

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-321

PHARMACOLOGY REVIEW(S)



FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Rheumatology Products
10903 New Hampshire Avenue, Silver Spring, MD 20993

**SUPERVISOR'S SECONDARY REVIEW
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION**

NDA number: 22-321
Drug Substance: Embeda (morphine sulfate and naltrexone hydrochloride)
PDUFA Goal Date: 30-Dec-2008
Sponsor: Alharma

Reviewer name: R. Daniel Mellon, Ph.D., Pharmacology Toxicology Supervisor
Division name: Division of Anesthesia, Analgesia, and Rheumatology Products
Review completion date: 1-Dec-2008

Recommendation: Approval

I have read Dr. Elizabeth Bolan's review of the nonclinical pharmacology and toxicology sections of NDA 22-321 and agree with her conclusion that the NDA may be approved. I also concur with her recommendations for the nonclinical portions of the labeling.

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

/s/

R. Daniel Mellon
12/1/2008 02:58:14 PM
PHARMACOLOGIST



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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22-321
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: June 30, 2008
PRODUCT: Embeda, morphine sulfate and sequestered
naltrexone hydrochloride
INTENDED CLINICAL POPULATION: Embeda is indicated for management of moderate
to severe chronic pain
SPONSOR: Alpharma Pharmaceuticals, LLC
DOCUMENTS REVIEWED: All nonclinical information in the above
submission
REVIEW DIVISION: Division of Anesthesia, Analgesia, and
Rheumatology Products (HFD-170)
PHARM/TOX REVIEWER: Elizabeth A. Bolan, Ph.D.
PHARM/TOX SUPERVISOR: R. Daniel Mellon, Ph.D.
DIVISION DIRECTOR: Bob Rappaport, M.D.
PROJECT MANAGER: Christopher Hilfiger

Date of review submission to Division File System (DFS): December 1, 2008

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

This NDA can be approved from a nonclinical pharmacology/toxicology perspective.

B. Recommendation for nonclinical studies

There are no recommendations for nonclinical studies.

C. Recommendations on labeling

The table below contains the draft labeling submitted by the Applicant, the proposed changes and the rationale for the proposed changes. For the final version of the label, please refer to the Action Letter. Note: The recommended changes from the proposed labeling are in red or strikeout font.

Applicant's proposed labeling	Reviewer's proposed changes	Rationale for changes
(b) (4)		

(b) (4)

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Alpharma has submitted an NDA for Embeda, an extended release morphine product with properties purported by the Applicant to confer abuse deterrence. The capsules are filled with individual pellets consisting of various layers of morphine sulfate (MOR), naltrexone HCl (NTX) and excipients designed to provide a controlled release profile for the MOR component of the drug product and to adequately sequester the NTX when the product is used as labeled. The Applicant states that upon crushing or chewing of the product the NTX will be released and should abate the liking and euphoric effects of MOR. The capsules contain a 25:1 fixed ratio of MOR to NTX and will be available in 20/0.8, 30/1.2, 50/2, 60/2.4, 80/3.2 and 100/4 mg/mg MOR/NTX. If taken as prescribed, MOR is released over a period of 12 hours and little or no NTX should be liberated. The indication sought by the Applicant is management of moderate to severe (b) (4) pain. This application was submitted via the 505(b)(2) pathway with the reference listed drugs as Kadian (NDA (b) (4)) for MOR and ReVia (NDA 18-932) for NTX. No pharmacology or toxicology studies were submitted in support of this NDA. The Applicant is relying on the data in the Kadian NDA (owned by Alpharma), the Agency's previous findings of safety and efficacy for Revia, and information from the literature. The Applicant has provided a review of the current literature for MOR and NTX.

B. Pharmacologic activity

Morphine is a phenanthrene opioid agonist that is relatively selective for mu opioid receptors; exhibiting a 10-fold higher selectivity for the mu receptor than for the delta and kappa opioid receptors. Morphine exerts its primary pharmacodynamic effect, analgesia, through activation of the mu opioid receptor. The pharmacology and toxicology of morphine have been well characterized.

C. Nonclinical safety issues relevant to clinical use

There are no nonclinical safety issues unique to this product relevant to clinical use for NDA 22-321.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-321

Review number: 1

Sequence number/date/type of submission: 000/June 30, 2008/original submission

Information to sponsor: Yes () No (X)

Sponsor and/or agent: Alpharma Pharmaceuticals, LLC

Manufacturer for drug substance: (b) (4)

Reviewer name: Elizabeth A. Bolan, Ph.D.

Division name: Division of Anesthesia, Analgesia, and Rheumatology Products

HFD #: 170

Review completion date: November 25, 2008

Drug:

Trade name: EMBEDA™

Code name: ALO-01, Kadian NT

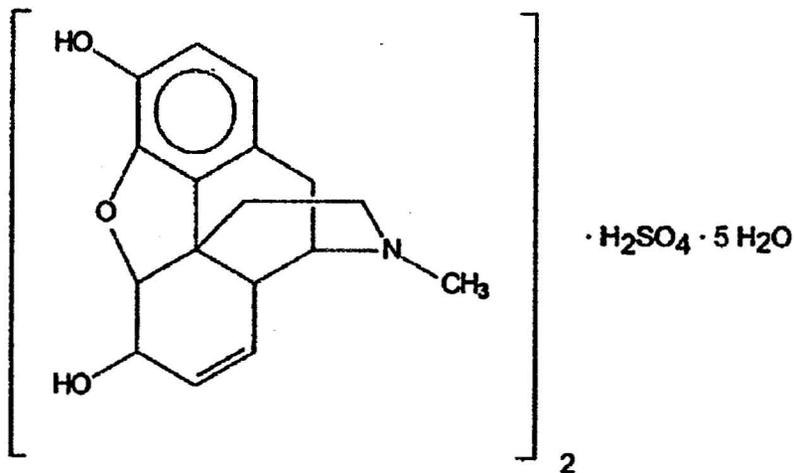
Generic name: **morphine sulfate**

Chemical name: morphinan-3,6- α -diol, 7,8-didehydro-4, 5- α -epoxy-17-methyl-, sulfate

CAS registry number: 64-31-3

Molecular formula/molecular weight: $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5 H_2O$ MW= 758.85

Structure:



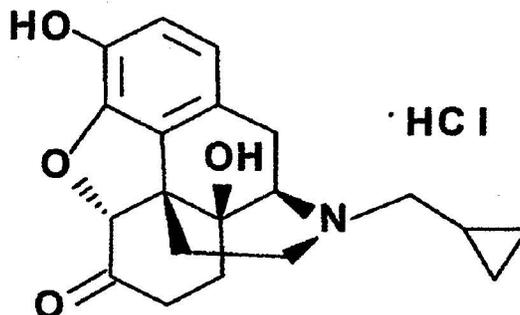
Generic name: **naltrexone hydrochloride**

