

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-321**

**OTHER REVIEW(S)**



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: March 30, 2009

To: **Bob A. Rappaport, M.D., Division Director  
Division of Anesthesia, Analgesia, and Rheumatology  
Products (DAARP)**

Through: **Jodi Duckhorn, M.A., Team Leader  
Division of Risk Management (DRISK)**

From: **Sharon R. Mills, BSN, RN, CCRP  
Patient Product Information Reviewer  
Division of Risk Management (DRISK)**

Subject: **DRISK Review of Patient Labeling (Medication Guide)**

Drug Name(s): **Embeda (morphine sulfate and naltrexone hydrochloride)  
Extended Release Capsules CII**

Application Type/Number: **NDA 22-321**

Applicant/sponsor: **Alpharma Pharmaceuticals**

OSE RCM #: **2009-477**

## 1 INTRODUCTION

Alpharma Pharmaceuticals submitted a 505(b)(2) New Drug Application, NDA #22-321 on February 28, 2008 and withdrew their NDA on April 22, 2008. The applicant resubmitted their NDA on June 30, 2008. The applicant is relying on the Agency's previous findings of efficacy and safety for Kadian (NDA 20-616), for which Alpharma owns the right of reference, and Revia (NDA 18-932, Naltrexone hydrochloride).<sup>1</sup>

This review is written in response to a request from DAARP for the Division of Risk Management to review the proposed Medication Guide for Embeda (morphine sulfate and naltrexone hydrochloride) Extended Release Capsules, submitted by the applicant on August 22, 2008.

## 2 MATERIAL REVIEWED

- Draft Embeda (morphine sulfate and naltrexone hydrochloride) Extended Release Capsules Prescribing Information (PI) submitted on June 30, 2008, revised by the Review Division throughout the current review cycle, and provided to DRISK on March 24, 2009.
- Draft Embeda (morphine sulfate and naltrexone hydrochloride) Extended Release Capsules Medication Guide (MG) submitted on August 22, 2008, and revised by the review division throughout the review cycle, and provided to DRISK on March 24, 2009.

## 3 DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft MG submitted by the Applicant has a Flesch Kinkaid grade level of 9.0, and a Flesch Reading Ease score of 55.5%. To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8<sup>th</sup> grade reading level). Our revised MG has a Flesch Kinkaid grade level of 8.2 and a Flesch Reading Ease score of 59.7%.

In our review of the MG, we have:

- simplified wording and clarified concepts where possible,
- ensured that the MG is consistent with the PI,
- rearranged information due to conversion of the PI to PLR format,
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

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<sup>1</sup> Cross-Discipline Team Leader Review, Ellen Fields, M.D., M.P.H., Clinical Team Leader, December 11, 2008, NDA 22-321.

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APFont to make medical information more accessible for patients with low vision. We have reformatted the MG document using the font APFont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are **bolded, underlined and italicized**.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

#### 4 CONCLUSIONS AND RECOMMENDATIONS

**We have the following comments on the proposed Medication Guide:**

1. We remind the Applicant of their requirement to comply with 21 CFR 208.24
  - A required statement alerting the dispenser to provide the Medication Guide with the product must be on the carton and container of all strengths and formulations. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):
    - “Dispense the enclosed Medication Guide to each patient.” or
    - “Dispense the accompanying Medication Guide to each patient.”
  - Sufficient numbers of Medication Guides should be provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each “usual” or average dose. For example:
    - A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
    - A minimum of one Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.
2. In the section “What is the most important information I should know about EMBEDA?”
  - In the first bullet of this section, the review division should clarify if it is appropriate to use “EMBEDA capsules” in this context. We deleted the word “capsules” throughout the MG where it did not seem appropriate since the product name is EMBEDA. We concur with the DDMAC comment to add information that rapid release of the capsule contents may result in death. We have added death, but have stated it differently. We added that it may cause you to have trouble breathing and lead to death. The instruction to swallow EMBEDA capsules whole or sprinkle the contents on apple sauce has been moved to the section “How should I take EMBEDA?”

- We added language stating that EMBEDA is not for use “as needed”. We concur with DDMAC. This information is part of the Boxed warning and should be included in the “What is the most important information I should know about EMBEDA?” in the MG.

3. In the section “What is EMBEDA?”

- The statement “The naltexone hydrochloride is confined within an inner core and surrounded by a protective barrier” is not patient-friendly. We have simplified this language to make it more patient-friendly.
- We disagree with DDMAC’s recommendation to place language about EMBEDA being a controlled substance (CII) in the section “What is the most important information I should know about EMBEDA?” The language in the box is directed to healthcare providers in this case. We compared the MGs for Actiq, Fentora and our recently completed review of Onsolis. All of the PIs contain this information and the corresponding language has been placed in the “What is TRADENAME?” section of the MG. We have placed the information here for consistency with other opioid MGs.
- Regarding the bullet that addresses the indication statement: The Indications and Usage section of the PI does not state that the product is only for adults. Likewise, pediatric use is not contraindicated. Pediatric language is addressed at the end of this section. The phrase “an extended period of time” is not patient-friendly. DAARP should clarify if “a long period of time” is acceptable for conveying the appropriate use of EMBEDA to patients.
- Language about not using EMBEDA prn has been added to the section “What is the most important information I should know about EMBEDA?” and we deleted the bullet from this section. This is also part of the Boxed warning.
- The bullet for physical dependence has been deleted here. The information is included in the section “What are the possible side effects of EMBEDA?” This is consistent with MGs for other opioid products including Actiq, Fentora, and our recent review of the Onsolis proposed MG.
- The information about EMBEDA being a controlled substance has been moved up within this section so that it is placed similarly as in other opioid MGs. This addresses a DDMAC comment in part. We have also made the language in the next 3 bullets consistent with the language in the approved Actiq and Fentora MGs, and our recently review of the Onsolis proposed MG.
- Pediatric language was added to be consistent with PI section 8.4.

4. In the section “Who should not take EMBEDA?”

- We deleted the pediatric statement at the beginning of the section. Language about pediatric use has been added to the end of the section above “What is EMBEDA?”
- The first three bullets in this section have been deleted. These are not labeled Contraindications.
- We concur with DDMAC that information about paralytic ileus should be included here because EMBEDA is contraindicated in this situation. We have added this information using patient-friendly language.

- Liver problems are not a labeled contraindication. We deleted this bullet “You have liver problems.”
5. In the section “How should I take EMBEDA?”
- We defer to the review division to address DDMAC’s comment #9 with regard to the statement “You can take EMBEDA with or without food.” We have simply made the language patient-friendly.
  - In the bullet “Swallow EMBEDA capsule whole” the review division should determine if it is appropriate to use “EMBEDA capsule.”
  - Regarding the bullet: “If you can not swallow capsules...” We concur with DDMAC’s suggestion to make this language more patient-friendly and have revised the bullet accordingly.
  - We have added instructions for how to take EMBEDA by sprinkling the contents of the capsule on a small amount of apple sauce, consistent with the PI. The applicant should add labeled figures adjacent to each step and reference the figure in the text. With regard to the amount of apple sauce to be used, the applicant should state an amount, such as a teaspoon. “A small amount” is vague. This should be clarified in PI sections 2.3 and 17.
  - The applicant should add an instruction and corresponding figure regarding the right way to dispose of the empty capsule.
  - Information on stopping EMBEDA and physical dependence was deleted from this section to be consistent with the approved Actiq and Fentora MGs, and our review of the Onsolis MG. This information is included in the section “What are the possible side effects of EMBEDA?”
  - Information about safe disposal of unused capsules has been moved to the section “How should I store EMBEDA?”
6. In the section “What should I avoid while taking EMBEDA?” we deleted the bullet about drinking alcohol because it is redundant. The concern about drinking alcohol while taking EMBEDA is addressed in the section “What is the most important information I should know about EMBEDA.
7. In the section “What are the possible side effects of EMBEDA?”
- We disagree with DDMAC’s comment that information about paralytic ileus should be added here. This is a contraindication to use of EMBEDA. Language about this problem has been addressed in the section “Who should not take EMBEDA?” The review division should address DDMAC’s comment #12 and advise DRISK what cutoff to use for adverse reactions to list as common side effects of EMBEDA. We have already addressed additional side effects listed in PI section 17 as common and were not included in the proposed MG. Review and revise the list of common side effects accordingly.
  - We have made the language in the bullet about physical dependence, and the bullet about abuse or addiction, consistent with the language in the approved Actiq, Fentora MGs and in our recent review of the proposed Onsolis MG.
  - Anaphylaxis is listed in the Warnings and Precautions section of the PI, although rare, and seen with a similar product. However, this information should be included with the serious side effects in this section and we have added this

information. We recommend adding an instruction in section 17 so that healthcare providers tell patients to get medical help right away for the listed symptoms of a severe allergic reaction.

