

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-321

CROSS DISCIPLINE TEAM LEADER REVIEW



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANALGESIA, ANESTHESIA, AND RHEUMATOLOGY PRODUCTS
10903 NEW HAMPSHIRE AVENUE, BLDG 22, SILVER SPRING, MARYLAND 20993

Addendum to CDTL Memo
NDA 22-321
Embeda

DATE: July 7, 2009

REVIEWER Ellen Fields, M.D., M.P.H.
Clinical Team Leader
DAARP

DRUG EMBEDA extended release capsules (morphine sulfate/naltrexone): 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

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

Background

Alpharma submitted NDA 22-321 for Embeda (extended-release morphine sulfate and naltrexone) on ~~July~~^{June} 30, 2008, for the management of moderate to severe pain when a continuous around-the clock opioid analgesic is needed for an extended period of time. Embeda is a reformulation of Alpharma's previously approved product, Kadian (NDA 20-616), and was submitted as a 505(b)(2) application relying on previous findings of safety and efficacy for Kadian and Revia (NDA 18-932, naltrexone hydrochloride).

Embeda capsules are comprised of individual pellets containing morphine sulfate with a sequestered naltrexone hydrochloride inner core. According to the Applicant, if taken as prescribed, morphine is released in an extended-release profile. The opioid antagonist naltrexone is designed to remain sequestered in the core of each pellet. However, upon crushing or chewing of the pellets, both the morphine and naltrexone would be available and absorbed as an immediate-release dosage form. The Applicant maintains that the absorbed naltrexone will mitigate the drug-liking and euphoric effects of the morphine and will deter drug tampering and diversion. Due to the purported abuse-deterrent attributes of this formulation, the application was granted priority review status with a 6-month review clock.

Risk Evaluation and Mitigation Strategy

In accordance with section 505-1 of the FDCA, the Division determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for all modified-release opioids to ensure that the benefits of the drugs outweigh the risks, including, but not limited to the risks of: 1) use in non-opioid-tolerant individuals; 2) abuse; and 3) overdose, both accidental and intentional. To that end, the Division has been considering what REMS elements should be implemented across the class of modified-release opioids to address the risks of abuse, misuse, overdose, and addiction. Due to the large number of modified-release opioids on the market, it became clear that a single REMS for this class of drugs would be the most effective way to mitigate the risks of this group of medications while reducing the burden on the healthcare system.

As part of the filing communication sent to the Applicant on September 4, 2008, the Applicant was informed that a Risk Mitigation and Evaluation Strategy (REMS) would be necessary for the EMBEDA NDA. The Applicant submitted a proposed REMS on September 23, 2008, which was reviewed by the clinical team and the Office of Surveillance and Epidemiology (OSE). The reviewers concluded that this iteration of the Embeda REMS was not adequate to address the safety and safe use of the product, and did not meet the current standards that will be required for all modified-release opioids.

The PDUFA date for EMBEDA was December 30, 2008. At that time, the only outstanding review issue was the REMS. The Division did not take an action on the NDA, instead opting to work with the Applicant to formulate an appropriate REMS. It became clear to the Division and other parts of the Agency involved with the development of the "class REMS" for all modified-release opioids that development and implementation of the class REMS will be a lengthy process. It was determined that as there are existing modified-release morphine products on the market, and EMBEDA offered no novel risk, that an interim REMS could be implemented that would allow for approval of EMBEDA, as long as the Applicant was in agreement that they would adopt the larger modified-release opioid class REMS once it was developed.

A REMS information request letter was issued to the Applicant on April 30, 2009 stating that the REMS for EMBEDA should include a Medication Guide, a Communication Plan, and a Timetable for Submission of Assessments. The Communication Plan is to be targeted to healthcare providers who are likely to prescribe EMBEDA and will support implementation of the elements of the REMS. At a minimum, the Communication Plan should include the following as stated in the April REMS IR letter:

1. Educational materials for prescribers that address at least the following:
 - a) Proper patient selection
 - b) Appropriate product dosing and administration
 - c) General opioid use including information about opioid abuse and how to identify patients who are at risk for addiction
 - d) The risks of abuse, misuse, overdose, and addiction from exposure to opioids, including EMBEDA
 - e) The risks of EMBEDA including:
 - (1) The risk of overdose caused by exposure to an essentially immediate-release form of morphine due to breaking, chewing, crushing or dissolving EMBEDA
 - (2) The risk of overdose due to prescribing EMBEDA at doses of 100 mg/4 mg or greater to opioid non-tolerant patients
 - f) Information to counsel patients on the need to store opioid analgesics safely out of reach of children and household acquaintances
 - g) The importance of providing each patient a Medication Guide with each prescription and instructing the patient to read it.
2. A description of the audience for the communication plan, stating specifically the types and specialties of healthcare providers to which the communication plan will be directed as well as the professional medical associations and societies. These may include American Medical Association, American Pain Society, American Academy of Pain Medicine, American Academy of Family Physicians, American Academy of Physical Medicine and Rehabilitation, American Society of Anesthesiologists, American Osteopathic Association, American Academy of Neurology.
3. A schedule for when and how the plan's materials are to be distributed to healthcare providers and medical associations.

Refer to the April REMS IR letter for requirements regarding the REMS Assessment Timetable. It was determined that Elements to Assure Safe Use were not required for the EMBEDA REMS at this time.

The Applicant submitted a REMS proposal on June 5, 2009 which was reviewed by the review team. Comments regarding the contents of the REMS were then conveyed to the Applicant in a letter dated June 18, 2009. Since that time there have been ongoing discussions between the review team and the Applicant which has led to a final, acceptable REMS for EMBEDA that includes the required elements as discussed above.

Pediatrics

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. As a new combination, EMBEDA triggers the requirements under PREA.

On October 29, 2008, the Division met with the Pediatric Research Committee (PERC) and agreed upon the pediatric studies to be conducted to fulfill the PREA requirements. The pediatric plan is as follows:

- The pediatric study requirement for ages birth to less than two years will be waived because necessary studies are impossible or highly impracticable. This is because the number of pediatric patients with chronic pain in this age group is small.
- The pediatric studies for ages 2 to 17 years for this application will be deferred because this product is ready for approval for use in adults and the pediatric studies have not been completed.
- The 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. The required studies are listed below.
 1. Pediatric efficacy, safety, and pharmacokinetic (single- and multiple-dose) study 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.

Final report submission date: July, 2011

2. 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.

Final report submission date: February, 2012

An age-appropriate formulation must be developed for the youngest age groups. The age appropriate formulation should retain the extended-release properties of the adult formulation; however the abuse resistant aspects of the adult formulation do not have to be maintained. If this is not possible, the efforts regarding development of the formulation must be documented and submitted to the Agency.

Label

Final labeling, including carton and containers were agreed upon with the Applicant.

Recommended Regulatory Action

Approval

The implementation of the agreed upon REMS will adequately mitigate the risks associated with EMBEDA, so that the benefits of EMBEDA will outweigh the potential risks that accompany its use.

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

/s/

Ellen Fields
7/16/2009 03:35:34 PM
MEDICAL OFFICER

Cross-Discipline Team Leader Review

Date	December 11, 200 7 ⁸
From	Ellen Fields, M.D., M.P.H., Clinical Team Leader
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 22-321
Applicant	Alpharma
Date of Submission	July 30, 2007 June 30, 2008
PDUFA Goal Date	December 31, 2008
Proprietary Name / Established (USAN) names	Embeda/morphine sulfate extended-release and naltrexone hydrochloride
Dosage forms / Strength	Oral capsules/ 20mg, 30mg, 50mg, 60mg, 80mg and 100mg
Proposed Indication	Management of moderate to severe pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time
Recommended:	Approval

Material Reviewed/Consulted	
OND Action Package, including:	
Primary Medical Officer Review	Jin Chen, M.D., Ph.D.
Statistical Reviews	Katherine Meaker, M.S. Dionne Price, Ph.D. Thomas Permutt, Ph.D.
Clinical Pharmacology Review	Srikanth Nallani, Ph.D. Suresh Doddapaneni, Ph.D.
Pharmacology Toxicology Reviews	Elizabeth Bolan, Ph.D. Daniel Mellon, Ph.D.
CMC Reviews	Chikhale, Ph.D. Ali Al-Hakim, Ph.D.
DDMAC	Michelle Safarik, PA-C
DSI	Susan Leibenhaut
OSE/DMEPA	Richard Abate, RPh Kellie Taylor, Pharm D, MPH Denise Toyer, Pharm D Carol Holquist, RPh
OSE/DRISK	Pending
CSS	James Tolliver, Ph.D. Silvia Calderon, Ph.D. Michael Klein, Ph.D.