Chemical name: morphinan-6-one, 17-(cyclopropylmethyl)-4,5-alpha-epoxy-3,14-dihydroxy-, hydrochloride

CAS registry number: 16676-29-2

Molecular formula/molecular weight: C₂₀H₂₃NO₄•HCl MW=377.46

Structure:



Relevant INDs/NDAs/DMFs:

<i>IND/ND/MF</i>	<i>drug/compound</i>	<i>Sponsor</i>	<i>Division</i>	<i>status</i>
IND 70,853	Kadian NT	Alpharma	DAARP	active
(b) (4)				

NA= not applicable

Drug class: opioid receptor agonist, narcotic (with sequestered opioid receptor antagonist)

Intended clinical population: management of moderate to severe chronic pain

Clinical formulation: Embeda (ALO-01) is an extended release MOR capsule with properties purported by the Applicant to confer abuse deterrence. The capsules are comprised of individual pellets containing layers of MOR, NTX and various excipients to provide a controlled release profile for the MOR and to sequester the NTX when the product is used as labeled. (b) (4)

The capsules contain a 25:1 fixed ratio of MOR to sequestered NTX and will be available in capsules containing 20/0.8, 30/1.2, 50/2, 60/2.4, 80/3.2 and 100/4 mg/mg of MOR/NTX. If taken as prescribed, MOR is released over a period of 12 hours. The Applicant states that upon crushing or chewing of the product the sequestered

NTX will be released and should abate the liking and euphoric effects of MOR (see clinical review by Dr. Jin Chen for details).

Excipients

All of the excipients in the Embeda formulation are found in approved drug products. However, in some cases the levels of the excipients in the Embeda drug product will exceed levels in previously approved drugs when the MFDI of MOR is consumed. The excipients in the Embeda formulation, their function and amounts are presented in Table 1.

The majority of the components of the Embeda formulation (ethylcellulose, talc, (b) (4), hydroxypropyl cellulose, polyethylene glycol and diethyl phthalate) are found at similar levels in the approved Kadian drug product (Table 1). The intended clinical population for the Embeda product is similar to that of Kadian. Embeda is expected to be used at similar dose and duration to Kadian. Kadian has been on the market since 1996 and extensive clinical experience exists. No excipient-related safety signals have arisen with Kadian. The excipients which are common to both the Embeda and Kadian formulations are considered to be qualified.

Several excipients in the Embeda formulation (ascorbic acid, sodium chloride and sugar spheres) are commonly found in food products and have GRAS status (Table 1). Magnesium stearate and sodium lauryl sulfate are found at higher levels in FDA approved products than in the Embeda formulation and appear in the Inactive Ingredients Database (Table 1). Excipients that have GRAS status or appear at higher levels in the Inactive Ingredients Database are considered qualified.

Dibutyl sebacate and (b) (4) are not found in the Kadian formulation but are found in other FDA approved drug products (Table 1). The levels of dibutyl sebacate in Embeda will exceed levels in previously approved drugs when the maximum daily dose (MDD) of MOR is consumed. Dibutyl sebacate and (b) (4) are discussed in detail below.

<i>Table 1</i>		<i>Embeda formulation</i>			
<i>excipient</i>	<i>function</i>	<i>amount per 100 mg capsule of Embeda, mg</i>	<i>amount per 5 100 mg capsules of Embeda*, mg</i>	<i>amount per 20 100 mg capsules of Embeda**, mg</i>	<i>rationale for acceptability of amounts in Embeda</i>
ethylcellulose				(b) (4)	Kadian
magnesium stearate					IIG
dibutyl sebacate					max TDI in IIG 86 mg
talc					Kadian

(b) (4)		(b) (4)	in approved product
			Kadian
hydroxypropyl cellulose	(b) (4)		Kadian
ascorbic acid			GRAS
sodium lauryl sulfate			IIG
sodium chloride			GRAS
polyethylene glycol			Kadian
diethyl phthalate			Kadian
sugar spheres			GRAS

*5 100 mg capsules equal 500 mg of morphine which is the dose below which the majority of patients who use morphine containing products consume on a daily basis.
 **20 100 mg capsules equal 2 g of morphine which is the maximum feasible daily dose as determined by DAARP clinicians.

Kadian= the ingredient is found in the approved Kadian formulation at similar levels.

IIG= the ingredient is found in the FDA Inactive Ingredients Database at higher levels than present in the Embeda formulation.

GRAS= the ingredient is considered **“Generally Recognized as Safe”** at levels found in the Embeda formulation.

Dibutyl Sebacate

Dibutyl sebacate (CAS # 109-43-3) is the dibutyl ester of sebacic acid. It is used in pharmaceutical applications as a plasticizer for film coating of tablets or granules. Dibutyl sebacate is also used as a flavoring additive in several food products and a lubricant in shaving lotions. Other commonly used names for dibutyl sebacate include:

(b) (4)

Dibutyl sebacate is present in levels up to 86 mg TDI in approved drugs as listed in the FDA Inactive Ingredients Database. The TDI of dibutyl sebacate from the Embeda drug product if the MDD of MOR was consumed is (b) (4). This amount would exceed this currently approved level (86 mg TDI) by (b) (4). However, according to reports in the literature and the prescribing data for MOR products from the OSE consult (see **“Determination of the maximum daily dose of morphine” below**) show that the majority of patients take < 500 mg/day (Levy MH and Samuel TA, 2005) With a daily dose of

Embeda of < 500 mg, the amount of dibutyl sebacate consumed would be < (b) (4) TDI which is below approved levels. Dibutyl sebacate is a commonly used (b) (4) and the amounts in the Embeda drug product for the small portion of the population of patients who require the very high doses of MOR should not present any unique toxicological concerns. No further toxicologic evaluation is necessary.



In the Embeda formulation, (b) (4) is a component (b) (4) used to (b) (4) of MOR. It is found in similar levels in the Kadian drug product as well as several other approved products. Extensive clinical experience with Kadian exists and no excipient-related safety signals have arisen. The levels of (b) (4) in the Embeda formulation do not present any toxicologic concern.



The generic ER oxycodone (ANDA 75-923) is owned by Endo Pharmaceuticals and was approved in September 2004. Prior to approval, Endo was sued for patent infringement by Purdue Pharma. In January of 2004, all claims were dismissed against Endo and the Agency issued an approval letter for ANDA 75-923. **The ruling in Endo's favor was overturned at a later date and in January 2007, the approval of ANDA 75-923 was converted to a tentative approval. This tentative approval will remain in effect until the contested patents expire. The product can not be marketed with a tentative approval. In issuing the original approval in 2004, the Agency had assessed the safety of ANDA 75-923. Although the Endo generic ER oxycodone product is currently under tentative**

approval and is not marketed for legal reasons, **the Agency's conclusions on the safety of the formulation still stands.** Therefore, the level of (b) (4) in the Embeda formulation, which is less than in the approved generic ER product, does not present any unique toxicologic concerns and is considered acceptable.

Residual monomer specifications (NF) for (b) (4) are set at NMT (b) (4)% for (b) (4) and (b) (4) for (b) (4). Actual measured levels of monomers were (b) (4)% for each individual monomer. The total residual monomer specification (NF) for (b) (4) is set at NMT (b) (4)%. Actual measured levels of total monomers were (b) (4)%. The specifications for the monomers for both (b) (4) polymers are acceptable from a toxicology perspective. The chemistry reviewer has found the specifications and the NF methods acceptable (see CMC review by Dr. Elsbeth Chikhale).

Determination of the maximum daily dose of morphine

The maximal dosing information for MOR is relevant to this review in that the ICH specifications for impurity levels for the drug substance and the drug product as well as the acceptable levels of total amount of inactive ingredients are based on the total daily dose of the drug substance.

The development of tolerance to the effects of an opioid precludes easily defining a MDD. The reduced effectiveness as a result of tolerance necessitates increased dosing in order to maintain the desired therapeutic effect. Therefore, in an opioid tolerant individual, very high daily doses are theoretically possible. Because the dosing is tailored to the individual needs of the patient it not possible to set a MDD that fits all patients. In a review entitled "Management of Cancer Pain", Levy and Samuel (2005) state:

Although pain can be controlled in most patients with 240 mg or oral morphine per day or less (Coyle N et al., 1990), patients with severe cancer pain may require 1,200 to 1,800 mg of oral morphine per day (Brescia FJ et al., 1992) and a few patients may require 1,000 to 4,500 mg of parenteral morphine per hour (Foley KM, 1993).

The Division consulted the Division of Epidemiology in the Office of Surveillance and Epidemiology (OSE) in order to obtain a sense of the current utilization patterns and trends for MOR products to aid in their determination of an MDD for MOR. Using **information from Verispan's Vector One National (VONA) and Physician's Drug and Diagnosis Audit (PDDA) databases**, the consult summarized the dispensed prescriptions of oral MOR sulfate products by strength and daily dose prescribed by office-based physicians in an outpatient setting for years 2002 through August 2008. The most commonly prescribed daily dose was 60 mg/day followed by 120 mg/day which accounted for (b) (4) respectively, of the share of total oral MOR sulfate prescriptions written in 2008 (Jan-Aug). The largest daily dose was 480 mg/day which accounted for (b) (4) of the written prescriptions in 2008 (Jan-Aug; See OSE consult by Laura Governale dated October 3, 2008).

Using the current MOR prescribing data provided in the OSE consult, their own clinical experiences and references from the literature, the clinicians in DAARP have determined that a reasonable MDD of MOR in an opioid tolerant individual is 2 g/day.

Impurities in the morphine drug substance

The qualification threshold according to the ICH Q3A (R2) guidance for impurities in the drug substance for a MDD of ≤ 2 g/day is 0.15% or 1 mg/day intake, whichever is lower. In order to remain below the ICH threshold for qualification for an MDD of 2 g for MOR, the specification for impurities in the MOR drug substance must be set at (b) (4)%. The Applicant has set the specifications for impurities in the drug substance at (b) (4) (A)% (unless otherwise noted, see Table 2) and no further qualification will be necessary. Specific impurities are discussed below.

(b) (4)
For NDA 22-321, (b) (4) and (b) (4) are the DMF holders for the MOR sulfate drug substance. (b) (4) is an impurity found in the MOR sulfate drug substance which contains an (b) (4) structural alert for genotoxicity. The (b) (4) moiety has been demonstrated to be reactive with DNA resulting in genotoxicity and mutagenicity (b) (4). As potentially genotoxic substances present a safety concern, the Agency maintains that such substances should be tested for their genotoxic potential or reduced to acceptable levels. Current Agency policy on acceptable levels for potentially genotoxic agents is NMT 1.5 mcg/day.

In May, 2007, (b) (4) submitted study reports for a Bacterial Reverse Mutation Assay (Ames test) and an *In Vitro* Mammalian Chromosome Aberration Test with (b) (4) to DMF (b) (4). These studies were reviewed by Dr. R. Daniel Mellon in a review dated January 7, 2008. (b) (4) was found to be negative in both assays and will be considered by the Agency to be negative for genotoxic potential. The above studies were also submitted to (b) (4). Since (b) (4) was determined to be non-genotoxic under the conditions of the assays conducted, acceptable levels for (b) (4) will be based on specifications (as per ICH Q3A and ICH Q3B) for levels of an ordinary non-genotoxic impurity for (b) (4). The current specification of NMT (b) (4)% for (b) (4) proposed by the Applicant for the drug substance is adequate (Table 2).

Normorphine

Normorphine has been shown to be a minor human metabolite of MOR (Brunk SF and Delle M, 1974). The current specification of NMT (b) (4)% for normorphine proposed by the Applicant for the drug substance is adequate (Table 2).

(b) (4)
(b) (4) is an FDA approved compound and has a long history of safe use. The current specification of NMT (b) (4)% for (b) (4) proposed by the Applicant for the drug substance is adequate (Table 2).

(b) (4)
 (b) (4) is an FDA approved compound and has a long history of safe use. The current specification of NMT (b) (4) % for (b) (4) proposed by the Applicant for the drug substance is adequate (Table 2).

<i>Table 2 Specifications of morphine sulfate drug substance impurities</i>		
<i>Impurity</i>	<i>Specification limit</i>	<i>Acceptable?</i>
(b) (4)	(b) (4)	yes
(b) (4)	(b) (4)	yes
(b) (4)	(b) (4)	yes
(b) (4)	(b) (4)	yes
(b) (4)	(b) (4)	yes
(b) (4)	(b) (4)	yes
(b) (4)	(b) (4)	yes

Impurities in the naltrexone drug substance

The specifications for identified impurities found in the NTX drug substance are below ICH Q3A (R2) thresholds for qualification of 0.15% or 1 mg/day intake for an MDD of ≤ 2 g/day of NTX (Table 3). Specific impurities and the determination of the MDD of NTX are discussed below.

