

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-321

SUMMARY REVIEW



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

Summary Review for Regulatory Action

Date	August 13, 2009
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia and Rheumatology Products
Subject	Division Director Summary Review
NDA #	22-321
Applicant Name	Alpharma Pharmaceuticals LLC
Date of Submission	June 30, 2008
PDUFA Goal Date	December 31, 2008
Proprietary Name / Established (USAN) Name	Embeda/ Morphine sulfate and naltrexone HCl
Dosage Forms / Strength	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
Proposed Indication	For the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Jin Chen, M.D.; Ph.D.
Statistical Review	Katherine Meaker, M.S.; Dionne Price, Ph.D.; Thomas Permutt, Ph.D.
Pharmacology Toxicology Review	Elizabeth A. Bolan, Ph.D.; R. Daniel Mellon, Ph.D.
CMC Review	Elsbeth Chikhale, Ph.D.; Ali Al-Hakim, Ph.D.; Patrick Marroum, Ph.D.
Microbiology Review	N/A
Clinical Pharmacology Review	Srikanth C. Nallani, Ph.D.; Suresh Doddapaneni, Ph.D.
DSI	Susan Leibenhaut, M.D.; Constance Lewin, M.D.
CDTL Review	Ellen Fields, M.D.
OSE/DMEPA	Richard Abate, R.Ph., M.S.; Kellie Taylor, Pharm.D., M.P.H.; Carol Holquist, R.Ph.
OSE/DRISK (and risk management reviewers from other divisions/offices)	Jeanne Perla, Ph.D.; Mary Willy, Ph.D.; Marcia Britt, Ph.D.; Jodi Duckhorn, M.A.; Sharon Mills, BSN, RN CCRP; Mathilda Fienkeng, Pharm.D.; Twyla Thompson, Pharm.D.; Afrouz Nayernama, Pharm. D.; Claudia Karwoski, Pharm. D.
Controlled Substance Staff	James Tolliver, Ph.D.; Silvia Calderon, Ph.D.; Michael Klein, Ph.D.
DDMAC	Mathilda Fienkeng, Pharm.D.

OND=Office of New Drugs

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DSI=Division of Scientific Investigations

DRISK=Division of Risk Management

CDTL=Cross-Discipline Team Leader

DDMAC=Division of Drug Marketing, Advertising and Communications

1. Introduction

Alpharma Pharmaceuticals LLC has submitted a new drug application for an extended-release formulation of morphine. This reformulation was developed to provide, via the addition of sequestered naltrexone, a product that may result in less euphoria in some individuals if tampering occurs, as the release of naltrexone would antagonize the effect of the morphine. Therefore, for some individuals, compared to currently approved extended-release morphine products there is the potential of less abuse occurring via tampering. It should be noted, however, that abuse and misuse by taking multiple intact pills would not be affected by this formulation. Although Alpharma relies on their own NDA for Kadian (NDA 20-616, currently owned by Actavis Elisabeth LLC) as reference for the safety and efficacy of the morphine component of Embeda, they have submitted this application as a 505(b)(2) NDA referencing the Agency's previous findings of the safety of naltrexone HCl from NDA 18-932 for Revia. The sponsor has submitted data from a number of clinical pharmacology studies to support that, on average, Embeda's effect on "likeability" is decreased (for some but certainly not all subjects) when the product's controlled-release features are tampered with by crushing or extraction. I do note, however, that the decreased "likeability" is an overall average and some individuals still had maximal likeability scores and a euphoric effect was experienced by most subjects. This review will

focus on the quality of that data, on the potential impact of those effects on abuse, misuse and diversion, and on the adequacy of the sponsor's proposed Risk Evaluation and Mitigation Strategy (REMS) for this product. The sponsor has also submitted a single efficacy study (as per prior agreement with the Division) and an open-label safety study. The efficacy study clearly demonstrates that this extended-release morphine formulation provides adequate analgesic efficacy in patients suffering from chronic moderate to severe pain, and the efficacy and safety studies did not demonstrate any unusual or unexpected safety concerns.