1. Introduction

Prescription drug abuse, specifically of opioid analgesics, is an escalating public health problem in the United States. The Agency has encouraged Sponsors to develop novel products that may mitigate this abuse while continuing to maintain the availability of these important drug products for the millions of patients who suffer from chronic pain. In response to this, some pharmaceutical manufacturers have been developing formulations of approved opioid moieties designed to be “abuse-resistant,” “tamper-resistant,” “abuse-deterrent” or of similar terminology.

There have been two opioid/antagonist combination products approved in the United States; Talwin NX (pentazocine/naloxone) approved in 1982, and Suboxone (buprenorphine/naloxone), approved in 2002. Neither has been formally evaluated regarding their effect on abuse. There is data to support that both products are still abusable despite the addition of an opioid antagonist.

The Agency has been clear that an explicit claim regarding reduced abuse liability will not be permitted into product labeling without compelling evidence from one or more large-scale, long-term epidemiology studies demonstrating a decrease in abuse accompanied by a benefit pertaining to drug-related morbidity and mortality in the community. The Agency has communicated to Sponsors that certain information related to the formulation may be included into appropriate parts of the label; however the specific language allowed in the label remains a review issue.

Alpharma submitted NDA 22-321 for Embeda (extended-release morphine sulfate and naltrexone) for the management of moderate to severe pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time. Embeda is a reformulation of Alpharma’s previously approved product, Kadian (NDA 20-616).

This is a 505(b)(2) submission 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).

Embeda capsules are comprised of individual pellets containing morphine sulfate with a sequestered naltrexone hydrochloride inner core. According to the Applicant, if taken as prescribed, morphine is released in an extended-release profile. The opioid antagonist naltrexone is designed to remain sequestered in the core of each pellet. However, upon crushing or chewing of the pellets, both the morphine and naltrexone would be available and absorbed as an immediate-release dosage form. The Applicant maintains that the absorbed naltrexone will mitigate the drug-liking and euphoric effects of the morphine and will deter drug tampering and diversion.

This review will discuss in detail the following issues related to this NDA submission:

- Findings regarding the efficacy and safety of Embeda as they relate to the proposed indication
- The pharmacokinetic properties of the formulation; intact and tampered

- Abuse liability associated with the intact and tampered formulation
- The potential impact of Embeda on mitigation of abuse

2. Background

The development of Embeda was conducted under IND 70,853. As previously stated, it is a Schedule II opioid analgesic (reformulation of Kadian extended-release morphine sulfate capsules) comprised of individual pellets containing morphine sulfate with a sequestered naltrexone hydrochloride inner core. The capsule strength is determined by the number of pellets within the capsule. The proposed indication is the same as that for Kadian; management of moderate to severe pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time.

In addition to Kadian, there are three other approved extended-release morphine products in the United States; MS Contin, Oramorph SR, Avinza and Kadian.

Both Pre-IND and Pre-NDA meetings were held during which the Applicant was advised regarding efficacy and safety data that would be required to support approval. The Division conveyed to the Applicant that even if Embeda is shown to be bioequivalent to Kadian, if under normal use there is any systemic exposure to naltrexone, one adequate and well-controlled efficacy trial would be required to demonstrate that the exposure to naltrexone does not affect the analgesic efficacy of Embeda or lead to withdrawal symptoms during normal use. In addition, the safety database must include at least 500 patients exposed to Embeda (100 for six months and 50 for one year). In order to obtain a labeled claim regarding a decrease in abuse potential for Embeda, a post-marketing epidemiologic study must be performed to provide evidence that in fact the product is associated with a decrease in abuse.

The Applicant sought to conduct their primary Phase 3 efficacy trial under a Special Protocol Agreement (SPA) which was accepted following three sets of revisions by the Applicant. The final agreement included the following major aspects of the study design: titration to effect followed by randomized withdrawal, primary endpoints (landmark change in pain intensity), and the primary analyses including imputation methods for missing data, and sensitivity analyses.

The clinical development plan also included studies to demonstrate the appropriate pharmacological ratio of naltrexone to morphine, and was intended to demonstrate that this ratio would mitigate the euphoric and drug liking effects of the immediate release of the entire morphine dose upon chewing or crushing. The low dose of naltrexone (up to 4mg per capsule) was not intended to protect an individual from an overdose of morphine. A clinical alcohol interaction study was also conducted.

To further evaluate the potential for oral or IV drug abuse, Embeda was subjected to laboratory extraction studies focusing on common solvents and extraction techniques.

This NDA was initially submitted on February 28, 2008; however filing was refused due to deficiencies in the safety database. The NDA was resubmitted on June 30, 2008, and accepted for review.

Embeda is not approved for use outside the United States.

3. CMC/Device

The primary CMC review was conducted by Elsbeth Chikhale, Ph.D., with supervisory concurrence by Ali Al-Hakim, Ph.D. .

According to Dr. Chikhale's review, the application is recommended for Approval pending final labeling.

The following is a summary Dr. Chikhale's review.

Drug product and drug substance

Drug product

The drug product is a capsule for oral administration, containing multilayer pellets. Each pellet contains two active ingredients: morphine sulfate (drug substance with extended release profile) and naltrexone (deterrent component which should not be release under normal use), along with several non novel excipients. The capsules have been formulated into 6 dose-proportional strengths: 20/0.8, 30/1.2, 50/2.0, 60/2.4, 80/3.2, and 100/4.0 mg morphine sulfate/naltrexone HCl per capsule. Different size/strength capsules are filled with proportional amounts of the pellets. For all strengths, the amount of naltrexone HCl is 25 times smaller than the amount of morphine sulfate. The Applicant requested a biowaiver for Embeda strengths below 100mg, which was granted by Patrick Marroum, Ph.D. from ONDQA.

The following is a schematic representation of a cross-section of a pellet (from Dr. Chikhale's review).



(b) (4)

The proposed container closure system is (b) (4) HDPE bottles with cotton coil and a child-resistant cap with an induction seal. The proposed storage condition is at room temperature and the expiry date is 24 months. The provided stability data supported the proposed shelf life at room temperature.

Drug Substances

Both morphine sulfate and naltrexone are previously approved drug substances produced by chemical synthesis. The DMFs related to each drug substance were reviewed and found adequate to support this NDA.

All facility inspections have been completed and the Offices of Compliance and New Drug Quality Assessment have determined them to be acceptable. A categorical exclusion was granted for the environmental assessment.

4. Nonclinical Pharmacology/Toxicology

The primary Nonclinical Pharmacology/ Toxicology review was conducted by Elizabeth Bolan, Ph.D., with supervisory concurrence by Daniel Melloñ, Ph.D. The following is a summary of that review.

No new nonclinical pharmacology or toxicology studies were submitted in support of this NDA. The Applicant relied on data in the Kadian NDA (owned by the Applicant), previous findings of efficacy and safety for Revia, and information from the literature. The Applicant provided a review of the current literature for morphine and naltrexone.

Dr. Bolan's review focused on labeling recommendations that include the following:

(b) (4)

There was no recommendation for additional nonclinical studies by Drs. Bolan or Mellon. From the Pharmacology/Toxicology perspective, this application is recommended for approval.

5. Clinical Pharmacology/Biopharmaceutics

The primary Clinical Pharmacology and Biopharmaceutics review was conducted by Srikanth Nallani, Ph.D., with supervisory concurrence by Suresh Doddapaneni, Ph.D. The following is a summary of that review.

The clinical pharmacology program was geared towards comparing systemic levels of morphine between EMBEDA and the reference product KADIAN. In addition, the development plan aimed to demonstrate the utility of naltrexone sequestered in the EMBEDA pellets to deter drug tampering and abuse. Clinical pharmacology studies were conducted to establish the appropriate pharmacological ratio of naltrexone to morphine that would result in mitigation of positive subjective effects of morphine (e.g., drug liking) associated with crushing or chewing Embeda.

Biopharmaceutics studies were conducted characterizing the pharmacokinetics of morphine with both the labeled use and abuse of EMBEDA. These studies included an alcohol interaction study.

Neither intrinsic nor extrinsic factors (other than alcohol) were studied during the development program. The Applicant is relying on the previously approved drug Kadian for this information.

From the Pharmacology/Biopharmaceutics perspective, this application is recommended for approval

Bioequivalence of Embeda to Kadian

EMBEDA is bioequivalent to KADIAN under fasting conditions with respect to C_{max} and AUC after single dose administration of 100mg as established in study ALO-01-07-101. The pharmacokinetic parameters of serum morphine from both products are tabulated below in the table from Dr. Nallani's review. T_{max} of morphine is earlier in subjects receiving Embeda when compared to Kadian. This does not have clinical significance since patients receive this drug around the clock.

Table 1

Summary of Pharmacokinetic Results for Morphine (N=34)

Parameter*	EMBEDA (A)	KADIAN® (B)
AUC _{0-t} (ng·h/mL)	310.9 (25.30%)	304.52 (25.8)
AUC _{inf} (ug·h/mL)	384.01 (24.10%)	390.98 (29.90%)
C _{max} (ng/mL)	12.31 (36.80%)	13.19 (45.70%)
T _{max} (h)	7.5(2.50-18.00)	10 (6.00-24.00)
Half-life (h)	28.8 (39.90%)	33.83 (34.60%)

*Geometric mean (CV%) is presented for AUC and C_{max}, median (range) for T_{max} and arithmetic mean (CV%) for half-life.

Food effect

EMBEDA may be taken with or without food, and may be taken by sprinkling the contents over applesauce, as demonstrated in study ALO-01-07-103. Morphine plasma levels with EMBEDA were bioequivalent under fasted vs. sprinkled over applesauce conditions; however a 22% decrease in C_{max} was noted when EMBEDA capsules were taken with food compared to fasting condition.

Naltrexone exposure with normal use of Embeda

Plasma naltrexone concentrations are low and highly variable following single and multiple dose administration of EMBEDA capsules according to Dr. Nallani's review. Plasma samples were collected in several single and multiple dose biopharmaceutics studies and analyzed for naltrexone and its metabolite 6-beta-naltrexol concentrations. Since naltrexone has a shorter half life (~ 6 hours), its longer half-life metabolite, 6-beta-naltrexol, levels may also be a marker of overall naltrexone exposure.

In the food effect study, plasma levels of naltrexone were analyzed following single-dose administration of EMBEDA in healthy volunteers under fasting conditions, fed condition or when capsule contents were sprinkled over apple sauce. Under fasting conditions for the intact capsule formulation, plasma naltrexone concentrations (fasting: range 4.46 to 20.8 pg/mL) were detected in 11 samples in three subjects; while the rest of the subjects (n=31) had plasma naltrexone levels below the quantitation limit (4.0 pg/mL) at all time points. Five subjects receiving capsule contents sprinkled over applesauce had fifteen samples with plasma naltrexone levels in the range of 5.74 to 64.5 pg/mL, while the rest of the subjects (n=27) did not have naltrexone levels above the analytical method limit of quantitation. In only fifteen subjects (out of n = 34) receiving EMBEDA with high fat meal, plasma naltrexone levels were in the range of 4.05 - 132 pg/mL) at different time points.

In the long-term open-label safety trial (202) trough blood samples were analyzed for plasma morphine at multiple time points. The majority (>75%) of naltrexone concentrations were below the level of detection, although some subjects had a range of concentrations from 4pg/ml to 25pc/ml.

Clinical pharmacokinetics of morphine and naltrexone under "abuse" conditions

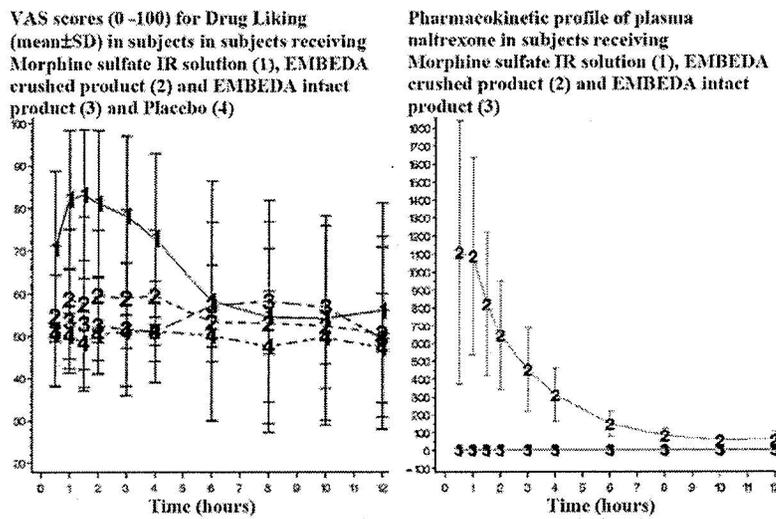
Four studies assessed the utility of naltrexone sequestered in the EMBEDA pellets to deter drug tampering and abuse.

Study ALO-KNT-201 was conducted to establish the appropriate pharmacological ratio of naltrexone to morphine that would mitigate drug liking and euphoric effects of morphine released by crushing or chewing Embeda. A variety of ratios of naltrexone to morphine were studied to assess the morphine induced euphoria in non dependent opioid experienced subjects under fasting conditions. A ratio of 1:25 resulted in optimal reduction in drug liking and euphoria, however drug-liking effects were highly variable among subjects, with some subjects reporting full liking (VAS=100), and some reporting less than average liking. Considering the high variability in the pharmacodynamic responses, the results must be viewed with caution in terms of claims related to abuse deterrence.

Employing the 1:25 ratio of naltrexone to morphine, EMBEDA was tested for its abuse liability in study ALO-01-07-205. The pharmacodynamic effects and safety of equivalent oral doses of whole and crushed EMBEDA versus morphine IR solution in opioid-experienced, non-dependent subjects were studied. Crushing EMBEDA resulted in (a) release of morphine comparable to an immediate release morphine oral solution (b) release of naltrexone comparable to an oral solution.

As shown in the figure below from Dr. Nallani’s review, large variability in pharmacodynamic response is noted in each treatment; however, average drug liking scores were lower in Embeda intact and crushed treatments when compared to morphine sulfate IR solution treatment. Four individuals receiving crushed Embeda product demonstrated strong liking (VAS score = 100) at few time points, despite the release and absorption of naltrexone from the crushed pellets.

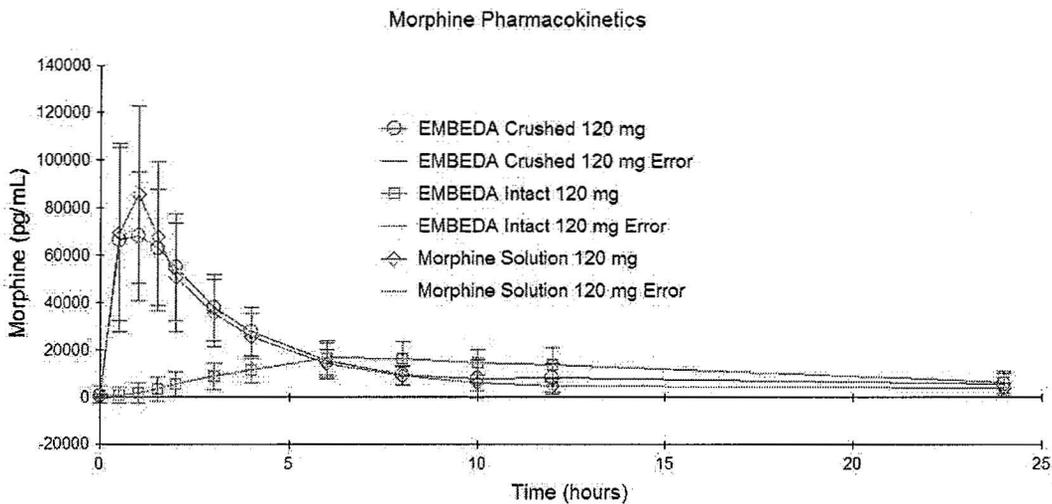
Figure 2



Note that there is no “1” line in the right hand figure because IR morphine solution does not contain naltrexone.

