



NDA 022321/S-016

**SUPPLEMENT APPROVAL
RELEASE FROM POSTMARKETING
REQUIREMENT/COMMITMENT**

AlPharma Pharmaceuticals, LLC
c/o: Pfizer Inc.
235 East 42nd Street
New York, NY 10017

Attention: Kathleen Collins
Director, Worldwide Regulatory Affairs

Dear Ms. Collins:

Please refer to your Supplemental New Drug Application (sNDA) dated and received September 17, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EMBEDA (morphine sulfate and naltrexone hydrochloride) extended-release capsules.

We acknowledge receipt of your amendments dated November 4, 2013, and March 26, April 30, May 7, June 6, July 7 and 9, and September 12, 23, and 24, 2014.

This "Prior Approval" supplemental new drug application proposes revisions to the **DRUG ABUSE AND DEPENDENCE** section of the Package Insert. Language describing the results of data from in vitro and in vivo abuse potential studies is added.

We have completed our review of this supplemental application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

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, 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 includes 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).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your supplemental application, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

At the September 24, 2009, joint meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and Drug Safety and Risk Management Advisory Committee (DSaRM) on another purportedly abuse-deterrent opioid formulation, the Committee recommended that postmarketing studies be conducted to assess whether the changes made to the formulation, which were intended to provide deterrence of misuse and abuse, actually result in a decrease in the serious risks of misuse and abuse, and their consequences, addiction, overdose and death. Consequently, we are applying this advice to all purportedly abuse-deterrent opioid formulations.

Since EMBEDA was approved on August 13, 2009, we have become aware of new information from the in vitro and in vivo abuse potential studies included in your supplemental application,

about the potential for misuse and abuse with EMBEDA. We consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of the serious risks of misuse and abuse and their consequences: addiction, overdose and death.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2804-1 Conduct epidemiologic investigations to address whether the properties intended to deter misuse and abuse of EMBEDA (morphine sulfate and naltrexone hydrochloride extended-release capsules) actually result in a significant and meaningful decrease in misuse and abuse, and their consequences, addiction, overdose, and death, in the community. The post-marketing study program must allow FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of EMBEDA. To meet this objective, investigations should incorporate recommendations contained in the FDA draft guidance Abuse-Deterrent Opioids—Evaluation and Labeling (January 2013), and proposed comparators need to be mutually agreed upon prior to initiating epidemiologic investigations. There must be sufficient drug utilization to allow a meaningful epidemiological assessment of overall and route-specific abuse deterrence.

The timetable you submitted on October 10, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 10/2015
Study Completion: 10/2019
Final Report Submission: 04/2020

Depending on the results of the above study, additional postmarketing investigations may be required to evaluate the effect of this formulation of morphine sulfate and naltrexone hydrochloride on misuse and abuse, and their consequences.

In light of this new postmarketing requirement, you are released from the following postmarketing requirement listed in our February 14, 2011, postapproval letter because it is superseded by PMR 2804-1:

- 1515-3: Conduct epidemiological studies to address whether the inclusion of naltrexone in the Embeda (morphine sulfate and naltrexone hydrochloride) capsules formulation will

result in a decrease in misuse and abuse, and their consequences: addiction, overdose, and death in the community.

We remind you that all other PMRs listed in our August 6, 2013, and September 10, 2013, postapproval letters are still open.

Submit the protocol and amendments to your IND 070853, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

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/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. 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 Lisa Basham, Senior Regulatory Health Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Acting Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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 on behalf of SHARON H HERTZ
10/17/2014