- While the proposed MG includes the adverse reactions identified in the Highlights section of the PI as most common (greater or equal to 10%) adverse reactions, section 17 of the PI states that vomiting, dizziness, pruritis, and headache are among the most common adverse reactions with EMBEDA. We have added these adverse reactions above. The information that is conveyed in the MG must be consistent with the information in the PI.
- The review division should determine whether the statement “These side effects may decrease with continued use” is accurate and appropriate. DDMAC comment #13 recommends deleting the statement.
- We have added the following statement to the end of the section, “What are the possible side effects of TRADENAME?”:  
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.  
This verbatim statement is required for all Medication Guides.<sup>2</sup>

8. In the section “How should I store EMBEDA?”

- We deleted the bullet telling patients to store EMBEDA in a safe place, because this is redundant. This information is already included in the “What is EMBEDA?” section.
- We added an instruction stating: “After you stop taking EMBEDA, flush the unused capsules down the toilet.”
- We deleted language about accidental overdose, because it is redundant. This information is already included in the “What is the most important information I should know about EMBEDA?” section.

Please let us know if you have any questions.

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<sup>2</sup> 21 CFR 208.20 (b)(7)(iii)

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/s/

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Sharon Mills  
3/30/2009 03:30:37 PM  
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn  
3/31/2009 08:33:00 AM  
DRUG SAFETY OFFICE REVIEWER

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

**Memorandum**

**Date:** March 13, 2009

**To:** Christopher Hilfiger  
Project Manager  
Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

**From:** Michael Sauers  
Regulatory Review Officer  
Division of Marketing, Advertising, and Communications (DDMAC)

**Subject:** 22-321  
DDMAC Medication Guide comments for EMBEDA Capsules

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DDMAC appreciates the opportunity to provide comments. We have reviewed the proposed Medication Guide for EMBEDA Capsules and offer the following comments:

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/s/

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Michael A Sauers  
3/13/2009 08:11:01 AM  
DDMAC CONSUMER REVIEWER

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**CLINICAL INSPECTION SUMMARY ADDENDUM**

**DATE:** January 26, 2009

**TO:** Christopher Hilfiger, Regulatory Project Manager  
Jin Chen, M.D., Medical Officer  
Division of Anesthesia, Analgesia and Rheumatology Products

**FROM:** Susan Leibenhaut, M.D.  
Good Clinical Practice Branch I  
Division of Scientific Investigations

**THROUGH:** Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I  
Division of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** #22-321

**APPLICANT:** Alpha Pharma Pharmaceuticals LLC

**DRUG:** Embeda (morphine sulfate extended-release with naltrexone hydrochloride)

**NME:** No

**THERAPEUTIC CLASSIFICATION:** Priority Review

**INDICATIONS:** management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time

**CONSULTATION REQUEST DATE:** October 1, 2008

**DIVISION ACTION GOAL DATE:** December 30, 2008

**PDUFA DATE:** December 30, 2008

## I. BACKGROUND:

On December 29, 2008 the Division of Scientific Investigations, Good Clinical Practice Branch I, submitted a clinical inspection summary (CIS) for NDA 22-321 to the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP). The CIS summarized the preliminary findings for inspections of three clinical investigators and (b) (4), the CRO responsible for electronic data capture, for Protocol ALO-KNT-301 entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Efficacy Study of Kadian NT (Morphine Sulfate Plus Naltrexone Hydrochloride Extended-Release) Capsules in Subjects with Moderate to Severe Chronic Pain Due to Osteoarthritis of the Hip or Knee" and the inspections of two clinical sites for Protocol ALO-KNT-302 entitled "A Long-Term, Open-Label, Safety Study of Kadian NT (Morphine Sulfate Plus Naltrexone Hydrochloride Extended-Release) Capsules in Subjects with Chronic Moderate to Severe Nonmalignant Pain."

At the time of the submission of the CIS, DSI noted that there was insufficient information to determine whether the efficacy data were acceptable in support of the application because the establishment inspection report (EIR) for (b) (4) was not yet available. We are issuing an addendum to the initial review because we have received and completed the review of the EIR of (b) (4) and additional data submitted with the other clinical inspections.

## II. RESULTS (by Site):

Name and Location of Contract Research Organization (CRO)	Protocol # and # of Subjects	Inspection Dates	Final Classification
(b) (4)	Protocol ALO-KNT-301	December 8 and 9, 2008	NAI

### Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. (b) (4)

- a. **What was inspected:** For Protocol ALO-KNT-301, the FDA inspector reviewed the organizational chart, contract / scope of work document, written procedures including discrepant patient report processing, the 24/7 HelpDesk call log, and the corrective action reports generated when (b) (4) was requested to correct database records after errors by site personnel. Brief Pain Inventory (BPI) values reported by two or three subjects at each of the three sites were compared with the data listings, and line listings of efficacy data (average BPI) for 24 subjects enrolled at Dr. Rodriguez site 147 were compared with the compact disc (CD) supplied by (b) (4).
- b. **General observations/commentary:** The firm (b) (4) was contracted by (b) (4) to create the diary pages, furnish the devices, maintain the database for diary information and provide a 24/7 HelpDesk function for problems and issues with the diaries. Daily BPI scores were transmitted directly to the CRO. Clinical sites had access to BPI data during the clinical trial and were supplied with a CD containing the BPI data at the conclusion of the trial. No discrepancies were noted in the comparisons between the line listings submitted by the sponsor and the data reviewed at (b) (4) and in the CD supplied by (b) (4) to Dr. Rodriguez site 147. The Establishment Inspection Report (EIR) states that the database is read-only accessible to the CRO/sponsor, but there is no mention of whether the CRO/sponsor has access to blinded or unblinded data.

According to the FDA investigator, inspection of the HelpDesk call log showed that calls involved problems with remote transmission of data, low battery alarms, and site errors that created “duplicate” records. The two instances when duplicate records might be created occurred when a site conducted training in “active” mode instead of training mode or when a subject who was no longer enrolled in the trial was not “terminated” in the device. In these cases data from the new subject were added to the record previously created. When duplicate records were created, the CRO would correct the error and this could be determined on the audit trail. Of the three clinical sites inspected, the issue with duplicate records due to failure to terminate subjects appropriately in the electronic device occurred in three subjects of the 33 subjects enrolled at Dr. Fishman’s site 126.

- c. **Assessment of data integrity:** The data from all inspected sites and from (b) (4), the contract research organization, appear acceptable in support of the proposed indication.

### **III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS**

Concerning data integrity, the data from all inspected sites and from (b) (4), the contract research organization, appear acceptable in support of the proposed indication.

*{See appended electronic signature page}*

Susan Leibenhaut, MD  
Good Clinical Practice Branch I  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Constance Lewin, MD, MPH  
Branch Chief  
Good Clinical Practice Branch I  
Division of Scientific Investigations

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/s/

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Susan Leibenhaut  
1/27/2009 10:01:33 AM  
MEDICAL OFFICER

Constance Lewin  
1/27/2009 10:45:15 AM  
MEDICAL OFFICER

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**CLINICAL INSPECTION SUMMARY**

**DATE:** December 29, 2008

**TO:** Christopher Hilfiger, Regulatory Project Manager  
Jin Chen, M.D., Medical Officer  
Division of Anesthesia, Analgesia and Rheumatology Products

**FROM:** Susan Leibenhaut, M.D.  
Good Clinical Practice Branch I  
Division of Scientific Investigations

**THROUGH:** Constance Lewin, M.D., M.P.H  
Branch Chief  
Good Clinical Practice Branch I  
Division of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections.

**NDA:** #22-321

**APPLICANT:** Alpharma Pharmaceuticals LLC

**DRUG:** Embeda (morphine sulfate extended-release with naltrexone hydrochloride)

**NME:** No

**THERAPEUTIC CLASSIFICATION:** Priority Review

**INDICATIONS:** management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time

**CONSULTATION REQUEST DATE:** October 1, 2008

**DIVISION ACTION GOAL DATE:** December 30, 2008  
**PDUFA DATE:** December 30, 2008

## **I. BACKGROUND:**

NDA 22-321 is submitted by Alpharma Pharmaceuticals for EMBEDA Capsules, an extended-release oral formulation containing pellets of morphine sulfate, an opioid receptor agonist, with an inner core of naltrexone hydrochloride, an opioid receptor antagonist, for the proposed indication of the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The naltrexone hydrochloride core is designed to lower the abuse potential. This core is intended to have no clinical effect when EMBEDA Capsules are taken as directed, but when the formulation is tampered with by crushing or chewing, the naltrexone is rapidly released and absorbed. There is a clinical concern that the addition of naltrexone to the product could lower the treatment effect or increase the side effects of the product even when taken as directed by causing withdrawal symptoms.

The goals of the inspection were to assess adherence to FDA regulatory requirements concerning investigator oversight, protocol compliance, validity of primary efficacy endpoint data, and protection of subjects' rights, safety, and welfare. The number of subjects randomized and proportion discontinued in a particular site was taken into account in selecting sites for auditing.