2. Background

The efforts by a number of pharmaceutical companies to develop abuse-deterrent formulations of extended-release potent opioid products began following the extensive abuse of OxyContin that started soon after its introduction into the market and that continues to this day. Over the past eight years, FDA and other government agencies have attempted to limit the abuse, misuse and diversion of OxyContin and other potent opioid drug products, including morphine, by a variety of mechanisms, including the addition of stronger warnings in the products' labels, educational programs directed at youthful abusers, the implementation of multi-component risk management programs (that include physician/prescriber/patient education, as well as surveillance and intervention strategies for signals of abuse and diversion), and participation in numerous public hearings, Congressional briefings and advisory committee meetings. Unfortunately, these efforts have seemingly had little impact as, over this same period, the abuse of prescription drug products has continued to increase, and the abuse of opioid drug products has become a major public health concern across the country.

One additional effort to intervene in the abuse of prescription opioid drug products that has been recommended by the Agency, as well as by numerous other stakeholders, is the development of "abuse-resistant" formulations. FDA has encouraged the development of these formulations but has also been clear that we will not approve new indications for or labeling that is suggestive of abuse resistance for these new formulations unless an application is accompanied by data from long-term epidemiological studies that clearly demonstrate that abuse, misuse and diversion have been reduced. However, in order to provide some incentive to sponsors, above and beyond their public health responsibility, we have noted that we would consider allowing limited data from studies that evaluated the abuse-resistant features of the products to be added to appropriate sections of the labeling. As abuse-resistant formulations generally fall into two categories, those with changes to physiochemical properties and those with changes to pharmacologic properties, this information would most likely reside in the Product Description or Clinical Pharmacology sections of the product insert.

This new extended-release formulation of morphine, Embeda, provides the addition of sequestered naltrexone, a narcotic antagonist which, when the product is tampered with, may result in a reduction in the euphoria associated with the abuse of opioids and, therefore, perhaps a reduction in abuse, or at least a reduction in abusers tampering with the tablets in order to try and get an immediate release of the narcotic component. The

sponsor has submitted a number of studies intended to document the abuse resistant features of Embeda. Considering the potential for this product to have both a positive and/or a negative public health impact, the Agency felt that it was essential that the application be discussed at a joint public meeting of the Anesthesia and Life Support Drugs and the Drug Safety and Risk Management Advisory Committees. The joint committee meeting was held on November 14th, 2008. The general consensus of the committee members was that the data submitted in this application did describe an incremental improvement in formulation that may limit the euphorogenic quality of the morphine component in some patients when the product is crushed in order to abuse it. The committee members' discussion is reviewed in more detail below.

While the data available from the Drug Abuse Warning Network (DAWN) and other longitudinal databases that attempt to capture signals and levels of drug abuse in the U.S. show morphine products to be at the lower end of the opioid abuse spectrum, it is clear from the history of opioid drug abuse that restrictive controls on one potent opioid lead to the abuse of other less restricted potent opioids. As such, it is essential at this time that all potent, extended-release opioid drug products have similar controls over their distribution and use. While the scheduling requirements under the Controlled Substances Act certainly provide one means of limiting abuse of these products, clearly additional controls are needed for this class of products. Therefore, the Agency is in the process of establishing the standards for a class-wide REMS for potent, extended-release opioid products. All approved products in this class, as well as products seeking approval in this class, will be held to the same standard for implementation of an adequately designed REMS. However, that process will take additional time. Therefore, based on the fact that Embeda does not carry any novel risks compared to the already approved and marketed long-acting opioid products, the Agency has determined that it may be approved with an interim REMS that will be similar to the risk management plans already in existence for those products. In addition, we do not want to delay potential improvements in formulation while awaiting the finalization of a complicated REMS program. Once the class REMS has been finalized, the sponsor has agreed to work with the Agency to implement a new REMS that will address any changes from the interim REMS.