(b) (4)
 The impurity (b) (4) contains an (b) (4) structural alert for genotoxicity. See discussion (b) (4) above. At the current specification of (b) (4) % in the drug substance and (b) (4) % in the drug product with a total daily intake of < 1 mg NTX the limit of NMT 1.5 mcg/day will be met (Tables 3 and 4).

<i>Table 3 Specifications of naltrexone hydrochloride drug substance impurities</i>		
<i>Impurity</i>	<i>Specification limit</i>	<i>Acceptable?</i>
(b) (4)	(b) (4)	yes
(b) (4)	(b) (4)	yes
(b) (4)	(b) (4)	yes
(b) (4)	(b) (4)	yes
(b) (4)	(b) (4)	yes
(b) (4)	(b) (4)	yes
(b) (4)	(b) (4)	yes
unknown related compounds	NMT (b) (4)	yes

Impurities in the Embeda drug product

The qualification threshold according to the ICH Q3B (R2) guidance for impurities/degradants in the drug product for an MDD of the drug substance administered per day (MDD of MOR is 2 g/day) is 0.2% or 3 mg TDI, whichever is lower. In order to remain below the ICH threshold for qualification, the specification for MOR-derived

impurities/degradation products in the drug product must be set at (b) (4)%. The Applicant has set the stability specifications for MOR-derived impurities/degradation products at (b) (4)% (Table 4) and no further qualification will be necessary. The MDD of NTX (see discussion below) is < 1 mg/day, therefore the qualification threshold according to the ICH Q3B (R2) guidance for impurities/degradants arising from the NTX drug substance is 1.0% or 50 mcg TDI, whichever is lower. The Applicant has set the stability specifications for NTX-derived impurities/degradation products at (b) (4) or below (Table 4) and no further qualification will be necessary. Specific impurities are discussed below.

(b) (4)
The Applicant submitted a request for a review of data relating to the qualification of (b) (4) (IND 70,853 SN-0024 IT/IC). (b) (4) is a degradant found in the NTX component of Kadian NT. Please refer to the review dated September 25, 2007 by Dr. Elizabeth Bolan for full review of SN-0024. Details relevant to NDA 22-321 are summarized below.

Stability studies have shown that (b) (4) is formed in the drug product. Based on extrapolated nine-month stability data, the Applicant noted that (b) (4) may reach a level of (b) (4) and possibly exceed ICH thresholds. The Applicant inquired about whether the regulatory limit for the impurity qualification would be based on the total amount of sequestered NTX present in the drug product or the released amount of the NTX when the product is taken as directed. There are no structural alerts for genotoxicity present in (b) (4).

It was communicated to the Applicant at the pre-NDA meeting on October 2, 2007 that the regulatory limit for the impurity qualification would be based on the total amount of NTX in the drug product using the MDD of MOR unless they could provide clear data-driven justification that only a portion of the total NTX is released from the drug product during labeled use. In addition, the Applicant would have to demonstrate that (b) (4) is released at a similar rate or magnitude as NTX (*i.e.* the (b) (4) is not preferentially leached out). If these criteria can be met, then the impurity specifications can be based on the amount of NTX that is released when the product is used as labeled.

The Applicant has adequately demonstrated that when the drug product is used appropriately systemic levels of NTX were very low (Study # ALO-KNT-302; see Clinical Pharmacology review by Dr. Srikanth Nallani for details). In an *in vitro* dissolution assay, the Applicant has shown that (b) (4) does not preferentially leach out of the NTX component of the drug product (Study # TR-0028). Therefore, the regulatory levels will be based on the total amount of NTX that is released. The threshold for qualification of impurities as per ICH Q3A (R2) in the drug substance for a maximum daily NTX dose of ≤ 2 g/day is 0.15% or 1 mg/day, whichever is lower. The threshold for qualification of impurities/degradants as per ICH Q3B (R2) in the drug product for a MDD of < 10 mg/day is 1% or 50 mcg/day, whichever is lower. The current specifications proposed by the Applicant for (b) (4) in the drug substance (NMT (b) (4)%) and the drug product (NMT (b) (4)) are acceptable (Tables 3 and 4).

(b) (4)
 See discussions above

<i>Table 4</i>			
<i>Specifications of Embeda drug product impurities/degradants</i>			
<i>Source</i>	<i>Impurity/degradant</i>	<i>Stability specification limit</i>	<i>Acceptable?</i>
<i>morphine</i>		(b) (4)	yes
			yes
			yes
			yes
<i>naltrexone</i>			yes
			yes
			yes
			yes

Route of administration: oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-321 are owned by Alpharma or are data for which Alpharma has obtained a written right of reference. Any information or data necessary for approval of NDA 22-321 that Alpharma does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Alpharma does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-321.

Studies reviewed within this submission:
 No new studies were submitted with this submission.

Studies not reviewed within this submission:
 No new studies were submitted with this submission.

2.6.2 PHARMACOLOGY

No new pharmacology studies were submitted by the Applicant. The following summary of morphine pharmacology was excerpted from a general morphine pharmacology review by Dr. BeLinda Hayes. Dr. Hayes' summary is denoted by indented text.

2.6.2.1 Brief summary

Morphine, a phenanthrene opioid, is one of the most effective analgesics and is the prototype against which all other opioids are measured. Morphine sulfate has been used for many years in the management of pain. It was first approved by the Food and Drug Administration (FDA) in September of 1984 under the trade name Duramorph[®] Preservative-free Injection (NDA 18-565; Baxter Healthcare) for intrathecal and epidural administration. Today, morphine sulfate is marketed in a variety of formulations, including oral solutions, immediate- and sustained-release tablets and capsules, suppositories and injectable preparations. Morphine is marketed under generic and brand name products including MS-Contin[®], Oramorph SR[®], Avinza[®], Duramorph PF[®], Depodur[®], and Kadian[®].

Morphine is an opioid agonist with activity at μ -, κ - and δ -opioid receptors. Activation of μ -opioid-receptors is associated with analgesia, respiratory depression, sedation, decreased gastrointestinal motility, euphoria and physical dependence. Morphine actions at the κ -opioid receptors are associated with spinal analgesia, miosis and psychotomimetic effects.

2.6.2.2 Primary pharmacodynamics

Mechanism of action:

Morphine mediates its primary pharmacodynamic effect, analgesia, through activation of μ -opioid receptors.

Drug activity related to proposed indication:

Mu opioid receptors are highly concentrated in regions of the central nervous system involved with the neuronal circuitry involved with the processing of nociceptive information; the periaqueductal and periventricular gray matter, ventromedial medulla and spinal cord. The pain modulating effects of morphine ensue from its direct inhibition of the ascending transmission of nociceptive information from spinal cord dorsal horn and to the activation of the pain control circuits that descend from the midbrain via the rostral ventromedial medulla to the spinal cord dorsal horn.

2.6.2.3 Secondary pharmacodynamics

Morphine's secondary pharmacological effects include dysphoria, euphoria, sedation, respiratory depression, decreased gastrointestinal motility and physical dependence.

These pharmacodynamic effects have been extensively reviewed in the published literature.

2.6.2.4 Safety pharmacology

Neurological effects: No nonclinical safety pharmacology studies were conducted to evaluate potential central nervous system safety concerns.

Cardiovascular effects: Animal studies had shown that morphine causes hemodynamic changes. In conscious dogs, morphine initially induced coronary vasodilation followed by a sustained reduction in coronary blood flow and significant coronary vasoconstriction followed by hypotension (Vatner SF et al., 1975). Morphine induces the release of histamine. High doses of morphine cause the release of histamine that induces peripheral vasodilation, with significant hypotension. In contrast to the results observed in dogs, when morphine was the sole medication administered to healthy humans, no hypotensive effects were observed; only stimulatory effects were observed. Morphine (0.07 mg/kg and 0.14 mg/kg) elicited a dose-dependent increase in mean arterial blood pressure, heart rate and oxygen consumption (Mildh LH et al., 2000) release (increase redness and itching at the injection site).

Morphine can cause hemodynamic changes and cardiovascular adverse reactions. These adverse effects include: bradycardia, sinus tachycardia, palpitations, hypotension, hypertension, orthostatic hypotension, diaphoresis, and syncope. Orthostatic hypotension is a secondary effects resulting from morphine-induced peripheral vasodilatation.

Pulmonary effects: Respiratory depression is a clinically significant effect of morphine. At high doses, morphine causes respiratory depression, pulmonary edema and respiratory arrest. Like other opioids, morphine decreases the responsivity of the brain stem respiratory center to CO₂ and depression of pontine and medullary centers via its action at the mu₂ opioid receptors.

Renal effects: The Applicant did not conduct formal safety pharmacology studies to evaluate potential renal safety concerns with morphine administration. A review of the literature did not identify any animal studies that specifically addressed morphine-related renal effects.

However, morphine does present some safety concerns in patients with HIV-associated nephropathy and renal failure. Patients with HIV-associated nephropathy are often intravenous users of heroin. Morphine is an active metabolite of heroin and has been associated with the renal interstitial fibrosis observed in heroin-associated glomerulosclerosis. *In vitro* studies have demonstrated that morphine has the potential to modulate proliferation of kidney fibroblasts (Singhal PC et al., 1998). Cultured rat kidney fibroblasts were exposed to morphine at concentrations in the range of 10⁻¹² M to 10⁻⁴ M for 24 hours or 48 hours.

At both incubation periods, low concentrations of morphine (10^{-12} M), induced proliferation of fibroblasts.

Chronic use of morphine in patients with renal failure should be used with caution (Angst MS et al., 2000). Morphine-6-glucuronide (M6G), a pharmacologically active metabolite of morphine is cleared via the kidney. In patients with renal failure, M6G will accumulate and allow opioid side effects to persist hours after plasma concentration of morphine has peaked and M6G plasma concentration has peaked.

Gastrointestinal effects: Gastrointestinal side effects are the major adverse effects associated with acute and chronic use of morphine. Inhibition of gastrointestinal motility (i.e., propulsive peristalsis) is a long-known classical effect of morphine. In addition to this effect, like other opioid drugs, morphine exerts a wide spectrum of other effects on the mammalian intestinal function. These effects include reduction in secretions (pancreatic, biliary, and electrolyte/fluid) and increases in intestinal fluid absorption and blood flow (Brown RD and Miller R, 1989). Morphine effects on gastrointestinal function are mediated via actions on opioid receptors within the central nervous system and through a direct action on peripherally located opioid receptors within the enteric nervous system (Parolaro D et al., 1977; Stewart JJ et al., 1978; Tavani A et al., 1990). Mu opioid receptors in the brain of mice (Porreca F and Burks TF, 1983; Porreca F et al., 1983) and rats (Koslo RJ et al., 1985) are involved in the CNS-mediation of morphine inhibition of gastrointestinal motility.

The pharmacological action of morphine on the gastrointestinal tract is manifested clinically. These clinical effects are presented in the following table.

GI Tract Site of Action	Pharmacological Action	Clinical Effect
Stomach	Decreased gastric motility	Anorexia
	Decreased pyloric tone	Nausea and vomiting
Small Intestine	Decreased pancreatic and biliary secretion	Delayed digestion
	Reduced propulsion	Delayed absorption of medication
	Increased fluid absorption	Hard and dry stool
Large Intestine	Increased non-propulsive contractions	Spasm, abdominal cramps, and pain
	Increased fluid absorption	Hard and dry stool
	Increased anal sphincter tone	Retention of gastrointestinal contents (incomplete evacuation)

Abuse liability: Morphine is a Schedule II controlled substance and is highly addictive. Psychological and physical dependence develop quickly to morphine. Morphine elicits euphoria by activating the brain's reward systems; specifically its binds to opioid receptors on neurons located in the

VTA and in the nucleus accumbens. Withdrawal symptoms associated with morphine addiction include drug craving, watery eyes, insomnia, diarrhea, running nose, yawning, dysphoria, chills and sweating.

2.6.2.5 Pharmacodynamic drug interactions

2.6.3 PHARMACOLOGY TABULATED SUMMARY

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

2.6.4.2 Methods of Analysis

2.6.4.3 Absorption

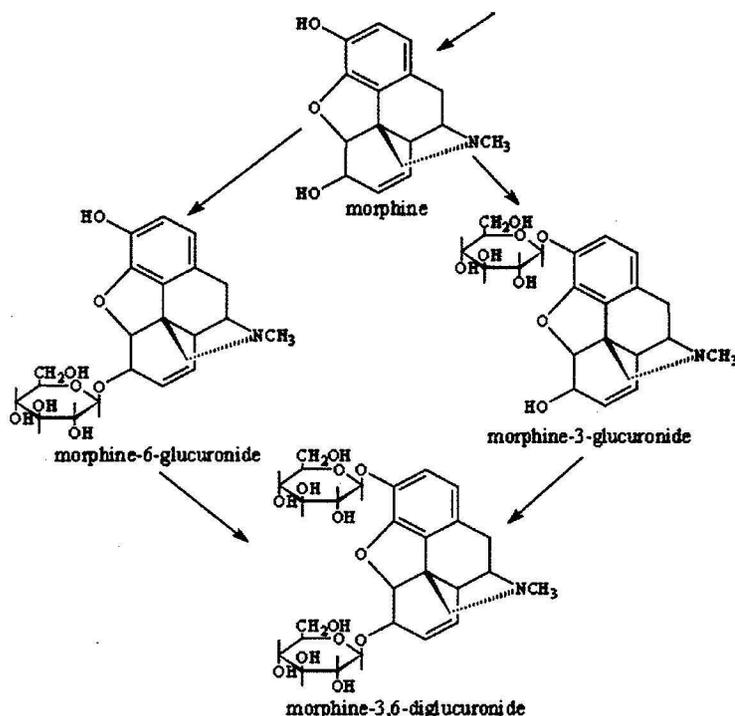
Absorption of morphine following oral administration is variable and decreased by extensive pre-systemic metabolism in both the liver and gut.

2.6.4.4 Distribution

Morphine is distributed to the intestinal tract, kidneys, liver, lungs, skeletal muscle, spleen and brain. Although the central nervous system is the primary site of action of morphine, only small quantities cross the blood-brain barrier. Morphine also crosses the placental membranes and has been detected in breast milk (Feilberg VL et al., 1989; Robieux I et al., 1990). The volume of distribution of morphine in humans is approximately 3 to 4 L/kg. Morphine is 30 to 35% reversibly bound to plasma proteins. Muscle tissue binding has been reported to be 54%.

2.6.4.5 Metabolism

Morphine metabolism is primarily by hepatic glucuronidation by uridine diphosphate glucuronosyl transferase (UGT) enzyme, with specific affinity for the UGT2B7 and UGT1A3 isozymes, (Armstrong SC and Cozza KL, 2003; Witter E and Kern SE, 2006). The isoenzyme is responsible for the formation of both major glucuronide metabolites of morphine; morphine-3-glucuronide (M3G, about 50%) and morphine-6-glucuronide (M6G, about 15%). M3G has no analgesic activity; whereas M6G has been shown to have analgesic activity but crosses the blood brain barrier poorly. Metabolism of morphine can also occur in the brain and the kidneys (Christrup LL, 1997). In humans, morphine is also metabolized to normorphine and normorphine-6-glucuronide (Yeh SY et al., 1977). Normorphine is formed by hepatic microsomal oxidation. Minor metabolites that have been identified in the urine of humans following large doses of chronically administered morphine include codeine (3-O-methyl morphine) and morphine N-oxide. Following oral administration, approximately 5% of the morphine undergoes N demethylation to normorphine and 10% metabolized to codeine.



2.6.4.6 Excretion

Morphine is eliminated in urine, feces and bile; with renal excretion being the major route of elimination. Approximately 10% of a dose of morphine is excreted unchanged in the urine. The majority of the dose of morphine is excreted in the urine as the metabolites M3G and M6G, with elimination of morphine occurring primarily as renal excretion of M3G. A small amount of the glucuronide conjugates are excreted in the bile, with minor enterohepatic recycling. Seven to 10% of administered morphine is excreted in the feces. The mean adult plasma clearance of morphine is approximately 20 to 30 mL/min/kg. The effective terminal half-life of morphine after intravenous administration is reported to be approximately 2 hours. Longer periods of plasma sampling in some studies suggest a longer terminal half-life of morphine of about 15 hours.

Reviewer's note (EAB): The Applicant for the current NDA has conducted a review of the published literature and identified a study which provides new information on the PK of morphine. (b) (4) has described the first evidence of (b) (4) formation in human tissue. In an *in vitro* human liver preparation, conversion of morphine to (b) (4) was shown to be NADP dependent and localized mainly to microsomes (b) (4). (b) (4) contains a structural alert for mutagenicity. Data to suggest that (b) (4) is not genotoxic are included in the DMF for the morphine drug substance. The levels of (b) (4) that are found in the drug substance and drug product for this NDA are acceptable.

2.6.4.7 Pharmacokinetic drug interactions

No new studies were submitted by the Applicant.

The known drug interactions involving morphine are pharmacodynamic. Coadministration of morphine with CNS depressants (i.e., sedatives or hypnotics, general anesthetics, tranquilizers, and alcohol) can result in additive CNS respiratory depressant effects. Agonist/antagonist analgesic (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) co-administered with morphine may reduce morphine's analgesic effect or may precipitate withdrawal symptoms.

2.6.4.8 Other Pharmacokinetic Studies**2.6.4.9 Discussion and Conclusions****2.6.4.10 Tables and figures to include comparative TK summary****2.6.5 PHARMACOKINETICS TABULATED SUMMARY****2.6.6 TOXICOLOGY****2.6.6.1 Overall toxicology summary**

General toxicology: No new studies were submitted by the Applicant.

Genetic toxicology: No new studies were submitted by the Applicant.

Carcinogenicity: No new studies were submitted by the Applicant.

Reproductive toxicology: No new studies were submitted by the Applicant. Studies from the literature suggest that morphine has adverse effects on male fertility in the rat and is associated with changes in selected hormone levels which play a role in rodent fertility. The label will be updated to include an overview of the findings.

Special toxicology: No new studies were submitted by the Applicant.

2.6.6.2 Single-dose toxicity

No new studies were submitted by the Applicant.

2.6.6.3 Repeat-dose toxicity

No new studies were submitted by the Applicant.

2.6.6.4 Genetic toxicology

No new studies were submitted by the Applicant.

2.6.6.5 Carcinogenicity

No new studies were submitted by the Applicant.

2.6.6.6 Reproductive and developmental toxicology

No new studies were submitted by the Applicant.

Formal toxicology studies have not been conducted on the reproductive and developmental effects of MOR. The Applicant is relying on the information described in the Kadian label as well as studies from the literature. Several published studies report impacts on fertility in male rats and teratogenic effects at maternally toxic doses. Currently, Kadian as well as other MOR products are considered Pregnancy Category C.

The Applicant is proposing to add wording to the label of Embeda regarding the effects of MOR on male fertility as well as a general statement about the effects of fertility in rodents due to changes in hormone levels. The statements are based on several papers from the literature that have been published since the approval of Kadian (Yim AJ et al., 2006; Cicero TJ et al., 2002; Cicero TJ et al., 1995; Cicero TJ et al., 1991). Details of the studies are summarized in Table 5 (table prepared by the reviewer). Although none of the studies from the literature were conducted under GLP, they appear to be adequate and support the conclusion that MOR has adverse effects on male fertility and general effects on selected male and female hormone levels. No studies in the literature were identified which directly assessed the effect of MOR on female fertility. Several studies in the literature have shown that MOR can have effects on female fertility when the female is not directly dosed with MOR. Male MOR-treated rats mated with drug naïve females showed adverse effects on female fertility (Table 5, Cicero TJ et al., 2002). Decreased fertility in female offspring from pregnant rats treated with MOR during the third trimester has also been observed (Kadian label). At the present time, the direct effects of MOR on female fertility are unclear and can not be included in the label. Refer to the executive summary for changes to the labeling proposed by the Applicant.

Citation	Methods	Fertility/Developmental Endpoints	Findings/Conclusions
Cicero <i>et al.</i> , 2002	Male rats were given increasing doses of morphine or saline for 14 days. Dosing began with 10 mg/kg s.c. BID. The morphine dose was increased daily in 5 mg increments until a max of 30 mg/kg s.c. BID was achieved and continued until day 14. On Days 14, 15 and 16 the morphine dose was decreased to 20 mg/kg s.c. BID On Days 15 and 16 the males were bred with drug naïve females.	<u>Male fertility assessments:</u> weight and histopathology of testes and epididymides, seminal vesicles, and prostate; sperm count, motility and morphology <u>Female fertility assessments:</u> fertility rates (vaginal plugs and pregnancies), pseudopregnancies, implantation sites and resorptions <u>Fetal assessments:</u> weight and gross abnormalities	Prostate and seminal vesicle weights were significantly lower in morphine-treated group. No other changes in male fertility assessments were observed. The fecundity index in females mated with morphine-treated males (81.6%) was significantly lower than controls (97.2%). A higher pseudopregnancy rate was observed in females mated with morphine-treated males (40.4%) than with controls (5.6%). The total number of implantation sites/rat was significantly decreased in females mated with morphine-treated males. The total number of primary corpora lutea/rat in females mated with morphine-treated males and number of morphine-derived fetuses were lower than controls but differences

			<p>were not statistically significant. No other differences in reproductive parameters were observed.</p> <p>No differences in fetal weight or gross abnormalities were observed in the offspring of morphine-treated males as compared to controls.</p> <p>The results suggest that paternal morphine exposure affects fertility and/or pre-implantation processes that lead to poor pregnancy outcome in drug-naïve females.</p>
Cicero <i>et al.</i> , 1991	<p>Adolescent male rats (age 27 days at start of study) were implanted with morphine or placebo pellets (one on study day 1, two on study days 4, 7, and 10)</p> <p>males were treated with morphine throughout puberty and mated with drug-naïve females when adulthood was reached</p>	<p><u>Male fertility assessments:</u> LH (serum and pituitary), testosterone (tes), corticosterone (from adrenal extracts), i-βE (immunoreactive beta-endorphin) and LHRH (from hypothalamic extract) weights of seminal vesicles and testes</p> <p><u>Fertility/fetal assessments:</u> number of pregnancies, number of pups/litter, male/female ratio, pup body weight, mortality rate and incidence of birth defects, gross indices of development</p> <p><i>Male offspring:</i> LH (serum and pituitary), testosterone, corticosterone (from adrenal extracts), i-βE and LHRH (from hypothalamic extract) weights of seminal vesicles and testes</p> <p><i>Female offspring:</i> LH (serum and pituitary), corticosterone (from adrenal extracts), i-βE and LHRH (from hypothalamic extract)</p>	<p>This paper studies the effects of adolescent morphine exposure on the sexual maturation of drug-treated male rats and their offspring.</p> <p><u>Treated males:</u> <i>tes:</i> as compared to controls tes was significantly decreased for 3 wks after morphine pellet insertion, no different from control at 4 weeks, significantly higher at 6 weeks, no differences from control by 9 weeks <i>serum LH:</i> significantly decreased up to 3 weeks post-morphine pellet implantation <i>LHRH:</i> moderately decreased (10-15%) up to 4 weeks post-morphine pellet implantation No significant differences from control for pituitary LH or i-βE or weights of seminal vesicles or testes.</p> <p><i>Fertility:</i> litter sizes were decreased in litters sired by morphine treated rats. No other fertility assessments were different from controls</p> <p><i>Male offspring (adult):</i> decreased testosterone, increased LH, decreased seminal vesicle weights, increased adrenal weights</p> <p><i>Female offspring (adult):</i> corticosterone and i-βE significantly increased in morphine sired female offspring</p>
Cicero <i>et al.</i> , 1995	<p>Male rats single dose of 25 mg/kg s.c. morphine</p> <p>24 h post-injection morphine treated males were bred with drug-naïve females</p>	<p><u>Fertility/fetal assessments:</u> pregnancies, total births, litter size, mortality rate, gross indices of development</p> <p>analgesic effects of morphine were assessed in offspring</p>	<p>No adverse effects on fertility rates</p> <p><i>Fetal outcome:</i> decreased litter size and increased mortality rate for offspring sired by morphine-treated males</p> <p>Male offspring sired by morphine-treated males showed enhanced sensitivity to the analgesic effects of morphine, female</p>

			offspring showed no differences. No differences were seen in baseline hotplate thresholds for either sex.
Yim <i>et al.</i> , 2006	<p>Female rats pre-mating dosing: 5 mg/kg s.c. morphine on alternate days for a total of seven doses</p> <p>pregnancy dosing: 3.5 mg/kg/day s.c. morphine beginning at day 17 of pregnancy for five days</p> <p>post-parturition dose: acute morphine challenge (1.5 mg/kg s.c.) or saline</p>	<p><u>Behavioral assessments:</u> Measured maternal behavior (pup retrieval, grouping, and nursing) and locomotor activity</p> <p><u>Biochemical assessments:</u> Measured striatal and hypothalamic concentrations of DA, DA metabolites (DOPAC and HVA) and serum levels of corticosterone</p>	<p>The objective of the study was to determine the effect of morphine treatment during pre-mating on the responsiveness of dams towards pups during lactation and whether morphine treatment late in pregnancy would sensitize locomotor activity after morphine challenge.</p> <p>Maternal behavior was disrupted in rats treated with morphine during pregnancy and acutely challenged with morphine.</p> <p>Increased locomotion, decreased striatal DA levels, increased striatal DA turnover and increased serum corticosterone levels were observed with pre-mating morphine treatment with morphine challenge</p> <p>No effects on dam weight or litter size were observed</p>

2.6.6.7 Local tolerance

No new studies were submitted by the Applicant.

2.6.6.8 Special toxicology studies

No new studies were submitted by the Applicant.

2.6.6.9 Discussion and Conclusions

Alpharma has submitted NDA 22-321 for Embeda, an extended release MOR product with properties purported by the Applicant to confer abuse deterrence. No pharmacology or toxicology studies were submitted in support of this NDA. The Applicant is relying on the data in the Kadian NDA (owned by Alpharma), **the Agency's previous findings of safety and efficacy for Revia**, and information from the literature. The Applicant has provided a review of the current literature for MOR and NTX.

The pharmacology and toxicology of MOR are well characterized. The Applicant submitted a review of literature for MOR. Several reports showing adverse effects of MOR on male fertility and changes in selected hormone levels in rat were reviewed. The studies appear to be valid and wording reflecting the adverse effects of MOR on male fertility as well as the effect of MOR on selected fertility-related hormone levels will be included in the label.

Systemic levels of NTX are very low when the drug is used as labeled. The nonclinical pharmacology and toxicology data would not provide any useful information to the provider and will not be included in the label. No pharmacology or toxicology studies with NTX were submitted in support of NDA 22-321. The Applicant has provided a review of the current literature for NTX. Since it has been shown that there is limited

systemic exposure to NTX (See Clinical Pharmacology review by Dr. Srikanth Nallani), literature reports regarding NTX were not reviewed for this NDA.

The Embeda capsules are comprised of individual pellets containing layers of MOR, NTX and various excipients to provide a controlled release profile for the MOR and to sequester the NTX when the product is used as labeled. All of the excipients in the Embeda formulation are found in approved drug products and do not present any toxicologic concern. However, (b) (4) dibutyl sebacate will exceed levels found in previously approved drugs when the MDD of MOR is consumed. A toxicological assessment of the level of dibutyl sebacate in the Embeda drug product has been provided and it has been determined that at the levels in the proposed formulation, dibutyl sebacate does not pose any unique toxicologic concerns.

2.6.6.10 Tables and Figures

2.6.7 TOXICOLOGY TABULATED SUMMARY

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: NDA 22-321 was submitted via the 505(b)(2) pathway with the reference listed drugs as Kadian (NDA (b) (4) for MOR and ReVia (NDA 18-932) for NTX. No pharmacology or toxicology studies were submitted in support of this NDA. The Applicant is relying on the data in the Kadian NDA (owned by Alpharma), the Agency's previous findings of safety and efficacy for ReVia, and information from the literature. The Applicant has provided a review of the current literature for MOR and NTX. There are no outstanding nonclinical issues with NDA 22-321.

Unresolved toxicology issues (if any): none

Recommendations: From a nonclinical pharmacology/toxicology perspective this NDA may be approved.

Suggested labeling: The following recommendations are being proposed for the nonclinical sections of the label. For the final version of the label, please refer to the Action Letter. Note: The recommended changes from the proposed labeling are in red or strikeout font.

(b) (4)

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[Redacted] (b) (4)

[Redacted] (b) (4)

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(b) (4)

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/s/

Elizabeth Bolan
12/1/2008 02:50:52 PM
PHARMACOLOGIST

R. Daniel Mellon
12/1/2008 02:56:27 PM
PHARMACOLOGIST
I concur.

PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST

NDA/BLA Number: 22-321

Applicant: Alpharma

Stamp Date: 6/30/08

Drug Name: Embeda (extended release morphine with sequestered naltrexone)

NDA/BLA Type: 505(b)(2) DAARP/OND/CDER/FDA

On **initial** overview of the NDA application for Refuse to File (RTF): **Fileable**

	Parameters	Yes	No	Comment
1	On its face, is the pharmacology section of the NDA/BLA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section of the NDA/BLA indexed and paginated in a manner allowing substantive review to begin?	X		
3	On its face, is the pharmacology/toxicology section of the NDA/BLA legible so that substantive review can begin?	X		
4	Are all required (*) and requested BBIND studies (in accord with 505(b1) and (b2) including referenced literature) completed and submitted in this NDA/BLA (carcinogenicity*, mutagenicity*, teratogenicity*, effects on fertility*, juvenile studies, acute and repeat dose adult animal studies*, maximum tolerated dose determination, dermal irritancy, ocular irritancy, photo co-carcinogenicity, animal pharmacokinetic studies, safety pharmacology, etc)?	X		No new studies were submitted.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies been conducted with the appropriate formulation?			<i>Not applicable</i> No toxicology studies were conducted.

6	Is (are) the excipient(s) appropriately qualified (including interaction between the excipients if applicable)?	X	
7	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor <u>submitted</u> a rationale to justify the alternative route?	X	
8	Has the sponsor <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?		<i>Not applicable</i> No new studies were submitted.
9	Has the sponsor submitted all special studies/ data requested by the Division during pre-submission discussions with the sponsor?	X	
10	Are the proposed labeling sections relative to pharmacology, reproductive toxicology, and carcinogenicity appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X	
11	Has the sponsor submitted any toxicity data to address impurities, new excipients, leachables, etc. issues.		X The impurity specifications in the proposed drug substance (morphine) currently exceed ICH guidelines. This is a review issue.
12	Has the sponsor addressed any abuse potential issues in the submission?	X	
13	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		<i>Not applicable</i>
14	From a pharmacology/ toxicology perspective, is the NDA/BLA fileable? If ``no`` please state below why it is not.	X	

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Nonclinical Comments to Sponsor:

The Division has determined that your justification for the maximum feasible daily intake (MFDI) of 2 g of morphine is unacceptable. In consulting with the clinicians in DAARP, our current estimate of an MFDI for morphine in an opioid tolerant patient population is 5 g/day. The ICH guideline impurity thresholds will be based on this dose. Please refer to the clinical comments for details.

Specifications for several impurities (b) (4) in the morphine drug substance currently exceed the ICH Q3A(R2) thresholds for qualification. Reduce the specifications for the impurities to (b) (4) total daily intake, whichever is lower or qualification will be necessary unless higher thresholds can be scientifically justified. Adequate qualification should include:

- Minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
- Repeat dose toxicology of appropriate duration to support the proposed indication.

*We note that the minimal genetic toxicology screen for morphinone has been completed.

(b) (4) are found as impurities in the morphine drug substance at levels which currently exceed ICH Q3A(R2) guidelines. However, both compounds are well characterized, have been previously approved by the Agency and do not present toxicologic concern at the proposed specifications. Therefore, the proposed specifications for these two substances in the drug substance (b) (4) respectively) and drug product (b) (4) respectively) are acceptable for a total daily dose of 5 g of morphine.

Normorphine has been shown to be a human metabolite of morphine and the proposed specifications for the drug substance (b) (4) and drug product (b) (4) are acceptable for a total daily dose of 5 g of morphine.

Reviewing Pharmacologist: Elizabeth A. Bolan, Ph.D. 8/12/08
Date

Team Leader: Dan Mellon, Ph.D. 8/13/08
Date

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

/s/

Elizabeth Bolan
8/13/2008 09:31:26 AM
PHARMACOLOGIST

R. Daniel Mellon
8/13/2008 09:38:37 AM
PHARMACOLOGIST
I concur.