On average, peak morphine levels were 4-fold higher (range 1.4- to 7-fold) and achieved quickly (shorter Tmax) in subjects receiving crushed EMBEDA compared to intact product. AUC levels were higher by 12% in crushed EMBEDA compared to intact product. The plasma morphine profile was comparable between crushed EMBEDA and morphine sulfate oral solution treatment. Cmax for all the treatments were significantly different compared to morphine sulfate oral solution; Cmax of EMBEDA crushed was 94.3%, while Cmax with EMBEDA whole was 23.4%. Relative bioavailability of morphine, in terms of AUC, was 115% in EMBEDA crushed group compared to morphine oral solution, while EMBEDA intact capsules had a relative bioavailability of 83%. Median Tmax was approximately 1 hour for EMBEDA crushed and morphine sulfate oral solution and 8 hours for EMBEDA whole. These results are illustrated in the figure below from Dr. Nallani’s review.

Figure 3



Generally, a majority of the subjects who showed any reduction in post-dose Drug Liking compared to MSIR had at least a 20% minimum reduction following EMBEDA whole administration (65.1%) and at least a 30% minimum reduction following EMBEDA crushed administration (53.1%). The highest percent reductions observed were in the 40-49% range, occurring at an incidence of 15.6% following EMBEDA whole administration and in 25.0% of subjects following EMBEDA crushed administration.

Alcohol interaction

An alcohol interaction study (ALO-01-07-103) was conducted to compare single-dose bioavailability of Embeda capsules when dosed with water, 4%, 20%, and 40% alcohol. Compared to intact Embeda consumed with water under fasting conditions, the pharmacokinetics of morphine were not significantly altered when Embeda was coadministered with 4% and 20% alcohol. However, coadministration with 40% alcohol resulted in dose-dumping. On average, a 2-fold higher C_{max} of morphine was noted compared to Embeda consumed with water. There was variability among subjects, with resulting C_{max} values between 1.4 and 5.0 fold increase. Plasma AUC was not significantly different between treatments. Adverse event rates increased when Embeda 60mg was consumed with increasing amounts of alcohol (nausea, vomiting, dizziness, and headache).

These results are in contrast to the *in vivo* alcohol interaction study carried out with Kadian, where no dose-dumping of morphine was detected.

The results of study ALO-01-07-103 also indicated that co-administration of alcohol had no effect on the sequestration of naltrexone.

General Biopharmaceutics

The proposed EMBEDA formulation strengths (20–100 mg) are compositionally proportional. The Applicant has adequately compared the dissolution profiles for each strength of EMBEDA and KADIAN. Additionally, the Applicant has demonstrated bioequivalence of the EMBEDA

to KADIAN 100 mg strength. Based on this evidence the Applicant requested a biowaiver for the EMBEDA strengths below 100 mg, which was granted.

6. Clinical Microbiology

This section is not relevant to this product.

7. Clinical/Statistical- Efficacy

The primary clinical review was completed by Jin Chen, M.D., Ph.D., with my concurrence, and the Statistical Review was completed by Kate Meaker, M.S., with concurrence from Dionne Price, Ph.D., and Thomas Permutt, Ph.D. The discussion below includes aspects of these reviews where noted.

The determination of the efficacy of Embeda was based on one adequate, placebo-controlled Phase 3 clinical trial. Because this NDA was submitted as a 505(b)(2) application relying, in part, on the findings of efficacy and safety for the already approved products Kadian (extended-release morphine sulfate) this was found acceptable by the Division.

Study *ALO-KNT-301* was a multicenter, randomized, double-blind, placebo-controlled, 12-week multiple-dose Phase 3 efficacy trial of Embeda utilizing a randomized withdrawal design, and carried out in adult patients with moderate to severe pain due to osteoarthritis of the hip or knee. The study was executed under a Special Protocol Assessment.

Five-hundred forty-seven patients over the age of 21 years with moderate to severe chronic pain due to OA of the hip or knee, and in otherwise general good health, were recruited into the open-label Titration Phase, which was followed by randomization and double-blind treatment. Inclusion into the study required a primary diagnosis of Functional Class I-II OA of the hip or knee based on ACR criteria, and an average 24-hour pain intensity of ≥ 5 on the 11-point BPI (*Brief Pain Inventory*) scale at the Baseline Visit. Subjects were required to have met at least one of the following criteria:

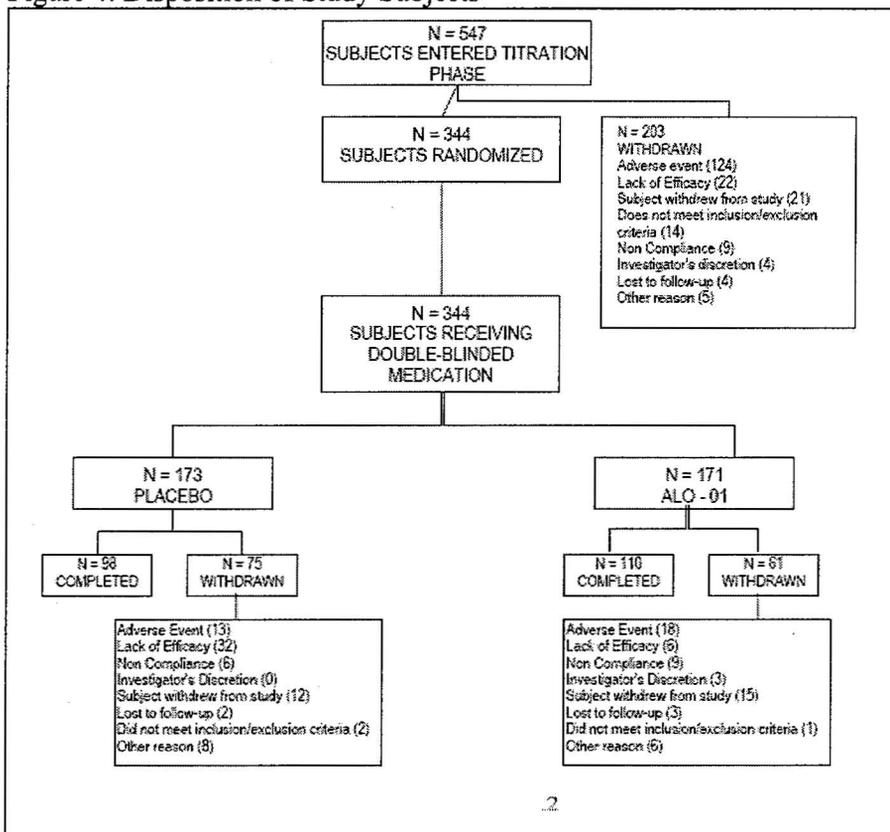
- a. inability to consistently control target joint pain with non-opioid analgesics (e.g., NSAIDs) or tramadol; OR
- b. required opioid treatment (single or combination product) with the equivalent of ≤ 40 mg/day of oral morphine sulfate.

After screening, subjects underwent a washout period for analgesics and other prohibited medications to establish a pain flare of ≥ 5 on 11-point BPI scale at the baseline visit. They then entered a Titration Phase lasting up to six weeks which consisted of open-label treatment with Embeda. Opioid-naïve subjects were started on 20mg Embeda at bedtime for the first three nights, and opioid-tolerant patients started with 20mg BID. All were titrated to an effective dose; the maximum allowed dose was 80mg BID. The effective dose (responder) was defined as that which resulted in “pain on average in the last 24 hours” ≤ 4 BPI score over the last 4-days and with minimum 2-point decrease from baseline.