3. CMC

The CMC review team has found that this application can be approved from a product quality perspective. The following summary of Dr. Chikhale's review is reproduced from pages 4 and 5 of Dr. Fields' review:

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 released 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)



(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

No new non-clinical pharmacology or toxicology data were submitted. The review team found the application to be approvable pending certain labeling changes which have been agreed to by the sponsor.

5. Clinical Pharmacology/Biopharmaceutics

As per Dr. Nallani's review, Embeda is bioequivalent to Kadian under fasting conditions, whereas the Cmax was decreased by 22% for Embeda when taken with food. Plasma levels of naltrexone and its active metabolite 6-β-naltrexol, when detectable, were low and highly variable following single- and multiple-dose administration of intact capsules. Plasma levels of naltrexone ranged from 4 to 132 pg/mL; although the large majority of samples were below the limit of quantitation, 4.0 pg/mL.

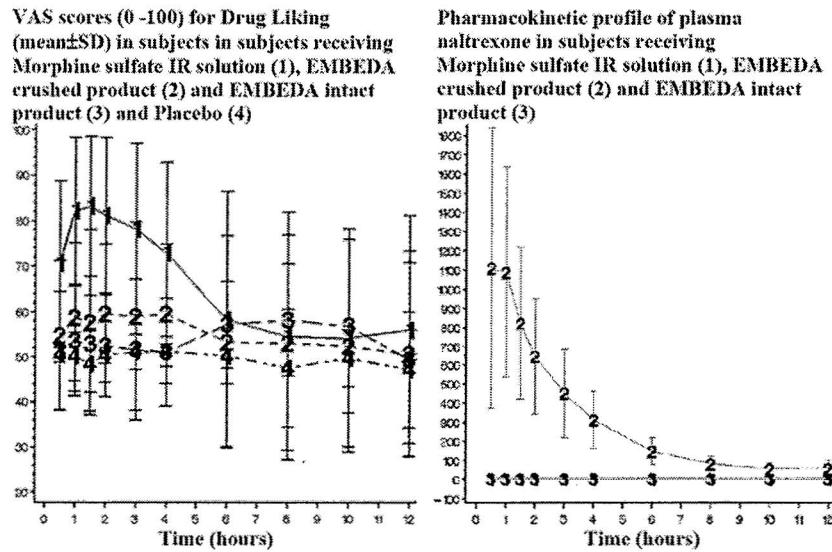
A number of studies were undertaken to assess the abuse resistant features of this novel product. Dr. Fields provides a concise summary of that data as reproduced below from pages 7 to 9 of her review:

