DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 22-321 **NDA APPROVAL**

Alpharma Pharmaceuticals, LLC/King Pharmaceuticals
King Pharmaceuticals Research & Development, Inc.
4000 CentreGreen Way, Suite 300
Cary, NC 27513

Attention: Kenneth B. Touw, PhD
Senior Vice President, Regulatory Affairs

Dear Dr. Touw:

Please refer to your new drug application (NDA) dated June 30, 2008, received June 30, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for EMBEDA (morphine sulfate and naltrexone hydrochloride) Extended-Release Capsules, 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, 100 mg/4 mg.

We acknowledge receipt of your submissions dated February 28, April 11 and 22, July 1, 22, and 29, August 22 and 26, September 8, 9, 23, and 24, October 1, 3, 7, 9, 10, 13, 28, and 31, November 3 and 21, and December 8 and 11, 2008, and June 5, 25, and 29, July 1, 7, 8, 13, 16, and 29, and August 7, 2009.

This new drug application provides for the use of EMBEDA (morphine sulfate and naltrexone hydrochloride) Extended-Release Capsules, 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, 100 mg/4 mg for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format submitted on June 25, 2009.

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 July 8, 2009, submission containing final printed carton and container labels.

We remind you of your August 13, 2009, agreement to add a flag to the 100mg/4mg-strength container label stating "For opioid-tolerant patients only."

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.

We are waiving the pediatric study requirement for ages birth to less than two years because necessary studies are impossible or highly impracticable. This is because the number of pediatric patients with chronic pain in this age group is extremely small.

We are deferring submission of your pediatric studies for ages 2 to 17 years until February 29, 2012, because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1515-1. Deferred pediatric efficacy, safety, and pharmacokinetic (single- and multiple-dose) study under PREA for the treatment of moderate to severe pain, when a continuous, around-the-clock opioid analgesic is needed for an extended period of time in pediatric patients ages 12 to 17 years.

Final Protocol Submission Date: November 2009
Study Completion Date: April 2011
Final Report Submission: July 2011

1515-2. Deferred pediatric efficacy, safety, and pharmacokinetic (single- and multiple-dose) study under PREA for the treatment of moderate to severe pain, when a continuous, around-the-clock opioid analgesic is needed for an extended period of time in pediatric patients ages 2 to <12 years.

Final Protocol Submission Date: November 2010
Study Completion Date: November 2011
Final Report Submission: February 2012

Submit final study reports to this NDA. Use the following designator to prominently label all submissions: "**Required Pediatric Assessment(s)**".

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Your proposed REMS, submitted on August 7, 2009, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

As you know, we are considering what REMS elements should be implemented across the class of modified-release opioids to address the risks of abuse, misuse, overdose, and addiction. Once that determination is made, as discussed, we will notify you in writing and you will be required to submit a modified REMS incorporating those elements.

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

1. An evaluation of patients' understanding of the serious risks of EMBEDA.

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

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

4. An evaluation of healthcare providers' awareness and understanding of the serious risks associated with EMBEDA (for example, through surveys of healthcare providers).

5. Specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that healthcare provider awareness is not adequate.

6. An analysis and summary of surveillance and monitoring activities for abuse, misuse, overdose, and addiction and any intervention taken resulting from signals of abuse, misuse, overdose, and addiction.

7. Based on the information provided, an assessment and conclusion of whether the REMS is meeting its goals and whether modifications to the REMS are needed and if so, proposed modifications.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)vii) and including any updates to the status information since the annual report was

prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that 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 FDCA.

Prominently identify any submission containing the REMS assessment or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

N 22-321 REMS ASSESSMENT

NEW SUPPLEMENT FOR N 22-321
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR N 22-321
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, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

METHODS VALIDATION

Validation of the method was reviewed and found acceptable and, therefore, does not need to be validated further by FDA Laboratories.

EXPIRATION DATING PERIOD

An expiration dating period of 24 months is granted to the EMBEDA Capsules in HDPE bottles, stored at 20-25ºC, excursion permitted to 15-30°C (59°-86°F).

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

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, Regulatory Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

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

Enclosures (4): Package Insert
Medication Guide
Carton and Container Labels
REMS

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

/s/

BOB A RAPPAPORT
08/13/2009