Responders (N=344) from the Titration Phase entered the 12 week, fixed-dose, double-blind Maintenance Phase. They were randomized at approximately a 1:1 ratio to receive either the

“effective dose” of Embeda determined during the Titration Phase or placebo. Subjects randomized to the placebo group were tapered off Embeda using a double-blind, double-dummy design over a maximum of two weeks. Clinic visits occurred every week for the first two weeks, followed by every two weeks up to Week 12. Subjects were then tapered off study drug over a period of up to two weeks, followed by an end of study visit.

Figure 4: Disposition of Study Subjects



Approximately 37% of the subjects entering the Titration Phase dropped out primarily due to adverse events (61% of dropouts), and few due to lack of efficacy (10%). During the Maintenance Phase, 36% of the subjects who received Embeda dropped out of the study compared to 43% who received placebo. Withdrawal due to adverse events and lack of efficacy in the Embeda group compared to the placebo group were 10.5% vs. 7.5% (adverse events) and 3.5% vs. 18.5% (lack of efficacy) respectively.

There were no important differences between the study groups in terms of baseline characteristics, demographics, concomitant medications and medical history.

Assessments during clinic visits included, but were not limited to vital signs, review of electronic diaries, adverse event assessments, use of concomitant and rescue medications, and Clinical and Subjective Opiate Withdrawal Scales (COWS and SOWS).

The primary efficacy measurement was pain intensity (average pain in past 24 hours) as measured on an 11-point Brief Pain Inventory (BPI) and entered daily into an electronic diary at home by the study subjects. Additional secondary pain measurements obtained at home included worst pain and least pain in past 24 hours, and pain right now. In-clinic pain assessments were also recorded. Details regarding secondary efficacy assessments can be found in Dr. Chen's review.

The primary endpoint was the mean change of weekly BPI diary average pain scores from randomization baseline (last seven days of Titration Phase) to Week 12. The primary analysis was carried out on the ITT population which included all subjects who were randomized into the Maintenance Phase of the study and took at least one dose of double-blind study medication after randomization. Differences in the efficacy endpoints between Embeda and placebo were analyzed using ANCOVA with treatment as categorical factor and randomization baseline as covariate.

BOCF/LOCF mixed method was used to impute dropouts to the end of treatment (week 12) by the following rules:

- For drop-outs due to opiate withdrawal symptoms ($COWS > \text{randomization baseline } COWS$, and $COWS \geq 13$), impute the Randomization Baseline (least pain) for placebo group and the Screening Baseline (worst pain) for Embeda group. (BOCF)
- For drop-outs due to AEs, impute the Screening Baseline. (BOCF)
- For dropouts due to any other reason (non-AE and non-COWS), impute the average of the last seven days of maintenance phase. (LOCF)

An important aspect of the analysis was that subjects who dropped out of the study due to withdrawal symptoms not be given a favorable imputation score, since withdrawal symptoms resulting from treatment represent a lack of tolerability to the drug, even if the subject had experienced a decrease in pain intensity.

The results of the primary analysis showed that Embeda was statistically superior to placebo at the $p < 0.05$ level ($p = 0.045$). Table 2 below from Dr. Chen's review shows the Applicant's primary analysis, in addition to the *post hoc* LOCF analyses and protocol specified sensitivity analyses.

Table 2: Analysis results of primary efficacy endpoint in ITT population

Analysis method	Pain Intensity, <i>mean(SD)</i>		P-value ^a
	Placebo N=173	Embeda N=170	
Primary Imputation Method ^b			
Baseline	3.2 (1.07)	3.3 (1.30)	
Week 12	3.5 (2.13)	3.1 (1.99)	
Change from Baseline to Week 12	0.3 (2.05)	-0.2 (1.94)	0.0445
LOCF Imputation Methods (<i>post hoc</i>)			
Baseline	3.2 (1.07)	3.3 (1.30)	
Week 12 ^c	3.4 (2.05)	3.1 (1.97)	
Change from Baseline to Week 12	0.2 (1.97)	-0.2 (1.92)	0.1041
Week 12 ^d	3.6 (2.19)	3.2 (2.03)	
Change from Baseline to Week 12	0.3 (2.13)	-0.1 (1.97)	0.0347
Sensitivity Analyses (protocol-specified)^e			
Randomization Baseline (Method 1)			
Week 12	3.1 (1.58)	2.9 (1.59)	
Change from Baseline to Week 12	-0.2 (1.32)	-0.4 (1.34)	0.1223
Screening Baseline (Method 2)			
Week 12	4.3 (2.49)	3.9 (2.54)	
Change from Baseline to Visit Y+12 Weeks	1.1 (2.37)	0.6 (2.31)	0.0489
Screening or Randomization Baseline (Method 3)			
Week 12	3.9 (2.38)	3.3 (2.13)	
Change from Baseline to Week 12	0.7 (2.17)	0.0 (1.91)	0.0051

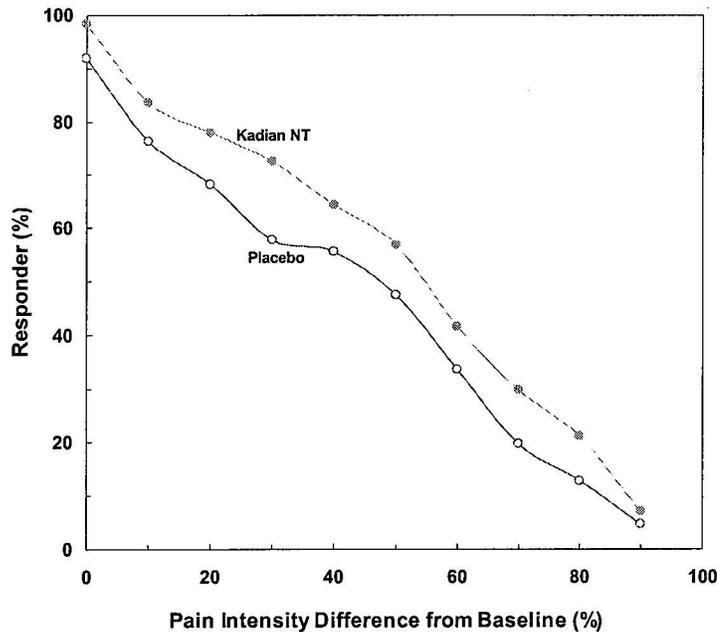
- a. Means and standard deviations from an ANCOVA model with treatment as categorical factor and randomization baseline score as a covariate.
- b. Primary imputation method: BOCF or LOCF, depending on reasons for dropouts (see paragraph above table)
- c. Alternative imputation (LOCF): dropouts due to lack of efficacy or administrative reasons imputed with the average of the last 7 days of available diary data (but not more than 2 days past drug discontinuation)
- d. Alternative imputation (LOCF): dropouts due to lack of efficacy or administrative reasons imputed with the last diary entry (but not more than 2 days past drug discontinuation)
- e. Sensitivity analyses (protocol-specified):
 - Method 1: **Randomization Baseline** (the end of titration, e least pain) for all dropouts in both groups
 - Method 2: **Screening Baseline** (end of washout right before titration, worst pain) for all dropouts in both groups
 - Method 3: **Screening Baseline** for dropouts due to AEs and **Randomization Baseline** for dropouts due to other reasons in both groups.

Kate Meaker, the statistical reviewer confirmed the Applicant's efficacy analysis.

Two of the three protocol specified sensitivity analyses were statistically significant in favor of Embeda. The analysis that utilized **Randomization Baseline** (least pain) for all dropouts in both treatment groups did not show significance.

An exploratory cumulative responder analysis was performed by the Applicant, the results of which are illustrated in the figure below from Dr. Chen’s review. The analysis was based on pain intensity difference (%) from baseline to Week 12 using the in-clinic BPI score. Dropouts were defined as non-responders. According to Ms. Meaker’s statistical review “A continuous responder analysis, based on percentage change from baseline, is not applicable to this withdrawal study design because neither the screening nor randomization baseline provides clarity as the denominator. Eligibility required achieving adequate pain relief after titration, so the screening baseline pain score is not the frame of reference to assess efficacy. On the other hand, after titration a randomization baseline score of zero was ideal pain relief. For subjects with a denominator close to zero, very small unit changes result in large percent changes. Another factor is that patients who have no change in pain are classified as not improving, when that is actually a benefit to the patient in this study design. Thus a continuous responder analysis would not provide clear information regarding efficacy.”