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

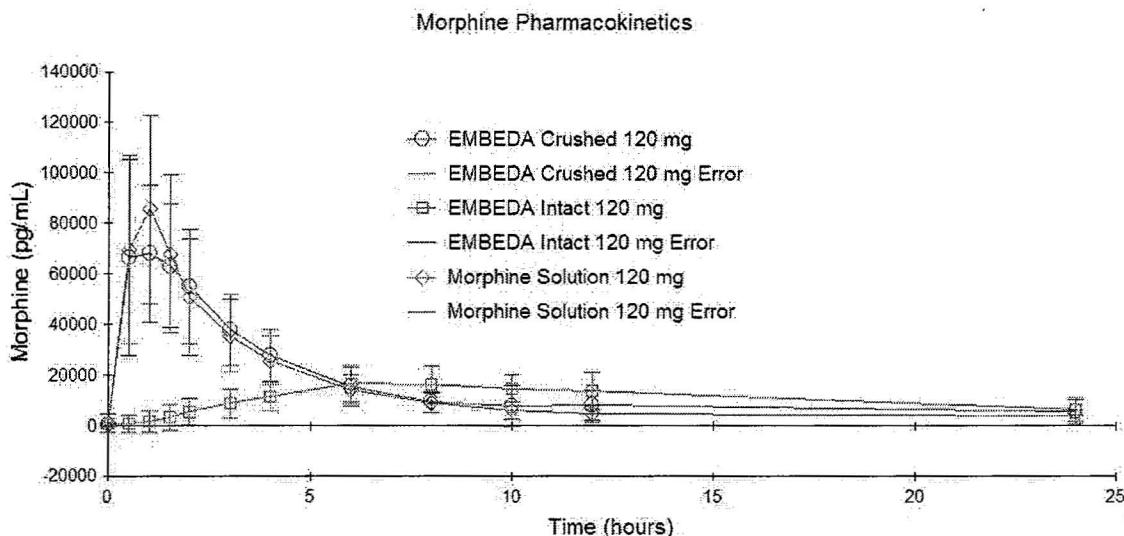


Note that there is no "1" line in the right hand figure because IR morphine solution does not contain naltrexone.

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

Best Available Copy



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.

Of note, a clinical alcohol interaction study did demonstrate dose dumping with co-administration of 40% alcohol. Cmax increased by 1.4 to 5.0 fold. A previously conducted in vivo alcohol interaction study with Kadian did not demonstrate dose dumping. The results of the clinical study detected no effect of alcohol on the sequestration of naltrexone. The clinical review team concluded that the increase in Cmax noted in the clinical study is not likely to result in a clinically concerning level of toxicity, and I concur. This finding has been adequately addressed by the inclusion of appropriate information in the product labeling.

6. Clinical Microbiology

There are no clinical microbiology concerns for this application.

7. Clinical/Statistical-Efficacy

Study ALO-KNT-301 was a randomized, double-blind, placebo-controlled trial that compared Embeda to placebo in the management of pain in subjects with moderate to severe chronic pain due to osteoarthritis of the hip or knee. An open-label titration to effect phase was followed by randomization and double-blind treatment with either the effective dose reached during the titration phase or placebo for twelve weeks. Symptoms

of opioid withdrawal were documented for the double-blind period. Ms. Meaker and Drs. Chen and Fields have provided thorough and complete reviews of this trial and the reader is referred to those reviews for further details of the study design and conduct.

The primary endpoint was the mean change of weekly Brief Pain Inventory daily average pain scores from randomization baseline (last seven days of the titration phase) to Week 12. The following table from page 13 of Dr. Fields' review summarizes the results of the primary outcome analysis:

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

Analysis method	Pain Intensity, mean(SD)		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 (post hoc)			
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.

The secondary endpoint analyses were supportive of the above findings.

8. Safety

Drs. Chen and Fields have fully assessed the safety data in this application and concluded that there were no unusual or unexpected adverse events or laboratory results, i.e., the safety profile of Embeda appears to be equivalent to other high potency extended-release opioid drug products. I concur with their conclusions.

In addition to the safety profile for the patient, we must also consider the public health concerns related to abuse and misuse of a potent opioid drug product such as Embeda. The added naltrexone is meant to reduce the abuse of the product compared to other extended-release morphine products. However, the data from the studies submitted by the sponsor to support this feature do not provide particularly compelling evidence. From pages 3 and 4 of Dr. Tolliver's review for CSS:

...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 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 analysis¹ 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 analysis³ 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.
 - [REDACTED]

(b) (4)

¹ 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.

- 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 Cmax value was approximately 2-fold higher, while the time (Tmax) to reach Cmax 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.²
- 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.

However, as Dr. Fields notes in her review, based on a discussion with Dr. Klein it was clear that these recommendations were not intended to be post-marketing commitments. I do not think the first two recommendations would provide additional useful data. The third recommendation may be appropriate when the class-wide REMS for long-acting, potent opioids is implemented. However, for the interim REMS, the sponsor will not be required to undertake this evaluation as the risk management programs for the currently

² Johnson et al (2008). Journal of Pain, 9 (4): 330-336.

approved long-acting morphine products do not require a similar evaluation of their impact on actual abuse.

