

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-321

CHEMISTRY REVIEW(S)

Embeda™
(morphine sulfate and naltrexone hydrochloride)
Extended Release Capsules
NDA 22-321

**Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls**

Background: This is a 505 (b)2 application. The sponsor referenced Kadian®; morphine sulfate extended release drug product capsules (NDA 20-616). The sponsor claimed that “this opioid formulation has the potential to deter prescription opioid abuse (POA) and its intrinsic features provide specific safety advantages to a vulnerable subset of the target population”.

The applicant claimed that Embeda™ drug product (100 mg/4.0 mg) is bioequivalent to 100 mg Kadian® and, therefore, requested a biowaiver for Embeda strengths below 100 mg. The Biowaiver request was reviewed and granted accordingly.

Applicant: Alpharma Pharmaceuticals LLC.
One New England Ave.
Piscataway, NJ 08854

Indication: Management of moderate to severe pain

Presentation: The drug product capsules (20/0.8, 30/1.2, 50/2, 60/2.4, 80/3.2 and 100/4 mg (morphine sulfate/naltrexone hydrochloride)) will be packaged (HDPE) bottle filled with 100 capsules for each strength, closed with a foil heat induction seal child resistant (CR) (b) (4) closure.

EER Status: Acceptable

Consults: EA - Categorical exclusion provided
Statistics - N/A
Methods Validation - Acceptable (not necessary to be forwarded to Agency laboratory).
Clinical Pharmacology- Biowaiver granted
Pharmacology/toxicology - Acceptable
Microbiology - N/A

Original Submission: Feb-28-2008

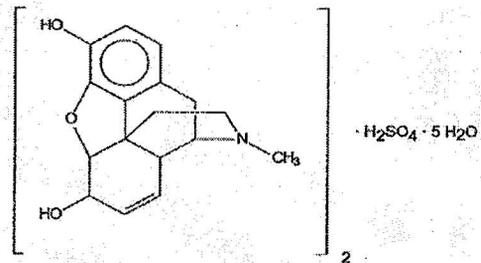
Post-Approval CMC Agreements: None beyond the typical stability commitment.

Drug Substances:

1- Morphine Sulfate.

Chemical name, molecular formula, molecular weight and chemical structure of morphine sulfate are provided below.

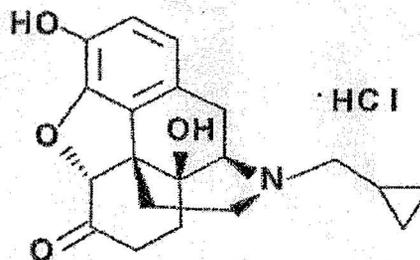
- 7,8-didehydro-4,5 α -epoxy-17-methylmorphinan-, 5 α ,6 α -diol sulfate (2:1) (salt) pentahydrate
- Molecular formula: (C₁₇H₁₉NO₃)₂ · H₂SO₄ · 5H₂O
- Molecular Weight: 785.85 g/mol
- Chemical structure:



The applicant referenced DMFs (b) (4) and (b) (4) for the CMC information regarding Morphine sulfate. The DMFs were reviewed and found adequate to support the NDA.

2- **Naltrexone HCl.** Chemical name, molecular formula, molecular weight and chemical structure of Naltrexone HCl are provided below.

- N-cyclopropylmethyl-14-hydroxydihydromorphinone hydrochloride
- Molecular Formula: C₂₀H₂₃NO₄ · HCl
- Molecular Weight: 377.46 g/mol
- Chemical Structure:



The applicant referenced DMF (b) (4) for the CMC information regarding Naltrexone HCl. The DMF was reviewed and found adequate to support the NDA.

Conclusion: Drug substances are acceptable.

Drug Product

The drug product is an extended release capsule for oral administration, containing multilayer pellets. Each pellet contains two active ingredients: morphine sulfate (drug substance with extended release profile) and naltrexone (opioid antagonist, intended as an abuse deterrent component), in addition to several excipients.