Figure 5: Cumulative responder analysis of pain intensity difference from baseline to Week 12; ITT population



Ms. Meaker performed an alternate exploratory analysis where patients were categorized by the direction of change from randomization baseline to Week 12. As shown in the table below from Ms. Meaker’s review, the percent of patients whose pain did not return (worsen) after randomization was lower in the Embeda group than in the placebo group.

Table 3: Study 301 Average Pain in last 24 hours - Change from Randomization to Week 12

	Pain worsened	Pain did not change	Pain improved
Embeda N=170	69/170 41%	9/170 5%	92/170 54%
Placebo N=173	88/173 51%	5/173 3%	80/173 46%

Additional secondary efficacy endpoints provide supportive evidence in favor of the analgesic efficacy of Embeda. Details regarding these endpoints may be found in Dr. Chen’s review.

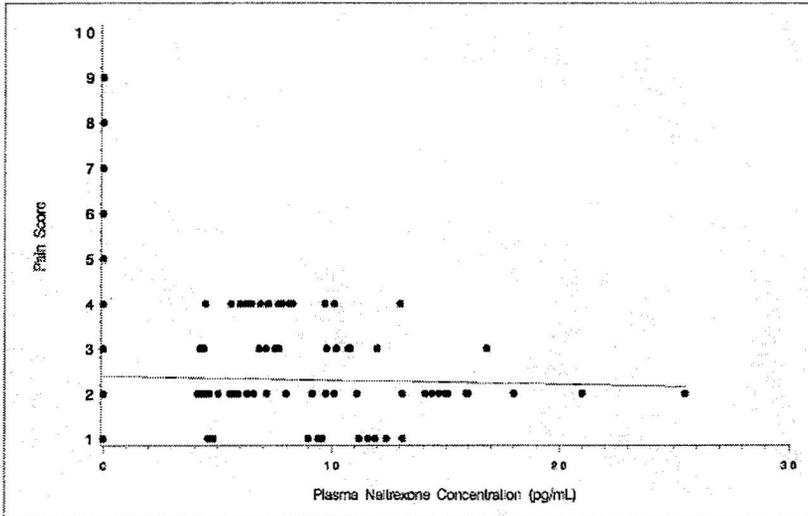
In terms of population subgroups (gender, age, race) there were no notable differences in the mean changes for the treatments.

The effect of naltrexone on efficacy

An important efficacy concern for Embeda is whether the sequestered naltrexone would be absorbed to the extent that it could compromise the analgesic effects of morphine sulfate. Pharmacokinetic studies discussed in Section 5 show that in the majority of subjects measured, exposure to naltrexone was below the level of detection, and in those where there were plasma levels detected, they were very low.

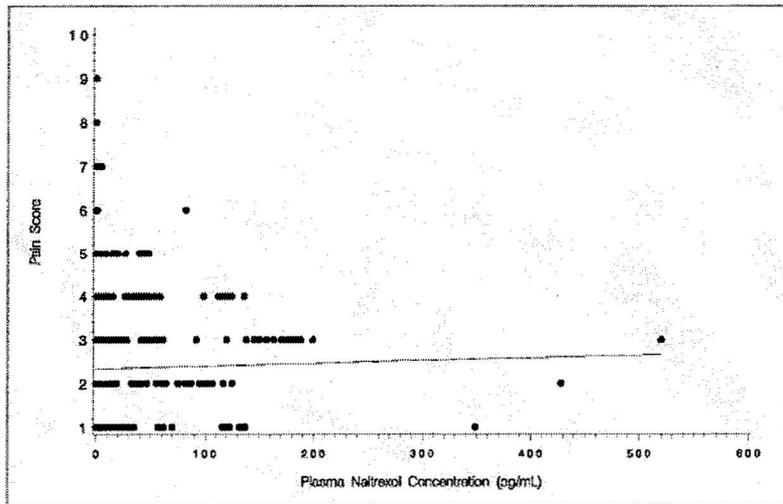
The correlation between the plasma profile of naltrexone/6-β-naltrexone and the analgesic effects of Kadian NT was assessed in the Phase 2 Study ALO-KNT-202 (active-controlled PK and efficacy trial with Kadian as a comparator). Plasma naltrexone or 6-β-naltrexone was detectable at multiple time-points in approximately 10% and 82% of patients, respectively. Comparisons of the detectable naltrexone and/or 6-β-naltrexol concentrations with the time-matched pain intensity score showed that there was no correlation of pain scores to naltrexone but slight correlation to 6-β-naltrexol as noted in the figures below.

Correlation of naltrexone concentration in plasma with the time-matched pain intensity score. (Applicant's figure from Dr. Chen's review)



Source of data: Section 14.2.1, Ad Hoc Figure 2.

Correlation of 6-β-naltrexon concentration in plasma with the time-matched pain intensity score. (Applicant's figure from Dr. Chen's review)



Source of data: Section 14.2.1, Ad Hoc Figure 1.

It does not appear from the available data that the extent of the exposure to naltrexone has a clinically significant effect on the efficacy of Embeda. In the event that there is some negative impact on efficacy due to exposure to naltrexone under normal use, titration to effective analgesia should make this issue clinically unimportant.

In summary, the Phase 3 study indicates that Embeda is statistically superior to placebo for the primary endpoint, and provides sufficient evidence for efficacy for the proposed indication.

The minimal systemic exposure to naltrexone in a small proportion of subjects does not appear to negatively impact the efficacy of this product.

8. Safety

The safety database includes a total of 1251 subjects treated with at least one dose of Embeda from nine clinical trials; 168 subjects were healthy adults who received a single dose treatment in Phase 1 trials, and 1083 adult subjects were from three multiple-dose Phase 2 and 3 trials in subjects with chronic pain due to osteoarthritis:

- Phase 2
 - ALO-KNT-202: active controlled 2 week trial
- Phase 3
 - ALO-KNT-301: placebo-controlled 12-week double-blind efficacy trial
 - ALO-KNT-302: 12-month open-label safety trial

The overall exposure to Embeda met the Division's requirements. One-hundred twenty-four subjects received multiple doses of Embeda for at least 12 months, and 84 for at least 6 months to one year.

The mean exposure by dose was as follows:

Study	N	Mean daily dose (range)	Mean duration
301 (Placebo controlled)	547	43mg (20-160)	11 weeks
302 (open-label)	465	85mg (45-222)	26 weeks
202 (active-controlled)	71	(120-180mg)	2 weeks

The Applicant pooled the Phase 2 and 3 studies as follows for the analysis of safety:

- Blinded short-term studies: ALO-KNT-202, ALO-KNT-301
 - Broken down by open-label titration phase and double-blind phase
- Open-label, long-term study: ALO-KNT-302

There were no deaths reported during the clinical development program. A total of 45 subjects experienced one or more serious adverse events, all reported during the two phase 3 trials; 12 subjects Study 301 and 33 from Study 302. Fourteen subjects withdrew from study 302 due to an SAE, and no individual SAE led to the discontinuation of more than one subject. SAEs that may have been related to study drug include gastrointestinal inflammation, pancreatitis, vomiting, and cholelithiasis. The remainder of SAEs did not appear related to study drug and were likely due to underlying medical conditions and concurrent medications.

The table below illustrates discontinuations due to adverse events in the Phase 2 and 3 studies.