The protocols inspected include:

- A. ALO-KNT-301 entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Efficacy Study of Kadian NT (Morphine Sulfate Plus Naltrexone Hydrochloride Extended-Release) Capsules in Subjects with Moderate to Severe Chronic Pain Due to Osteoarthritis of the Hip or Knee"
- B. ALO-KNT-302 entitled "A Long-Term, Open-Label, Safety Study of Kadian NT (Morphine Sulfate Plus Naltrexone Hydrochloride Extended-Release) Capsules in Subjects with Chronic Moderate to Severe Nonmalignant Pain"

Protocol ALO-KNT-301 was a randomized, double-blind, placebo-controlled study with a primary efficacy variable of change from baseline to Visit Y + week 12 of the Brief Pain Inventory (BPI) score of average daily pain. The BPI scale ranges from 0 (no pain) to 10 (pain as bad as you can imagine).

Protocol ALO-KNT-302 was an open-label, safety study of 12 month duration. Safety was assessed by the incidence of treatment-emergent adverse events (TEAEs), Clinical Opiate Withdrawal Scale (COWS) and other clinical parameters. For this Protocol, only the safety data and reasons for discontinuation were validated.

**II. RESULTS (by Site):**

<b>Name and Location of Clinical Investigator (CI) and Contract Research Organization (CRO)</b>	<b>Protocol # and # of Subjects</b>	<b>Inspection Dates</b>	<b>Final Classification</b>
CI #1 Devon Phillip Briggs, MD (b) (4)	Protocol ALO-KNT-301 17 Subjects	November 5 to 7, 2008 and November 12, 2008	Pending (Preliminary classification VAI)
CI #2 Christopher Chappel, MD (b) (4)	Protocol ALO-KNT-302 20 Subjects	November 17 to 18, 2008	Pending (Preliminary classification NAI)
CI #3 Steven Elliott, MD (b) (4)	Protocol ALO-KNT-302 16 Subjects	November 17 to 19, 2008	NAI
CI #4 Ritchard Fishman, MD (b) (4)	Protocol ALO-KNT-301 33 Subjects	November 18 to December 9, 2008	Pending (Preliminary classification OAI)
CI #5 Roberto Rodriguez, MD (b) (4)	Protocol ALO-KNT-301 36 Subjects	November 13 to 20, 2008	Pending (Preliminary classification VAI)
CRO (b) (4)	Protocol ALO-KNT-301	December 8 to 9, 2008	Pending (Preliminary classification NAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Devon Phillip Briggs, MD

(b) (4)

**Note:** Observations noted for this site are based on communications with the FDA inspector. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

- a. **What was inspected:** For Protocol ALO-KNT-301, there were 35 subjects screened at the site, 17 subjects enrolled, and 2 subjects completed the study. Records for all subjects were reviewed during the inspection.
- b. **General observations/commentary:** There was no evidence of under-reporting of adverse events. The reasons for study subject discontinuations were verifiable. Primary efficacy data could not be verified at the sites because of the trial design and data flow procedures. Daily BPI scores were transmitted directly to the CRO. At the conclusion of the trial, clinical sites were supplied with a compact disc (CD) containing the BPI data. Clinical sites had access to BPI data during the clinical trial, but no record of the BPI data was kept at the clinical site to verify the accuracy of the data on the CD provided by the sponsor to the site at the conclusion of the study.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the safety data generated by this site appear acceptable. Please see Section III below concerning the validity of the efficacy data.

2. Christopher Chappel, MD

(b) (4)

**Note:** Observations noted for this site are based on communications with the FDA inspector. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

- a. **What was inspected:** For Protocol ALO-KNT-302, there were 23 subjects screened at the site, 16 subjects were enrolled and 3 subjects completed the study. Records for all subjects were reviewed during the inspection. There was no evidence of under-reporting of adverse events. The reasons for subject discontinuations were verified.
- b. **General observations/commentary:** There was no evidence of under-reporting of adverse events. The reasons for subject discontinuations were verifiable.

- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the safety data generated by this site appear acceptable in support of the respective indication.

3. Steven Elliott, MD

(b) (4)

- a. **What was inspected:** For Protocol ALO-KNT-302, there were 18 subjects screened, 16 subjects were enrolled and 3 subjects completed the study. All subject records were reviewed during the inspection. There were 13 early terminations subjects due to adverse events, lack of efficacy, withdrawal of consent and failure to adhere to study requirements (positive for other pain medications.)
- b. **General observations/commentary:** There was no evidence of under-reporting of adverse events. The reasons for study subject discontinuations were verifiable.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the safety data generated by this site appear acceptable in support of the respective indication.

4. Ritchard Fishman, MD

(b) (4)

**Note:** Observations noted for this site are based on communications with the FDA inspector and the FDA Form 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

- a. **What was inspected:** For Protocol ALO-KNT-301, there were 55 subjects screened, 33 subjects were enrolled and 14 subjects completed the study. Sixteen subject records were reviewed during the inspection.
- b. **General observations/commentary:** There was no evidence of under-reporting of adverse events. The reasons for subject discontinuations were verifiable. Primary efficacy data could not be verified at the sites because of the trial design and data flow procedures. Daily BPI scores were transmitted directly to the CRO. At the conclusion of the trial, clinical sites were supplied with a compact disc (CD) containing the BPI data. Clinical sites had access to BPI data during the clinical trial, but no record of the BPI data was kept at the clinical site to verify the accuracy of the data on the CD provided by the sponsor to the

site at the conclusion of the study. There were the following regulatory violations:

- i) The inspection was classified by the FDA field investigator as OAI because of evidence of theft or diversion of the investigational drug. Two bottles of pills, totaling 45 pills were missing and a report of Lost Property was made to the Los Angeles County Sheriffs Department and the Department of Justice Drug Enforcement Agency.
- ii) Contemporaneous data collected at each subject's visit was not maintained by the site. This data was only available on compact disc which was provided to the site by the (b) (4) the contract research organization (CRO) after the close of the study.
- iii) The investigation was not conducted in accordance with the investigational plan:
  - a. In three instances, the eDiary was not reset between subjects. It appears that this error was corrected at the CRO.
    - i. Subject 1260001 completed the trial on 3/24/07, and additional BPI scores were reportedly entered on the same unreset eDiary by Subject 1260023 from 5/14-24/07.
    - ii. Subject 1260009 was a screen failure and additional BPI scores were reportedly entered on the same unreset eDiary by Subject 1260014.
    - iii. Subject 1260010 was a screen failure and additional BPI scores were reportedly entered on the same unreset eDiary by Subject 1260011.
  - b. For eleven subjects, certain study procedures were not performed. These included the following:
    - i. For subject 1260012 the Urine Drug Screen was not performed.
    - ii. Visit Y+1 study procedures were not performed as required by protocol. (For subject 1260053, the visit was not performed and for subject 1260001, medication was not dispensed correctly. COWS was not performed for subjects 1250001 and 1260035.)
    - iii. Visit Y+12 study procedures were not performed as required by protocol. (Weight, physical examination or safety laboratory tests were not performed for subjects 1260012, 1260014, 1260042 and 1260044. COWS not performed for subject 1260035.)
    - iv. Early termination COWS was not performed for subject 1260001.
    - v. Post treatment follow-up was not performed for subjects 1260014, 1260044 and 1260050, and was out of window for subject 1260004.
    - vi. Subject 1260045 was continued in the study while on ibuprofen even though this was a prohibited medication.

- c. **Assessment of data integrity:** The safety data generated by this site appear acceptable. Please see Section IV below concerning the validity of the efficacy data.

5. Roberto Rodriguez, MD

(b) (4)

**Note:** Observations noted for this site are based on communications with the FDA inspector. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

- a. **What was inspected:** For Protocol ALO-KNT-301, 36 subjects were screened, 24 subjects were enrolled and 18 subjects completed the study. All subject records were reviewed during the inspection.
- b. **General observations/commentary:** There was no evidence of under-reporting of adverse events. The reasons for subject discontinuations were verifiable. Primary efficacy data could not be verified at the sites because of the trial design and data flow procedures. Daily BPI scores were transmitted directly to the CRO. At the conclusion of the trial, clinical sites were supplied with a compact disc (CD) containing the BPI data. Clinical sites had access to BPI data during the clinical trial, but no record of the BPI data was kept at the clinical site to verify the accuracy of the data on the CD provided by the sponsor to the site at the conclusion of the study. There were the following regulatory violations:
- i) The clinical investigator (CI) did not maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. Specifically data collected in the electronic diaries was transmitted to (b) (4) the contract research organization (CRO), and no copies were retained at the clinical site. At the conclusion of the trial, access to this data was terminated and the clinical site was provided with a copy of the final data on a compact disc (CD). It is not possible to compare the data contained on the CD with data that was entered into the system.
  - ii) An investigation was not conducted in accordance with the investigational plan because eligibility criteria were not reviewed for three subjects (11YZ, 12 SPC and 14 ZR), for subject 0017YR maintenance visits were conducted out of the window on seven occasions, and for subject 005 the Clinical Opiate Withdrawal Scale (COWS) was not obtained on visit Y.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the safety data generated by this site appear acceptable. Please see Section IV below concerning the validity of the efficacy data.

6.

(b) (4)



**Note:** Observations noted for this site are based on communications with the FDA inspector. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

- a. **What was inspected:** For Protocol ALO-KNT-301, the FDA inspector reviewed the contract / scope of work document, written procedures, the 161 page HelpDesk call log, and the 22 corrective action reports generated when they were requested to correct database records after errors by site personnel. BPI values reported by two or three subjects at each of the three sites were compared with the data listings.
- b. **General observations/commentary:** No regulatory violations were cited during the inspection.
- c. **Assessment of data integrity:** The FDA inspection was not completed in accordance with directions provided by DSI and, as a result, did not include procedures to validate the primary endpoint adequately. The audit trails on the CDs supplied to the CIs at the conclusion of the study are not sufficient to ensure validity of the efficacy data.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Concerning data integrity, safety data from all sites appear acceptable in support of the proposed indication. Due to limitations of the inspection of (b) (4), we have insufficient information to determine whether the efficacy data are acceptable in support of the application.

The inspections of Drs. Fishman, Briggs, and Rodriguez found regulatory violations as noted above concerning inadequate recordkeeping due to the deficiency in the trial design that did not require contemporaneous retention of the data downloaded from the eDiaries.

The final classifications for all sites except Dr. Elliot's are pending. An addendum to this clinical inspection summary will be forwarded to the review division should additional observations of clinical and regulatory significance, resulting in a change in these recommendations, be discovered after reviewing the EIRs.

*{See appended electronic signature page}*

Susan Leibenhaut, MD  
Good Clinical Practice Branch I  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Constance Lewin, MD, MPH  
Branch Chief  
Good Clinical Practice Branch I  
Division of Scientific Investigations

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**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

## Memorandum

**Date:** December 17, 2008

**To:** Christopher Hilfiger - Regulatory Project Manager  
Division of Anesthesia, Analgesia, and Rheumatology Products  
(DAARP)

**From:** Mathilda Fienkeng, Pharm.D. – Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications.  
(DDMAC)

**Subject:** **DDMAC draft labeling comments**  
NDA 22-321 Embeda (morphine sulfate extended-release with  
sequestered naltrexone hydrochloride) Capsule for oral use C-II

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DDMAC has reviewed the proposed product labeling (PI) for Embeda (morphine sulfate extended-release with sequestered naltrexone hydrochloride) Capsule for oral use C-II (Embeda), submitted for consult on December 09, 2008. DDMAC notes that on April 18, 2008, it previously provided comments regarding the proposed label for Embeda (version sent April 9, 2008).

The following comments are provided using the updated proposed PI forwarded on December 08, 2008. These comments specifically pertain to the information in the PI that is directed to healthcare professionals. Comments regarding the consumer portion will be provided in a separate document.

### **GENERAL**

1. As presented, the label includes multiple versions of the tradename including:
  - *Embeda (morphine sulfate extended-release with sequestered naltrexone hydrochloride) Capsule for oral use.*
  - *EMBEDA Capsules*
  - *EMBEDA<sup>TM</sup> Capsule*

DDMAC recommends revising the PI to present the proposed tradename in a more consistent manner

2. The term (b) (4) and (b) (4) is used throughout the proposed PI. These terms are promotional in tone and we recommend either providing context or deleting them entirely.

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Mathilda Fienkeng  
12/17/2008 10:51:20 AM  
DDMAC REVIEWER

MEMORANDUM

Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research

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**Date:** December 2, 2008

**To:** Bob Rappaport, M.D., Director  
Division of Anesthesia, Analgesia and Rheumatology Products

**Through:** Michael Klein, Ph.D., Director  
Silvia Calderon, Ph.D., Team Leader  
Controlled Substance Staff

**From:** James M. Tolliver, Ph.D., Pharmacologist  
Controlled Substance Staff

**Subject:** NDA 22-321 EMBEDA (Morphine sulfate extended-release with Sequestered naltrexone hydrochloride) 20, 30, 50, 60, 80, and 100 mg Capsules.

**Indication:** Management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

**Company:** Alpharma Pharmaceuticals LLC (Alpharma)

**Submission:** NDA 22-321 is located in the EDR. CSS reviewed the following documents from the NDA:

- 1) *A Randomized, Double-Blind, Triple-Dummy, Single-Dose, Four-Way Crossover Study to Determine The Relative Bioavailability, Pharmacodynamic Effects and Safety of Equivalent Oral Doses of Whole and Crushed ALO-01 Versus Morphine IR in Opioid Experienced, Non-Dependent Subjects (ALO-01-07-205);*
- 2) *A Randomized, Placebo-Controlled, Double-Blind, Single-Dose, Three-Way Crossover Study to Determine the Relative Drug-Liking/Euphoria Effects of Intravenous Morphine Alone Or In Combination With Naltrexone in Opioid Experienced, Non-Dependent Male Subjects (ALO-01-07-106).*

(b) (4)



This review provides conclusions and recommendations to the Division of Anesthesia, Analgesia, and Rheumatology Products regarding the abuse potential and deterrent properties of EMBEDA.

### **Background:**

Alpharma has filed NDA-22-321 in support of the new product EMBEDA. This product combines extended-release morphine with sequestered naltrexone in polymer-coated, extended release pellets. This formulation is intended to be bioequivalent to the currently marketed KADIAN Capsules, with respect to the extended release properties of morphine sulfate. EMBEDA will be available as capsules containing 20, 30, 50, 60, 80 and 100 mg of morphine sulfate. Oral administration of the intact capsule is purported to result in the extended release from the pellets of morphine, but not the naltrexone. However, upon either crushing or chewing of the capsules, both morphine and the sequestered naltrexone are purportedly released thereby reducing or eliminating the effects, including euphoria, generally associated with morphine administration.

Data from the National Survey on Drug Use and Health (NSDUH), the Drug Abuse Warning Network (DAWN) and the Treatment Episodes Data Set (TEDS) show that the nonmedical use or abuse of prescription opioids is a significant problem in the United States. Increased rates of opioid-related mortality and admissions to emergency room departments and publicly funded substance abuse treatment facilities are reported.

Information on routes of administration involved in the nonmedical use or abuse of prescription opioids, including morphine products, is limited. A few literature articles report that ingestion, <sup>(b) (4)</sup> and intravenous injection are the main routes by which prescription morphine-containing products are used nonmedically<sup>1</sup>. Extended release formulations containing large amounts of opioids may undergo tampering by crushing or dissolution resulting in the release of large doses of drug. <sup>(b) (4)</sup>

### **Conclusions<sup>2</sup>**

CSS has reviewed the data provided by the Sponsor concerning the abuse resistant properties of EMBEDA. CSS has also reviewed the report on EMBEDA provided by the Division of Clinical Pharmacology and the Statistical Review and Evaluation report

<sup>(b) (4)</sup>

conducted by CDER's Office of Translational Sciences, Office of Biostatistics. Based upon these reviews, CSS concludes the following:

- Based on results of the naltrexone dose ranging study (ALO KNT 201), the Sponsor elected to use a ratio of naltrexone to morphine of 1:25 in the product (b) (4). Using the VAS Drug Liking Scale, this ratio resulted in a reduction of the maximum morphine-induced positive drug liking by at least 30% in 56% of subjects who completed the naltrexone dose ranging study. These results indicate that the amount of naltrexone available in the finished EMBEDA product will, upon crushing, produce only a limited reduction of the euphoric effects produced by morphine. Individuals taking crushed EMBEDA can still expect to experience a euphoric effect.
- Statistical analysis<sup>3</sup> of ALO-01-06-106 suggests that naltrexone in a ratio to morphine of 1:25, decreases up to two-thirds the euphoric effects produced by morphine when both are intravenously administered. This suggests that should one attempt to intravenously inject crushed EMBEDA, the released naltrexone would reduce somewhat the euphoria produced by the morphine.
- Statistical analysis<sup>3</sup> of ALO-01-07-205 suggests that the naltrexone available in EMBEDA can diminish some of the euphoria induced by morphine when EMBEDA is crushed and ingested. This study also shows, however, that the ingestion of either whole or crushed EMBEDA still produces a euphorogenic effect that is significantly larger than placebo and, in the case of some subjects, may approach or equal the euphorogenic effects produced by ingestion of immediate release morphine sulfate. Collectively, these results suggest that EMBEDA, both intact and crushed, retains a substantial abuse potential following oral administration.
- In vitro extraction studies show that:
  - Regardless of solvent used, crushing of EMBEDA pellets results in the immediate release or dumping of naltrexone, thereby increasing the difficulty of using crushed pellets to extract pure morphine for abuse purposes.
  - (b) (4)
  - 
  - 
  -

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<sup>3</sup> Statistical analysis of ALO-01-06-106 and ALO-01-07-205 was completed on November 5, 2008 by CDER's Office of Translational Sciences, Office of Biostatistics.

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- The concomitant ingestion of EMBEDA with 40% ethanol, but not 4% or 20% ethanol, resulted in limited dumping of morphine, but not naltrexone. Compared to EMBEDA administered with water, in the presence of 40% ethanol, the mean morphine C<sub>max</sub> value was approximately 2-fold higher, while the time (T<sub>max</sub>) to reach C<sub>max</sub> was decreased by half (from 8-9 hours to 4 hours). This dose dumping effect seen with EMBEDA contrasts to the lack of dose dumping observed with KADIAN in the presence of different concentrations of ethanol.<sup>4</sup>
- EMBEDA has not been directly compared to KADIAN in any of the extraction or human abuse potential studies conducted by the Sponsor.

### **Recommendations**

In order to more thoroughly evaluate the abuse potential and tamper resistant properties of EMBEDA, CSS recommends the Sponsor to conduct studies to provide the following:

- Percentage of morphine and naltrexone extracted from EMBEDA and morphine from KADIAN in water, and in 4%, 20% and 40% alcohol solutions or beverages for 30 min, 1 hour, 3 hours, 6 hours, 12 hours and 24 hours.
- Data from human abuse liability studies comparing the subjective effects, including euphorogenic and drug liking effects of EMBEDA (whole and crushed), to KADIAN (whole and crushed) Capsules.
- In addition, the Sponsor should provide a proposal on how it is planning to measure the impact of the addition of naltrexone in reducing the actual abuse of extended release oral morphine formulations, particularly considering that, at least according to DAWN, the abuse of KADIAN appears to be low.

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<sup>4</sup> Johnson et al (2008). Journal of Pain, 9 (4): 330-336.

## **Review:**

CSS has reviewed the data regarding the abuse liability and tamper resistant properties of EMBEDA. In addition to reviewing the reports provided by Alpharma, CSS reviewed the report on EMBEDA generated by the Division of Clinical Pharmacology, within the Office of New Drugs in CDER. For review of the studies ALO-01-07-106 and ALO-01-07-205, CSS relied upon the statistical analysis conducted by the Office of Translational Sciences, Office of Biostatistics within CDER.

### Naltrexone Dose Ranging Study (ALO KNT 201)

A restricted-randomized, double-blind, cross-over, placebo-controlled study was conducted with the primary objective to determine the appropriate naltrexone to morphine ratio required to abate the euphoric effects of morphine in opiate experienced, non-dependent recreational drug users. Twenty-seven subjects were used in this study. Treatments included oral administration of morphine (120 mg oral solution) with 2.4, 4.8, 9.6, 19.2 or 38.4 mg of naltrexone. Other treatments included morphine (120 mg as oral solution) alone and a placebo (no morphine or naltrexone).

The primary variables used to examine positive subjective effects were changes in the following scales as summarized by peaks, mean and the AUC: 1) VAS Drug Effect Questionnaire (DEQ) for liking; 2) Subjective Drug Value; 3) Addiction Research Center Inventory (ARCI) – Morphine Benzadrine Group; 4) Cole/ARCI Abuse Potential; and 5) Cole/ARCI Stimulation-Euphoria.

Using the various subjective scales, morphine oral solution (120 mg) was found to produce significant elevations for all variables (drug liking, euphoria, abuse potential) compared to placebo. With increasing doses of naltrexone there was a corresponding decrease in morphine-induced positive effects. Naltrexone 4.8 mg, representing a naltrexone to morphine ratio of 1:25, was the lowest dose that reliably (statistically or marginally significant) attenuated morphine induced euphoria. Using the VAS Drug Liking scale, 4.8 mg naltrexone reduced the maximum morphine-induced positive measure by at least 30% in 56% of subjects who completed the study.

In the study, negative drug effects were also assessed using the following scales: 1) VAS Bad Effects; 2) VAS Feeling Sick; 3) VAS Nausea; 4) ARCI LSD; 5) Cole/ARCI Unpleasantness Dysphoria; and 6) Cole/ARCI Unpleasantness Physical. Collectively using these scales, morphine (120 mg oral solution) alone was associated with negative effects which peaked at approximately 6 to 8 hours post dose. Administration of naltrexone with morphine tended to reduce morphine-induced negative effects. However, differences among the naltrexone treatments were not significant with respect to negative effects of morphine.

This study established the naltrexone to morphine ratio of 1:25 for purposes of product development. This ratio constituted the lowest dose of naltrexone (4.8 mg) that reliably provided limited (30%), and not full, attenuation of morphine induced euphoria in some

but not all subjects. A product formulated with this ratio of naltrexone to morphine would be expected to still produce some morphine-induced euphoric effects, and thereby continue to have an abuse potential.

Pharmacokinetics and Pharmacodynamic Effects of Oral Administration of Intact and Crushed ALO-01 Capsules Compared to Immediate Release Morphine and to Placebo – (Protocol Number ALO-01-07-205).

For evaluating ALO-01-07-106, CSS utilized the statistical analysis conducted by FDA/CDER Office of Translational Sciences, Office of Biostatistics. Both group statistical analysis and individual response data analysis were used.

A randomized, double-blind, triple-dummy, single-dose, four-way crossover study was conducted to determine the relative pharmacodynamics, pharmacokinetics and safety of orally administered crushed and whole ALO-01 compared to morphine sulfate immediate release (MSIR) and to placebo and of crushed ALO-01 to whole ALO-01. Thirty-two opioid experienced, non-dependent subjects were used in this study. All 32 subjects received all doses of the study drugs and completed all treatment sessions of the study without any major protocol violation.

Individuals selected for the study were required to tolerate a single oral dose of MSIR (120 mg) and to distinguish between a single oral dose (120 mg) of morphine and placebo on at least four of the following six measures: Visual Analog Scale (VAS) for Drug Liking, VAS for Overall Drug Liking, VAS for High, VAS for Good Effects, Addiction Research Center Inventory (ARCI)-Morphine-Benzedrine Group (MBG), and Subjective Drug Value (SDV).

ALO-01 (crushed and whole) and MSIR solution were dissolved in apple juice and administered as active drugs, while matching placebo capsules and apple juice were administered as placebo. Treatment groups included: 1) whole ALO-01 [2 x (60 mg morphine + naltrexone)]; 2) crushed ALO-01 [2 x (60 mg morphine + naltrexone)]; 3) MSIR solution (120 mg); and 4) placebo. Subjects were randomized to a treatment sequence based on a computer generated randomization schedule. Treatment sequence was according to a Williams Square design.

The primary endpoints of this study included the Drug Liking Visual Analogue Scale, Cole/ARCI Stimulation Euphoria Scale, Cole/ARCI Abuse Potential, Subjective Drug Value, ARCI MBG, and pupillometry.

Descriptive statistics including the mean, standard deviation, minimum (Min) response, first quartile (Q1), median (Med), third quartile (Q3) and maximum (Max) response for each treatment for each of the primary endpoints are shown in Table 1 below. The descriptive statistics in the table were calculated based on change from predose E<sub>max</sub> for the endpoints except the endpoints Drug Liking VAS and Subjective Drug Value for

which the calculation was based on Emax. Analysis of statistical significance among treatment pairs is provided in Table 2.

As can be seen in Tables 1 and 2, the mean VAS drug liking scores for ALO-01 whole and ALO-01 crushed ( $67.59 \pm 13.12$  and  $68.06 \pm 17.51$ , respectively) were significantly higher when compared to placebo ( $52.19 \pm 4.51$ ) but significantly lower when compared to 120 mg MSIR solution ( $89.47 \pm 12.63$ ). By contrast there was no difference between ALO-01 whole and ALO-01 crushed with respect to mean VAS liking scores suggesting that the naltrexone released upon crushing was successful in negating some of the euphoria produced by morphine.

However, examination of individual responses to the various treatments revealed wide variation of responses. Although the majority of individuals showed a decreased drug liking score compared to morphine solution alone when given either intact or crushed ALO-01, a small number of individuals displayed drug liking scores similar to those produced by MSIR solution when given either intact or crushed ALO-01.

As seen in Tables 1 and 2, based on the analysis of the responses to other primary scales (Cole/ARCI Stimulation-Euphoria Scale, Cole/ARCI Abuse Potential, Subjective Drug Value and ARCI MBG), the administration of ALO-01 whole or crushed resulted in statistically significant lower euphoric effects when compared to the MSIR, but significantly higher euphoric effects when compared to placebo. No significant differences between crushed and whole ALO-01 was found for any of the PD measures of interest.

Although ALO-01 both crushed and whole had lower mean and median responses than MSIR, for most endpoints, they had the same maximum responses as MSIR. This, again, reflects the wide variation in euphoric responses when measuring subjective scales..

A number of secondary endpoints were examined in the study. One of these endpoints, Bad Drug Effects VAS, was reviewed by CSS. The descriptive statistics are shown in Table 1. Treatment with either ALO-01 whole or ALO-01 crushed resulted in significantly lower mean and median scores for bad drug effects when compared with MSIR but significantly higher scores when compared to placebo treatment.

Table 1. Descriptive Statistics Conducted in Primary Endpoints for Clinical Study ALO-01-05-205 Submitted Under NDA 22321. Statistical analyses were conducted by CDER's Office of Translational Sciences, Office of Biostatistics.

Endpoint	TRT	Mean	Std Dev	Min	Q1	Median	Q3	Max	
Primary Endpoints	VAS Drug Linking	A	68.06	17.51	50	51.25	62	79.5	100
		B	67.59	13.12	51	56.25	66	74.75	100
		C	89.47	12.63	57	81.75	92.5	100	100
		D	52.19	4.51	50	51	51	51	75
	Subjective Drug Value	A	13.72	16.98	0.25	0.25	4.75	20.38	48
		B	14.22	15.46	0.25	1.06	8.25	20.38	48
		C	28.85	14.55	0.25	20.75	29.25	39.94	48
		D	2.73	7.08	0.25	0.25	0.25	0.25	26.75
	ARCI MBG*	A	9.53	10.41	0	1	5	16.5	35
		B	7.50	10.03	0	0	3	14.25	36
		C	17.28	10.91	0	8	18.5	27.75	36
		D	4.13	6.20	0	0	2	3.75	22
	Cole/ARCI Abuse Potential†	A	4.72	4.37	0	1	3.5	8	16
		B	4.28	3.52	0	2	3.5	6	14
		C	6.81	4.12	0	4	5.5	11	16
		D	1.84	2.44	0	0	1	3	12
	Cole/ARCI Stimulation—Euphoria	A	8.44	9.07	0	1	5	14.75	34
		B	7.09	9.65	0	0	3	11	36
		C	15.25	10.51	0	6	14	25	32
		D	4.28	6.35	0	0	2.5	4	22
Pupil Diameter (P/Min)	A	2.07	0.91	0.3	1.4	2	2.98	3.6	
	B	2.08	1.07	0	1.2	2.3	2.85	3.9	
	C	2.71	1.05	0.9	1.73	2.85	3.4	5.1	
	D	0.79	0.50	0.1	0.33	0.75	1.25	1.9	
Secondary Endpoints	VAS High*	A	54.66	34.48	0	17.25	64	82.5	100
		B	60.22	30.47	0	49.5	68.5	81.75	100
		C	90.22	11.68	61	81.5	97	100	100
		D	12.66	23.49	0	0	1	10.25	70
	VAS Bad Drug Effects	A	20.91	31.63	0	0	2	41.75	100
		B	23.13	31.49	0	0	5.5	49.5	100
		C	35.66	34.63	0	0	36.5	63.25	100
		D	8.03	17.52	0	0	0	3.5	51

\* Results are based on change from predose Emax

Treatment- A: ALO-01 crushed; B: ALO-01 whole; C: MSIR; D: Placebo

Table 2. Pairwise comparisons of treatment differences in mean Emax (or median change from predose Emax): p-values. Statistical analyses were conducted by CDER's Office of Translation Sciences, Office of Biostatistics.

Comparison	Primary Endpoint						Secondary	
	Liking	Euphoria	Potential	Value	MBG	Pupil	Bad**	High
C > D (Validation)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
A ≠ B	0.7143	0.4410	0.5366	0.8622	0.2152	0.2109	0.7126	0.3318
A > D	<0.0001	0.0019	<0.0001	0.0001	0.0005	<0.0001	0.0001	<0.0001
B > D	<0.0001	0.01525	0.0002	<0.0001	0.0149	<0.0001	0.0025	<0.0001
A < C	<0.0001	<0.0001	0.0005	<0.0001	<0.0001	<0.0001	0.0230	<0.0001
B < C	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0170	<0.0001
W-test p-value***	0.2662	0.8990	0.2823	0.0831	0.9118	0.8663	0.0010	0.4876

Liking: Drug Liking VAS  
 Euphoria: Cole/ARCI-Stimulation-Euphoria Scale  
 Potential: Cole/ARCI-Abuse Potential  
 Value: Subjective Drug Value  
 MBG: ARCI MBG  
 Bad: Bad Drug Effects VAS  
 High: High VAS  
 Pupil: Pupillometry  
 \* Null hypotheses are listed on page 9  
 \*\* P-values from Wilcoxon signed rank test  
 \*\*\* P-values from Shapiro-Wilk test  
 A: ALO-01 crushed  
 B: ALO-01 whole  
 C: MSIR  
 D: Placebo

Pharmacokinetics and Pharmacodynamic Effects of Intravenous (i.v.) Administrations of Morphine and Naltrexone – (Protocol Number: ALO-01-07-106)

For evaluating ALO-01-07-106, CSS utilized the statistical analysis of this study conducted by FDA/CDER Office of Translational Sciences, Office of Biostatistics.

A randomized, placebo-controlled, double-blind, single-dose, three-way crossover study was conducted for the primary objective of determining the relative drug-liking and euphoric effects of i.v. morphine alone to i.v. morphine combined with i.v. naltrexone following i.v. bolus doses. The rationale for the study was to simulate and characterize the effect of naltrexone on the pharmacodynamic profile of morphine if the oral dosage form was crushed and injected.

This study was conducted in 26 opioid experienced, non-dependent males. In order to determine that subjects were not opioid dependent, all subjects were subjected to an i.v. naloxone challenge in which they received a total of 0.4 mg i.v. naloxone. Subjects also were required to distinguish 10 mg i.v. morphine from placebo during the drug discrimination phase of the study which took place on days 1 and 3 of the study.

The dose ratio of i.v. morphine (30 mg) to i.v. naltrexone (1.2 mg) was the same as that found in a 30 mg capsule of ALO-01. Placebo consisted of sodium chloride 0.9% sterile diluent. The treatment phase constituted day 5 to day 19 of the study. Subjects were randomized to one of three sequential treatment doses using a crossover design. Each treatment dose was followed by a six day washout period. The treatments given included: 1) a single 30 mg i.v. dose of morphine plus a single i.v. naltrexone placebo; 2) a single 30 mg i.v. dose of morphine plus a single 1.2 mg dose of i.v. naltrexone; and 3) a single i.v. dose of morphine placebo plus a single i.v. naltrexone placebo.

For purposes of evaluating relative drug-liking and euphoric effects, the Drug Effects Questionnaire (DEQ) question #5, "How high are you now?" using a visual analog scale (VAS) of 0 to 100, was the primary pharmacodynamic endpoint in the study. A secondary endpoint for euphorogenic effects utilized the Cole/ARCI Stimulation Euphoria Scale (Emax), having a scale of 0 to 45.

The i.v. injection of naltrexone in combination with morphine was found not to affect the pharmacokinetics of morphine as measured in plasma. Based on partial areas under the curve (AUC), approximately 55% of the exposure to plasma morphine occurred in the first two hours and approximately 83% was achieved by 8 hours post dose.

Using the DEQ question #5 as the primary endpoint, it was found that treatment with placebo produced no effect in the subjects. By contrast, the i.v. administration of morphine alone or morphine + naltrexone (25:1) resulted in a significant maximum high (Emax) compared to placebo. However, when compared to placebo, the mean and median scores for maximum high were approximately 2.75 and 3.93 times higher following i.v. administration of morphine alone versus i.v. administration of morphine + naltrexone ( $85.31 \pm 13.09$  versus  $30.92 \pm 26.26$  for mean Emax, and 88.5 versus 22.5 for medians). Examination of individual response data, showed that approximately 69% (18/26) of subjects had at least 50% reduction in Emax High VAS by taking i.v. morphine with i.v. naltrexone compared to taking i.v. morphine alone, and approximately 54% (14/26) of the subjects had at least 70% reduction.

A reduction in morphine-induced (i.v.) maximum high produced by i.v. naltrexone was also observed utilizing the Cole/ARCI Stimulation Euphoria Scale. Using this secondary endpoint, the i.v. administration of either morphine alone or morphine + naltrexone (25:1) resulted in a significant mean Emax for euphoria, when compared to placebo. However the maximum euphoria produced by i.v. morphine alone was approximately 2-fold greater than that produced by morphine + naltrexone.

Collectively these data indicate that naltrexone was effective in reducing the euphoric effects produced by morphine when both are intravenously injected in a morphine/naltrexone ratio of 25:1. It should, however, be kept in mind that this study utilized i.v. solutions of morphine and morphine + naltrexone and not solutions derived from crushed ALO-01 capsules. With i.v. injection of the crushed contents of ALO-01

capsules it would be anticipated that the naltrexone would reduce, but not completely mitigate the euphoric effects produced by morphine.

Extraction Studies



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### Interactions with Alcohol Ingestion

An open-labeled, randomized, single-dose, 4 way crossover, 4 sequence pharmacokinetic drug interaction study between ALO-01 60 mg capsules and alcohol, was performed following their administration under fasting conditions in 32 healthy adult volunteers. The following four dosage regimens were administered: A) ALO-01 60 mg capsules with 4% ethanol; B) ALO-01 60 mg capsule with 20% ethanol; C) ALO-01 60 mg capsule with 40% ethanol; and 4) ALO-01 60 mg capsule with water. Blood samples were collected before dosing and at selected times up to 48 hours for morphine plasma determinations and to 168 hours for plasma levels of naltrexone and 6beta-naltrexol. Pharmacokinetic parameters monitored included area under the curve (AUC), maximum plasma concentration (C<sub>max</sub>), time to reach maximum plasma concentration (T<sub>max</sub>), plasma half-life (t<sub>1/2</sub>) and apparent first-order terminal elimination rate constant (k<sub>el</sub>). Subjects were monitored for adverse reactions to the study dosage regimens at screening and throughout the study.

It was found that the concomitant administration of either 4% or 20% alcohol with an ALO-01 60 mg capsule did not have any effect on the plasma levels of morphine over time. For both of these treatments, the pharmacokinetic parameters were similar to that of an ALO-01 60 mg capsule administered with water.

By contrast, the concomitant administration of 40% alcohol with an ALO-01 60 mg capsule did produce significant alterations to the plasma morphine concentration time profile. Compared to ALO-01 administered with water, in the presence of 40% alcohol the mean C<sub>max</sub> value was approximately 2-fold higher. In addition, with 40% alcohol the time (T<sub>max</sub>) to reach C<sub>max</sub> was significantly reduced from approximately 8-9 hours to 4 hours. Other pharmacokinetic parameters with respect to the plasma morphine time profile were not affected by 40% alcohol. These results show that with the concurrent administration of 40% alcohol both the rate and extent of bioavailability increased as reflected by the more rapid release of morphine from the ALO-01 capsules thereby achieving abnormally high plasma morphine concentrations. This dose dumping effect was selective for morphine considering that the concomitant administration of either 4%, 20% or 40% alcohol had no effect on the sequestration of naltrexone.

The concomitant administration of ethanol with ALO-01 capsules produced dose related increases of reported adverse events. The most frequently reported adverse events were headache, nausea, vomiting, dizziness and poisoning. Other adverse events included abdominal pain, pallor, loss of consciousness, fatigue, pruritus generalized, euphoric mood, peripheral coldness and photophobia. During the study 23 out of 32 total subjects reported a total of 226 adverse events of which 172 were considered related to the study medication. Adverse events were reported after dosing with all treatments. Both the number of reported adverse events and the number of individuals reporting these events

were similar between the ALO-01 plus water and ALO-01 plus 4% ethanol treatment groups. Upon increasing the ethanol dose to 20% and 40%, there was approximately a 3.5 and 5.5 fold increase, respectively, in the number of adverse events reported. The number of individuals reporting these events also increased at the higher ethanol doses (12 in water treatment group, 16 in 20% ethanol treatment group and 20 in the 40% ethanol treatment group).

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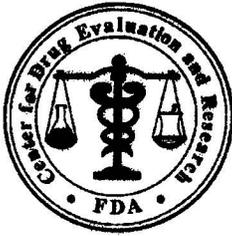
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James Tolliver  
12/2/2008 01:12:01 PM  
PHARMACOLOGIST

Silvia Calderon  
12/2/2008 01:49:45 PM  
CHEMIST

Michael Klein  
12/2/2008 02:28:33 PM  
PHARMACOLOGIST



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

**Date:** November 10, 2008

**To:** Bob Rappaport, MD  
Director, Division of Anesthesia, Analgesia, and Rheumatology Products

**Through:** Kellie Taylor, Pharm D, MPH, Team Leader  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

**From:** Richard Abate, RPh, MS, Safety Evaluator  
Division of Medication Error Prevention and Analysis

**Subject:** Label and Labeling Review for Embeda

**Drug Name(s):** 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, and 100 mg/4 mg

**Application Type/Number:** NDA 22-321

**Applicant/sponsor:** Alpharma Pharmaceuticals

**OSE RCM #:** 2008-1209

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## **EXECUTIVE SUMMARY**

The Label and Labeling Risk Assessment findings indicate that the presentation of information on the container labels and insert labeling introduces vulnerability to confusion that could lead to medication errors. Specifically, we raise concerns with the prominence of and the colors used to present the product strengths on the container labels, the lack of units of measurement (mg) for the strengths used insert labeling, and the use of trailing zeros throughout the labels and labeling. The Division of Medication Errors Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

## **1 BACKGROUND**

### **1.1 INTRODUCTION**

This review is in response to a request from the Division of Anesthesia, Analgesia, and Rheumatology Products for the assessment of the container labels and insert labeling for Embeda (NDA # 22-321) for evaluation to identify areas that could lead to medication errors. The proposed proprietary name was evaluated in a separate review.

### **1.2 PRODUCT INFORMATION**

Embeda (morphine sulfate and naltrexone hydrochloride) extended-release capsules are indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The Applicant's proposed labels and labeling expresses the strength based on the morphine component of the product. However, an email from ONDQA on October 30, 2008 states the strength should include both drugs. The 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, and 100 mg/4 mg strength capsules will be dosed as one capsule by mouth once or twice daily. The capsules may be swallowed whole or opened and the contents sprinkled over apple sauce prior to administration. The bottles each contain 100 capsules and are stored at room temperature.

The capsules contain extended-release pellets of morphine sulfate with the naltrexone hydrochloride sequestered beneath the morphine sulfate layer. The design of the product is intended to result in no clinical effects from the naltrexone hydrochloride when the product is taken as directed. However, crushing, dissolving, or chewing the pellets within the capsules in an attempt to misuse or abuse the product results in the rapid release and absorption of both the morphine sulfate and naltrexone hydrochloride. The amount of naltrexone hydrochloride in the capsules is intended to not put opiate tolerate patients into opiate withdrawal.

The Division of Medication Error Prevention and Analysis safety evaluator sent an email to the chemistry reviewer in the Office of New Drug Quality Assessment (ONDQA) September 22, 2008 to confirm the expression of the strength for this product. The response was received October 30, 2008 confirming the product needs to express the strengths of both morphine sulfate and naltrexone hydrochloride on the labels (e.g. 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg and

100 mg/4 mg). In addition, they recommended the established name be “morphine sulfate and naltrexone hydrochloride.”

## **2 METHODS AND MATERIALS**

This section describes the methods and materials used by medication error prevention staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.<sup>1</sup>

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.<sup>2</sup>

Because our staff analyze reported misuse of drugs, we are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. The medication error prevention staff uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted on June 30, 2008 the following labels and insert labeling for medication error prevention review (see Appendix A for images):

- Retail Container labels: 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, and 100 mg/4 mg
- Prescribing Information (no image)

## **3 RESULTS**

Our review of the container labels and insert labeling notes vulnerabilities that may contribute to medication errors.

The amount of naltrexone contained in Embeda 50 mg/2 mg and 100mg/4 mg capsules appears on the container labels and in the insert labeling using trailing zeroes.

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<sup>1</sup> National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

<sup>2</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

### **3.1 CONTAINER LABELS**

The established name is not displayed in accordance with 21 CFR 201.10(g)(2). Specifically, the established name does not appear to be at least half the size font of the proprietary name.

The strength of the product and the "CII" designation for the controlled substance classification are the most prominent information on the container labels. Additionally, the strength inaccurately displays only the morphine component.

The font color used for the strengths 30 mg/1.2 mg (purple) and 50 mg/2 mg (blue) are very similar and difficult to distinguish.

The font colors used for the strengths 20 mg/0.8 mg (yellow) and 80 mg/3.2 mg (light peach) are poorly contrasted against the white background and difficult to read.

The units of measure, mg, is in a smaller sized font compared to the strength and appears super scripted above the strength.

The net quantity of 100 capsules is small and difficult to read.

### **3.2 INSERT LABELING**

The product strengths appear throughout the labeling without a unit of measure. This differs from the container labels which include the unit of measure, mg.

The strength of the combination drug should represent both components of the product, morphine sulfate and naltrexone hydrochloride.

## **4 DISCUSSION**

The results of the Label and Labeling Risk Assessment found that the presentation of information and design of the proposed carton labels as well the presentation of information in the insert labeling vulnerable to confusion that could lead to medication errors.

### **4.1 THE USE OF TRAILING ZEROS**

Trailing zeros, an error prone dose designation<sup>3</sup>, appear on the container labels as part of the capsule contents and in Section 3 (STRENGTHS AND DOSAGE FORMS) of the insert labeling using trailing zeroes for the amount of naltrexone in the 50 mg/2 mg and 100 mg/4 mg capsules. The Agency launched a campaign on June 14, 2006, warning healthcare practitioners and consumers not to use error prone abbreviations, acronyms, or symbols including trailing zeroes. As part of the campaign, FDA agreed not to use such error prone designations in their approved product labeling. Additionally, the use of terminal zeros in the expression of strength or volume is not in accordance with the General Notices (page 10) of 2004 USP, which states, "... to help minimize the possibility of error in the dispensing and administration of the drugs...the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that

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<sup>3</sup> [www.ismp.org](http://www.ismp.org), "ISMP's List of Error Prone Abbreviations, Symbols, and Dose Designations," The Institute of Safe Medication Practices, 2006.

is followed by a terminal zero." We further note that the use of trailing zeros are specifically listed as dangerous abbreviations, acronyms, or symbols in the 2008 National Patient Safety Goals of The Joint Commission.<sup>4</sup>

## **4.2 CONTAINER LABELS**

### ***4.2.1 Presentation of the Established Name***

The established name must be at least one half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).

### ***4.2.2 Product Strength***

Embeda, containing both morphine sulfate and naltrexone hydrochloride, is a combination drug per 21 CFR 300.50 (a)(2). The Federal Food, Drug and Cosmetic Act requires the quantity of each drug in the established name to be printed on the label. Although the capsule contents lists the amount of naltrexone HCl on the side panel of the container label, the strengths on the labels provided do not reference the mg amount of the of the naltrexone in each capsule.

Additionally, the current container labels presents the strength as the most prominent information. While this information is necessary for healthcare providers to fill and dispense prescriptions of Embeda, both the proprietary and the established names are utilized first to identify the product. We believe the proprietary name should be at least as prominent on the container label as the strength to increase the ability of healthcare practitioners to identify the product.

Moreover, the colors used for the strengths 20 mg/0.8 mg (yellow) and 80 mg/3.2 mg (light peach) capsules lacks sufficient contrast providing poor readability against a white background. The prominence of the strength adds little to the readability of this presentation.

### ***4.2.3 Visual Similarities of the Container Labels***

The blue and purple colors the Applicant uses to distinguish the 30 mg/1.2 mg and 50 mg/2 mg strengths, respectively, are very similar in appearance and therefore make the strengths appear similar. Pharmacy staff usually store products on the shelves in sequential order of the strengths of the products. We believe it is likely the 30 mg/1.2 mg and 50 mg/2 mg strengths of Embeda will be store near each other on the pharmacy shelf if not side by side. Thus, given all three failure modes (the similarity of the colors, proximity on the pharmacy shelf, and the overall visual similarity of the container labels), we believe the current presentation of the strengths will result in a wrong strength medication error involving the 30 mg/1.2 mg and 50 mg/2 mg strengths.

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<sup>4</sup> [www.jointcommission.org](http://www.jointcommission.org), Official Do Not Use List, The Joint Commission, 2008.

Additionally, the net quantity is of 100 capsules is small and difficult to read. Pharmacy staff use this number to complete the required inventories of controlled substances. Although an error in counting the inventory is not likely to reach the patient, it could impact the practice of the pharmacy or pharmacy staff.

#### **4.2.4 Placement of the Unit of Measure (mg)**

The unit of measure (mg) appears to the right and above the numeric strength of the product. In addition, the font size of the unit of measure is much smaller and inconsistent compared to the numeric strength. The proposed presentation of the unit of measure does not appear on the same horizontal plain as the numeric strength. The horizontal plain assists reader's eye to follow the information from left to right. Therefore, we believe this presentation will result in the unit of measure being overlooked by healthcare providers.

#### **4.3 INSERT LABELING**

The Applicant presents the strength of Embeda in the insert labeling without a unit of measure. The unit of measure should always accompany the numbers. This is inconsistent with the container labels which include mg as the unit of measure. This lack of needed information may be confusing to healthcare providers.

### **5 CONCLUSIONS AND RECOMMENDATIONS**

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container labels and insert labeling introduces vulnerability to confusion that could lead to medication errors. The Division of Medication Errors and Prevention believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

#### **5.1 COMMENTS TO THE DIVISION**

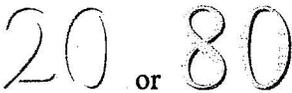
The Division of Medication Error Prevention and Analysis agrees with the Office of New Drug Quality Assessment regarding the recommended established name, Morphine Sulfate and Naltrexone Hydrochloride as well as the fact the strength needs to include both drugs as stated in an email dated October 30, 2008. Additionally, we have identified other areas of needed improvement and request the sponsor to be notified.

The Division of Medication Error Prevention and Analysis would appreciate feedback of the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the sponsor with regard to this review. If you have further questions or need clarifications, please contact Chris Wheeler, project manager, at 301-796-0151.

#### **5.2 COMMENTS TO THE APPLICANT**

The Division of Medication Error Prevention and Analysis has evaluated your container labels and insert labeling and requests you revise the following:

1. Embeda is a combination drug. The strength of a combination drug includes both the active ingredients it contains. Thus, the strengths of Embeda should be expressed as 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, and 100 mg/4 mg on all labels and labeling.
2. Container Labels
  - a. Revise the fonts of the proprietary and established names so that the established name is at least one half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).
  - b. Revise the prominence of the strength and the "CII" designation on the container label. We recommend that the font size used for the proprietary and established names be commensurate with the strength.
  - c. Revise the background and font colors used for the 30 mg/1.2 mg and 50 mg/2 mg strengths to more clearly differentiate these strengths.
  - d. Revise the presentation of the strengths for the 20 mg/0.8 mg and 80 mg/3.2 mg capsules to improve readability. (e.g. outline the numbers with black or other dark contrasting color.) The proposed color scheme does not provide sufficient color contrast against the white background.



20 . 80  
or
  - e. Revise the alignment of the unit of measure (mg) so that it appears in the same horizontal plane as the numeric strength.
  - f. Revise the font size of the unit of measure (mg) to be consistent with the font size of the numeric strength.
  - g. Eliminate the use of trailing zeroes, an error prone designation, throughout the labels and labeling. Present the amount of naltrexone as 2 mg and 4 mg in the 50 mg/2 mg and 100 mg/4 mg strength capsules, respectively.
  - h. Revise the prominence of the net quantity so that it is readable.
3. Insert Labeling
  - a. Add the unit of measure (mg) to the expression of the strengths throughout the insert labeling.

- b. Eliminate the use of trailing zeroes, an error prone designation, throughout the labels and labeling. Present the amount of naltrexone as 2 mg and 4 mg in the 50 mg/2 mg and 100 mg/4 mg strength capsules, respectively.

## **6 REFERENCES**

1. OSE Review #2008-1209, Proprietary Name Review for Embeda, Abate, R.

## **APPENDICES**

### **Appendix A: Retail Container Labels**

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Richard Abate  
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DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
11/10/2008 04:48:41 PM  
DRUG SAFETY OFFICE REVIEWER

**Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

**MEMORANDUM**

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**\*\*Pre-Decisional Agency Information\*\***

**Date:** April 18, 2008

**To:** Christopher Hilfiger – Regulatory Project Manager  
Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

**From:** Michelle Safarik, PA-C – Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**Subject:** DDMAC labeling comments for Embeda (morphine sulfate extended release with sequestered naltrexone hydrochloride) capsules  
NDA 22-321

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DDMAC has reviewed the proposed product labeling (PI) for Embeda (morphine sulfate extended release with sequestered naltrexone hydrochloride) capsules (Embeda) submitted for consult on March 18, 2008 (initial proposed PI) and April 9, 2008 (revised proposed PI).

DDMAC acknowledges this is 505(b)(2) application to Kadian (morphine sulfate extended-release) Capsules, CII (Kadian). We also acknowledge that DAARP informed the sponsor on April 10, 2008 of its likely decision of Refuse to File (RTF). A follow-up teleconference between DAARP and the sponsor was scheduled for April 17, 2008.

DDMAC's comments are provided using the revised proposed PI that was submitted on April 3, 2008. We assume the sponsor will re-file with this same label, but if not, we will be happy to evaluate any revised proposed labeling.

**Highlights**

**Indications and Usage**

1. As proposed, this section broadens the indication for Embeda. Therefore, we recommend including the important limitation to the indication (i.e., "Embeda is not indicated for acute/postoperative pain or if the pain is mild or not expected to persist for an extended period of time").

### **Dosage and Administration**

1. We recommend including context that Embeda 100 is only for use in opioid-tolerant patients, and that the pellets in the capsules are not to be crushed, dissolved, or chewed before swallowing.

### **Contraindications**

1. Per 21 CFR 201.57(c)(5), "Known hazards and not theoretical possibilities must be listed (e.g., if severe hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication)."

### **Warnings and Precautions**

1. As proposed, this section omits and minimizes the risks associated with Embeda therapy. Therefore, we recommend including more risk information from the Warnings and Precautions section of the proposed PI.

### **Adverse Reactions**

1. Is 10% an appropriate cutoff, since the most common adverse reactions of morphine therapy include more than constipation and nausea? As proposed, this section minimizes the risks of Embeda therapy.

### **Drug Interactions**

1. As proposed, this section minimizes the risks of Embeda therapy. Therefore, for consistency with the proposed PI, we recommend including "cimetidine" and "diuretics."

### **Full Prescribing Information**

#### **Boxed Warning**



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Michelle Safarik  
4/18/2008 09:27:13 AM  
DDMAC REVIEWER