9. Advisory Committee Meeting

The following questions were posed to the joint advisory committee members at the May 5th meeting:

1. a. Discuss the adequacy of the tools we have to assess the impact of a novel opioid formulation on abuse, misuse and diversion of the product in the community.
 - b. Discuss whether or not the available data suggest that this formulation will be less susceptible to abuse and misuse.
2. Many of the cases of addiction, overdose and death are associated with abuse of intact controlled-release opioid products. EMBEDA is formulated to release naltrexone only following physical manipulation.
 - a. Discuss whether inclusion of data on the release characteristics of the naltrexone in this new formulation into the product labeling could potentially mislead prescribers or patients into thinking that this new formulation, when taken as directed, is less likely to be addictive, or unlikely to be abused or result in addiction or overdose.
 - b. If you believe that patients or prescribers could be misled, discuss whether this risk is acceptable, considering the potential benefits of the changes to the formulation.
3. a. If, from Question 1, you believe that the data suggest that this formulation of controlled-release morphine is likely to reduce its abuse and misuse, discuss whether or not any of the data should be included in the product labeling.
 - b. If so, which specific data do you think should be incorporated into the labeling?

On pages 20 and 21 of her review, Dr. Fields summarizes the comments from the meeting as follows:

- 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 [redacted] (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

- 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 extremely 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.

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues.

12. Labeling

There are no outstanding labeling issues.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action
 - Approval
- Risk Benefit Assessment

Controlled-release potent opioid drug products are essential components of the analgesic armamentarium for the treatment of chronic pain. Not only do they provide convenience to patients by reducing the number of daily doses required, but they also provide a pharmacokinetic profile that results in reduced serum level peaks and troughs, and thereby an improvement in the consistency of effective analgesia and a potential reduction in opioid-related side effects that are often correlated with high peak serum levels. However, the abuse, misuse and diversion of these products have had a profound impact on the public health. Therefore, providing even an incremental decrease in the abuse of prescription opioid products would be an important public health achievement. While it is not clear at this time whether the tools that are currently available to measure the impact of formulation changes on the abuse, misuse and diversion of prescription opioid products are adequate to provide an accurate assessment, it should not preclude us from proceeding with these efforts. It is essential that we tread cautiously as we move forward, counterbalancing two equally important considerations. First, by approving this application might we potentially be promoting the product in a manner that would lead to misconceptions about its abuse potential? I do not think this is the case as the labeling clearly reflects the incremental nature of

reduction in likeability that occurs with naltrexone release from Embeda. In addition, the labeling clearly states that we do not know what if any impact this change in formulation might have on actual abuse and misuse. Counterbalancing this, if we were to not approve this product, or restrict its use, might we be limiting availability of a product for patients with chronic pain that is safe and effective when used properly? The interim REMS for Embeda does not restrict access to the product. The impact of restriction of opioid drugs is a factor that the Agency is seriously considering as we evaluate the potential features of a class-wide REMS.

It does appear that this novel formulation of morphine with naltrexone may provide an incremental reduction in the euphoria experienced by some abusers when the capsules are crushed. The data demonstrate, however, that a proportion of abusers are likely to still achieve a “high” even with the compromised product and the release of naltrexone, some having likeability scores of 100% in comparison to the likeability of immediate-release morphine solution. Nevertheless, as noted above, even an incremental change in the direction of possibly reducing abuse and misuse is likely to be important, as long as safety has not been compromised by the changes in formulation.

The sponsor has submitted an adequate interim REMS. (See discussion in Section 2 and below.)

- Required Postmarketing Risk Evaluation and Mitigation Strategy

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Embeda to ensure that the benefits of the drug 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. The Agency is currently considering what REMS elements should be implemented across the class of modified-release opioids to address the risks of abuse, misuse and overdose. As noted above, this application will be approved with an interim REMS and the sponsor has agreed to implement the class-wide REMS when that plan has been finalized by the Agency. The following has been reproduced from pages 2 and 3 of Dr. Fields’ addendum to her CDTL memo and summarizes the features of the Embeda interim REMS:

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.

...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.

- Post-Marketing Requirements (PMRs)

The only PMRs for this application are the pediatric studies in children ages 2 to 17 years described in Section 10 above.

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/s/

BOB A RAPPAPORT
08/13/2009