Table 4: Discontinuations due to Adverse Events

Study	Double-Blind				Open-label short term (titration periods)		Open-label long term
	202		301		301	202	302
Treatment	Embeda	Kadian	Embeda	Placebo	Embeda	Kadian	Embeda
Subjects in safety pop	71	71	171	173	547	111	465
Total withdrawals	1 (1%)	2 (3%)	61 (36%)	75 (43%)	203 (37%)	42 (38%)	307 (66%)
Withdrawals due to AEs	1 (1%)	1 (1%)	18 (11%)	13 (8%)	124 (23%)	29 (26%)	110 (24%)

In the double-blind period of study 301, the overall dropout rate for Embeda-treated subjects (36%) was less than placebo-treated subjects, however as expected, there were more dropouts due to adverse events in the Embeda treated group. In the open-label periods, both titration and long term, there was a similar proportion of dropouts due to adverse events. Of note is that during the open-label long-term trial, 66% of the study population dropped out at some point during the 12 month trial, the largest proportion due to adverse events, followed by non-compliance, withdrawal for “other reasons”, and lack of efficacy.

The most frequent adverse events leading to discontinuation in subjects receiving Embeda during all study phases were typical opioid-related adverse events, including nausea, constipation, vomiting, fatigue, dizziness, pruritus, and somnolence.

The most common treatment emergent adverse events occurring in subjects receiving Embeda during the blinded and open-label studies, short and long-term, included constipation, nausea, vomiting, somnolence, headache, dizziness, pruritis, and dry mouth. These events occurred in similar proportions of subjects who received Kadian, and at greater rates than those receiving placebo. These events are those typically related to opioid use. Details regarding these events may be found in Dr. Chen’s review.

Severe TEAEs were reported in 5% of the subjects receiving Embeda in the double-blind studies and 7% in the open label phases of studies 202 and 301. The majority were gastrointestinal events of constipation and nausea. During the long-term open-label study (302), 16% of subjects receiving Embeda reported severe TEAEs, which included constipation (3%), nausea (1.4%), and headache (1.9%).

The overall incidence of adverse events by duration of exposure in the long-term open-label Study 302 showed the highest rate (66%) of adverse events in the first 30 days of treatment compared to any other time interval over the 12 month period. The decrease in incidence of adverse events over time was likely due to dropouts early in the trial, and the development of

tolerance to this opioid. In terms of dose-dependency, the highest rate of adverse events during the 12-month open label trial occurred in the two lowest dosing groups of <80 mg/day and 80-120 mg/day compared to >120 mg/day. This was probably due to adverse events occurring during initiation and up-titration of dosing, as is common with opioid analgesics in general.

There were no clinically important changes in laboratory values or vital signs during noted in the safety database. Although there was not a formal study evaluating ECG changes, routine ECG recording was performed at screening during all clinical studies, and at six and 12 months during the long-term open-label study. ECG abnormalities were reported for seven subjects from study 302, none of which were determined to be related to study drug. The abnormalities included one myocardial infarction, one case of angina pectoris, three cases of bradycardia, one bundle branch block, and one congestive heart failure.

In terms of overall safety, no new or unexpected safety signals were detected during the review of the database submitted in this NDA.

Special Safety Concerns

Naltrexone-induced withdrawal

A safety concern regarding Embeda is whether the release of naltrexone from intact Embeda capsules could result in clinically significant opioid withdrawal symptoms. The Applicant explored this issue in studies ALO-KNT-301 and ALO-KNT-302.

Opioid withdrawal symptoms were primarily assessed with the Clinical Opiate Withdrawal Scale (COWS), which includes 11 common opiate withdrawal signs and symptoms. Each item is scored from 0-4 or 0-5 (various among different items) and total COWS score (sum of all item) is used to assess a patient's level of opioid withdrawal. The severity of opioid withdrawal based on the total COWS score is categorized as follows: mild (COWS=5-12), moderate (COWS=13-24), moderately severe (COWS=25-36) and severe withdrawal (COWS >36).

During study ALO-KNT-302, the COWS was administered to patients at Weeks 1 and 2, and then monthly up to 12 months or early termination, and during ALO-KNT-301, at Weeks 0, 1, 2, and 12 or early termination.

Overall, the mean COWS scores tended to decrease after baseline. The mean changes in total COWS scores from baseline at each visit up to 12 months in Study ALO-KNT-302 showed decreased from baseline at all three daily dosing levels. The subgroup analyses did not reveal clinically important opioid withdrawal symptoms associated with Embeda treatment by age, gender, race or opioid status (experienced vs. naïve) in both short-term and long-term studies.

There were five subjects in Study ALO-KNT-302, who experienced moderate opioid withdrawal symptoms (total COWS score ≥ 13) during the 12-month study. In all cases, the withdrawal symptoms appeared to be due to non-compliance (underdosing) with the study medication.

Naltrexone-related adverse events

In the 120-day Safety Update, the Applicant compiled all potential naltrexone-related adverse events from the three Phases 2 & 3 trials in chronic pain patients (ALO-KNT-202, ALO-KNT-301 and ALO-KNT-302). The adverse event data included opioid withdrawal symptoms and hepatic enzyme elevations. There did not appear to be any pattern of opioid withdrawal syndrome, but rather sporadic symptoms which may be associated with naltrexone, such as nausea, vomiting, insomnia, anxiety/irritability, lacrimation increased, abdominal pain, piloerection and rhinorrhea. However, rhinorrhea, piloerection, and lacrimation occurred at higher rates in placebo patients than those receiving Embeda, and anxiety/irritability occurred at a comparable rate to Embeda. The remaining adverse events are commonly associated with opioid use.

As noted in the Boxed Warning section of the label for Naltrexone tablets, naltrexone may induce hepatotoxicity at high dose (5 times recommended dose 50 mg/day). The only hepatic abnormalities noted in the safety database included approximately 8% of subjects in the 12-month open label trial with normal to high shifts in ALT or AST, four of which had ALT or AST elevation greater than 3xULN. The transaminase elevations were either transient or attributable to underlying medical conditions or concomitant medication use. In addition, six patients with ALT 2xULN at the entry of the study had the ALT return to the normal range during treatment with Embeda. The low naltrexone exposure from chronic administration of Embeda does not appear associated with hepatic adverse events.

In summary, no new or unexpected safety signals were detected during the review of this NDA. The adverse event profile for Embeda is similar to that of Kadian and other extended-release opioid analgesics. There do not appear to be any adverse events specifically attributable to the sequestered naltrexone, nor were any events of withdrawal found to be attributable to the presence of naltrexone in the formulation. No cases of withdrawal syndrome were reported.

9. Advisory Committee Meeting

A joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory committee was held on November 14, 2008. The joint committee was asked to provide guidance regarding whether Embeda is likely to be less susceptible to abuse and misuse than currently marketed extended-release morphine, and what language would be appropriate for inclusion in the product label regarding the physicochemical properties of the formulation and its role in the mitigation of abuse. They were also asked to comment regarding the tools currently available to evaluate the impact of purported "abuse resistant" formulations on abuse and misuse of prescription opioids, and how an "abuse resistant" claim could be obtained for Embeda and other products developed to mitigate abuse.

Following presentations by the Applicant and the Agency, the joint committee provided the following comments. No formal vote was taken regarding any of the issues discussed.

- The Embeda formulation may provide for a small, incremental effect on the abuse of extended-release morphine by limiting the abusability of the crushed capsule.

However, other common methods of abuse such as (b) (4) and injection may not be mitigated since the morphine is relatively easily extracted from the formulation in a selective manner that does not also extract the naltrexone.

- Some information related to naltrexone should be in the label so that patients will not be harmed by ingesting a crushed tablet, which could lead to either withdrawal symptoms or a decrease in analgesic efficacy.
- An “abuse resistant claim” cannot be included in the labeling at this time until the Applicant demonstrates that their formulation has had an effect on the actual abuse of the product. However, there was no consensus on how this claim could be established, and which evaluation tools might be most useful.

10. Pediatrics

A Pediatric Plan was included in the NDA submission (b) (4)

Since Duragesic is approved down to age two, the DAARP recommended that Embeda also be studied down to age two years. The Division met with the Pediatric Evaluation and Review Committee (PERC) on October 29, 2008, and they agreed that patients from age 2 to 17 must be studied to fulfill requirements under PREA.