The manufacturing process includes

(b) (4)

The applicant reported that EMBEDA™ drug product is an abuse deterrent formulation and provided *in-vitro* extraction studies which demonstrated that, if the pellets are crushed, dissolved or chewed, both morphine and naltrexone would be available and absorbed as an immediate release dosage form. Accordingly, the released and absorbed naltrexone would mitigate the liking and euphoric effects of the morphine and deter drug tampering and diversion.

The drug product capsules have 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. For all strengths, the amount of naltrexone HCl is 25 times smaller than the amount of morphine sulfate.

The applicant proposed shelf life of 24 months stored at room temperature conditions (20-25 °C, excursion permitted between 15 and 30 °C). The provided stability data support the requested expiry date of 24 months under the above storage conditions.

Conclusion: Drug product is satisfactory.

Additional Items: All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.

Overall Conclusion: From a CMC perspective, the application is recommended for approval.

Ali Al-Hakim, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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

/s/

Ali Al-Hakim
12/19/2008 03:59:08 PM
CHEMIST



NDA 22-321

**Embeda™
(morphine sulfate and naltrexone hydrochloride)
Extended Release Capsules**

Alpharma Pharmaceuticals LLC

**Elsbeth Chikhale, Ph.D.
ONDQA – DPA I – Branch II
for
Division of Anesthesia, Analgesia and Rheumatology
Products**



Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	8
I. Recommendations	8
A. Recommendation and Conclusion on Approvability.....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments	8
A. Description of the Drug Product(s) and Drug Substance(s)	8
B. Description of How the Drug Product is Intended to be Used	9
C. Basis for Approvability or Not-Approval Recommendation.....	10
III. Administrative.....	10
A. Reviewer's Signature.....	10
B. Endorsement Block.....	10
C. CC Block	10
Chemistry Assessment	11
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	11
S DRUG SUBSTANCE [Morphine sulfate, (b) (4)].....	11
S DRUG SUBSTANCE [Morphine sulfate, (b) (4)].....	11
S DRUG SUBSTANCE [Naltrexone HCl (b) (4)].....	16
P DRUG PRODUCT [Embeda, Capsules].....	21
A APPENDICES	97
R REGIONAL INFORMATION.....	98
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	99
A. Labeling & Package Insert	99
B. Environmental Assessment Or Claim Of Categorical Exclusion	99
III. List Of Information Requests Communicated	N/A



Chemistry Review Data Sheet

1. NDA 22-321
2. REVIEW #: 1
3. REVIEW DATE: 8-DEC-2008
4. REVIEWER: Elsbeth Chikhale, Ph.D.
5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Resubmission

30-JUN-2008

Amendment to original¹

7-OCT-2008

Amendment to original²

9-OCT-2008

Amendment to original³

21-NOV-2008

Amendment to original⁴

e-mail dated 3-DEC-2008

Amendment to original⁵

e-mail dated 4-DEC-2008

- 1) The 10/7/08 amendment provides for a response to an information request from the Agency dated 9/29/08.
- 2) The 10/9/08 amendment provides for a response to an information request from the Agency dated 9/8/08.
- 3) The 11/21/08 amendment provides for a response to an information request from the Agency dated 11/18/08.
- 4) The amendment (e-mail dated 12/3/08) provides for an agreement as a result of an information request from the Agency dated 12/3/08.
- 5) The amendment (e-mail dated 12/4/08) provides for a response to an information request from the Agency dated 11/18/08.

7. NAME & ADDRESS OF APPLICANT:

Name: Alharma Pharmaceuticals LLC.

Address: One New England Avenue
Piscataway, NJ 08854

Representative: Isabelle Lefebvre, Director, Regulatory Affairs

Telephone: (732) 465 – 3817



CHEMISTRY REVIEW



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: **Embeda™**
b) Non-Proprietary Name (USAN): morphine sulfate and naltrexone hydrochloride
c) Code Name/#: ALO-01 pellets: pellets inside the ALO-01 capsules
ALO-01 capsules: drug product
d) Chem. Type/Submission Priority:
 - Chem. Type: 4 (new combination)
 - Submission Priority: Priority

9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(2) application. The reference listed drug is Kadian® (morphine sulfate extended-release) Capsules, NDA 20-616

10. PHARMACOL. CATEGORY:

Morphine sulfate is an μ -opioid receptor agonist.
Naltrexone hydrochloride is an opioid antagonist.

11. DOSAGE FORM: capsules

12. STRENGTH/POTENCY: 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

13. ROUTE OF ADMINISTRATION: oral

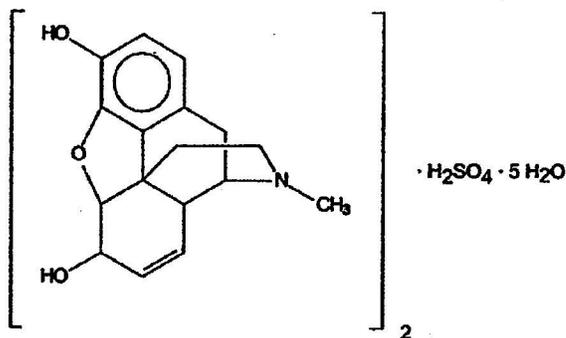
14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product Form Completed
 Not a SPOTS product

Chemistry Review Data Sheet

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

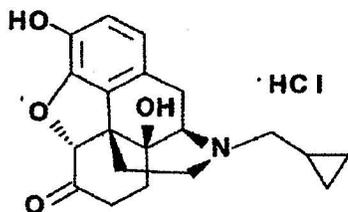
Morphine sulfate:

Chemical names:

- **Morphinan-3,6-diol,7,8-didehydro-4,5-epoxy-17-methyl,(5 α ,6 α)-, sulfate (2:1) (salt), pentahydrate**
- **7,8-didehydro-4,5 α -epoxy-17-methylmorphinan-, 5 α ,6 α -diol sulfate (2:1) (salt) pentahydrate**

Molecular formula: $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$

Molecular Weight: 785.85 g/mol

Naltrexone HCl:

Chemical names:

- **(5 α)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride**
- **N-cyclopropylmethyl-14-hydroxydihydromorphinone hydrochloride**

Molecular Formula: $C_{20}H_{23}NO_4 \cdot HCl$

Molecular Weight: 377.46 g/mol



CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	November 30, 2008	Reviewed by Elsbeth Chikhale, Ph.D.
	II		1	Adequate	November 30, 2008	Reviewed by Elsbeth Chikhale, Ph.D.	
	II		1	Adequate	November 30, 2008	Reviewed by Elsbeth Chikhale, Ph.D.	
	IV		3	Adequate	January 22, 2003	George Lunn, Ph.D.	
	III		3	Adequate	April 20, 2004	Reviewed by Sarah Pope, Ph.D.	
	IV		6				
	III		3	Adequate for these bottles	September 15, 2000	Donald Klein, Ph.D. as part of DMF strike force	
	III		4				
	III		4				
	III		4				
	III		4				
	III		4				
	III		4				
	III		4				



CHEMISTRY REVIEW



Chemistry Review Data Sheet

(b) (4)

(b) (4)	III		4			
---------	-----	--	---	--	--	--

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no relevant revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	70,853	Kadian NT
NDA	20-616	Kadian® (morphine sulfate extended-release) Capsules
NDA	18-932	ReVia® (naltrexone hydrochloride) Tablets

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biowaiver	Biowaiver granted	12/1/08	Patrick Marroum, Ph.D.
Biometrics	N/A		
EES	Acceptable	12/8/08	
Pharm/Tox	Approval	12/1/08	Beth Bolan, Ph.D.
CDRH	N/A		
Clinical Pharmacology	N/A		
Methods Validation	Acceptable	12/8/08	Elsbeth Chikhale, Ph.D.
DMEPA	pending		
DDMAC	pending		
EA	Categorical exclusion granted (consult not needed)	12/8/08	Elsbeth Chikhale, Ph.D.
Microbiology	N/A		

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 22-321

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view, the application is recommended for APPROVAL, however, final labeling will be done in coordination with the clinical division.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

1) 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 excipients. The capsules have 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. For all strengths, the amount of naltrexone HCl is 25 times smaller than the amount of morphine sulfate. Naltrexone is an opioid antagonist, intended as an abuse deterrent component. