory letter, dated March 9, 2011, on proposed promotional materials for Vivitrol, wherein OPDP advised Alkermes that the proposed material **(b)(4)**

Office of New Drugs

On October 12, 2018, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) sent an information request to Alkermes requesting that Alkermes "describe any efforts you have made to ensure that prescribers and patients are aware of the risk of overdose" for patients exposed to Vivitrol. On October 29, 2018, Alkermes responded in part stating that they have "undertaken numerous efforts to ensure that prescribers and patients are aware of the risk of overdose," and that one such measure undertaken by Alkermes was the "[i]nclusion of the risk of opioid overdose within the text of promotional materials for healthcare professionals, caregivers and consumers…"

OPDP is concerned that Alkermes continues to promote Vivitrol in a manner that fails to adequately present this important risk information in a truthful and non-misleading manner.

Conclusion and Requested Action

For the reasons discussed above, the print ad misbrands Vivitrol within the meaning of the FD&C Act and makes its distribution violative. 21 U.S.C. 352(n); 321(n); 331(a). See 21 CFR 202.1(e)(5).

OPDP requests that Alkermes immediately cease misbranding Vivitrol and/or cease introducing the misbranded drug into interstate commerce. Please submit a written response to this letter on or before December 16, 2019, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Vivitrol that contain statements such as those described above, and explaining your plan for discontinuing use of such materials, or, in the alternative, for ceasing distribution of Vivitrol. Because the violations described above are serious, we request, further, that your submission include

a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. In order to clearly identify the violative promotional piece(s) and/or activity and focus on the corrective message(s), OPDP recommends that corrective piece(s) include a description of the violative promotional piece(s) and/or activity, include a summary of the violative message(s), provide information to correct each of the violative message(s), and be free of promotional claims and presentations. To the extent possible, corrective messaging should be distributed using the same media, and generally for the same duration of time and with the same frequency that the violative promotional material was disseminated. If you believe that your products are not in violation of the FD&C Act, include your reasoning and any supporting information for our consideration.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901- B Ammendale Road, Beltsville, Maryland 20705-1266**. A courtesy copy can be sent by facsimile to (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA 864 in addition to the NDA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Warning Letter.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Vivitrol comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Andrew S.T. Haffer, Pharm.D. Director

Division of Advertising & Promotion Review 1

Office of Prescription Drug Promotion

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/

ANDREW S HAFFER
12/02/2019 01:42:16 PM

1 This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece(s) cited in this letter.

Promotional Material (/media/133459/download)

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