The following requirements have been conveyed to the Applicant regarding the Pediatric Plan. Pharmacokinetic, safety, and efficacy studies must be conducted in patients aged 2-17 years of age. An age appropriate formulation should be developed for patients for whom the adult formulation is not appropriate. The age appropriate formulation must retain the extended release properties of Embeda, but if an oral liquid formulation is required for the youngest age groups, the abuse resistant attributes do not need to be maintained. A timeline for the proposed studies must be included in the Pediatric Plan.

A waiver will be granted for studies in patients less than 2 years old. A deferral will be granted for studies in patients aged 2 to 17 until the adult formulation is approved.

11. Other Relevant Regulatory Issues

Division of Medication Error Prevention and Analysis (DMEPA) Consult

Two consults were completed by Richard Abate, RPh, MS of DMEPA, with concurrence from Kellie Taylor, Pharm D, MPH, Denise Toyer, Pharm D, and Carol Holquist, RPh. The first was the proprietary name review. The Proprietary Name Risk Assessment findings indicate that the proposed name, Embeda, does not appear to be vulnerable to name confusion that could lead to medication errors, and so DMEPA has no objection to the proposed proprietary name.

The second consult was the Label and Labeling Risk Assessment. The consult response stated concerns with the presentation of information on the container labels and insert labeling that introduce vulnerability to confusion that could lead to medication errors. Concerns specifically relate to 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, and the use

of trailing zeros throughout the labels and labeling. These risks should be addressed and mitigated prior to drug approval. Details regarding the recommendations may be found in Mr. Abate's review.

Controlled Substance Staff Consult (CSS)

A review of the NDA submission was completed by James Tolliver, Ph.D., of CSS with concurrence from Silvia Calderon, Ph.D. and Michael Klein, Ph.D. Dr. Tolliver reviewed the data provided by the Applicant concerning the abuse resistant properties of Embeda. Based on this review, CSS has concluded the following, excerpted from Dr. Tolliver's review.

- 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 to be marketed. 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 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 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)



- 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_{max} value was approximately 2-fold higher, while the time (T_{max}) to reach C_{max} 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.
- EMBEDA has not been directly compared to KADIAN in any of the extraction or human abuse potential studies conducted by the Applicant

In order to more thoroughly evaluate the abuse potential and tamper resistant properties of EMBEDA, CSS recommends the Applicant 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 Applicant 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.

In discussions with Michael Klein on 12/8/08, we determined that the above recommendations are not required post marketing commitments, but recommendations for further studies.

Division of Scientific Investigations (DSI)

Four study sites from Study ALO-KNT-301 and two study sites from Study ALO-KNT- 302 were selected for inspection to be carried out by the DSI. There are no outstanding issues based on the preliminary inspection of four of the study sites. The final results and conclusions regarding the remaining two sites are pending at this writing.

Division of Drug Marketing, Advertising and Communications Consult (DDMAC)

DDMAC performed a review of the Embeda label on April 18, 2008. The label reviewed was submitted in the April 3, 2008 NDA application which was a “refuse to file” due to deficiencies in the safety database. A comparison of that label with the one submitted on June X showed only minor editorial differences. DDMAC reconsulted on December 8, 2008 to review the most recently submitted label. At this time, the consult response is pending.

The recommendations in the original review included removal of promotional language and language that implies abuse resistance of the formulation. Refer to the DDMAC review for detailed comments.

OSE/DRISK Consult

This consult response is pending decisions made regarding the REMS requirement for this product.

12. Labeling

This label is written in PLR format and is currently under review by the Division and other members of the review team.

The proposed proprietary name, Embeda, has been accepted by DMETS. Important aspects of the label review include decisions regarding what language is appropriate for inclusion related to the presence of naltrexone in the formulation and its “abuse deterrent” properties. Overall, language in the label will be similar to the Kadian label, including the Boxed Warning, contraindications, warnings and precautions, preclinical information, and intrinsic and extrinsic factors. Because Embeda has been demonstrated to dose-dump *in vivo* when coingested with alcohol, an alcohol warning will be included in the Boxed Warning (unlike the Kadian Boxed Warning).

There will be no mention in the label that the presence of naltrexone will deter abuse, since this has not been demonstrated in “real use” situations; however there will be warnings regarding the chewing or crushing of Embeda that may cause release of both morphine and naltrexone.

Problems regarding the carton and container have been noted in the review by DMETS and will be addressed during the labeling review.

Details regarding the REMS requirements for this product, including a MedGuide, are currently under discussion between CDER and OCC.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

I recommend Embeda for Approval for the management of moderate to severe pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time.

Risk Benefit Assessment

Embeda has satisfactorily been shown efficacious for the proposed indication in one adequate and well-controlled efficacy trial in patients with chronic pain due to osteoarthritis of the knee or hip. One efficacy trial is considered adequate for this product as it was shown to be bioequivalent to Kadian (extended-release morphine sulfate capsules), which is the reference drug in this 505(b)(2) application. There are no new or unexpected safety signals associated with Embeda, and its safety profile is similar to that of other extended-release opioid analgesics. Importantly, the presence of sequestered naltrexone in the formulation does not result in clinically significant systemic exposure to naltrexone or appear to be associated with additional adverse events beyond those expected for an opioid analgesic, nor does its presence appear to negatively impact the analgesic efficacy of Embeda. Therefore, in terms of labeled use of Embeda (intact formulation), the data presented do not reveal any increased risk to the patient nor decrease in efficacy resulting from the presence of sequestered naltrexone.

When Embeda is crushed and taken orally, the subsequent release and absorption of morphine and naltrexone may result in very high levels of systemic morphine, and levels of naltrexone that in some users may mitigate the euphoria and “drug-liking” associated with the morphine. In persons who are opioid-tolerant, the release and absorption of naltrexone may lead to withdrawal symptoms. In persons who are opioid naïve, the immediate-release of the morphine may result in potentially fatal systemic exposure to morphine, despite the presence of naltrexone in the formulation. The amount of naltrexone sequestered in Embeda has not been shown to fully reverse the effects of the morphine component of the capsule, and it is highly unlikely that this would occur given the low dose of naltrexone in the capsules.

The label for Embeda will contain strong and clear warnings regarding crushing or chewing of the capsules prior to ingestion and administration via routes other than the intended oral route.

(b) (4). A postmarketing epidemiologic study must be conducted that shows that this formulation is associated with a decrease in abuse in the general population.

Recommendation for Postmarketing Risk Management Activities

The requirement regarding a Risk Evaluation and Minimization Strategy (REMS) for this product is currently under discussion between CDER and OCC. While a REMS will likely be required, specific details are yet to be worked out regarding FDAAA requirements and specific details of the REMS itself. A memo detailing the risk management activity for this product will follow when these decisions are made.

Recommendation for other Postmarketing Study Commitments

Studies in the pediatric population are required according to PREA as outlined in Section 10 of this review.

The Controlled Substance Staff has recommended the following as a post-marketing study. Following discussion with Michael Klein, it is recommend that it be done on a voluntary basis, as the currently proposed labeling adequately manages the risks of extraction of morphine and naltrexone by stating the correct administration is via intact capsules/pellets.

- 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.

In discussions with CSS it was determined that the Applicant should be encouraged to conduct the following studies, and that a claim for “abuse resistance/deterrence” for Embeda can only be obtained when decreased abuse liability is demonstrated in the intended population based on postmarketing data.

- 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 Applicant 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.

Dr. Chen has recommended that a study be conducted to assess potential precipitation of opiate withdrawal syndrome associated with naltrexone release from intact Embeda in opioid-dependent patients. During the development program for Embeda, there were no cases of withdrawal syndrome reported in either opioid naïve or opioid experienced subjects. It appears unlikely that opioid withdrawal would result in opioid dependent patients given the low level of absorbed naltrexone from intact capsules even after prolonged use, the lack of any cases of opioid withdrawal syndrome reported during the development program, and the titration to effect method of use for opioid analgesics. Additionally, it would be unethical to induce opioid withdrawal in the patient population.

Other than the pediatric trials required by PREA, there are no required post-marketing study commitments.

Recommended Comments to Applicant

None

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/s/

Ellen Fields
12/11/2008 02:47:57 PM
MEDICAL OFFICER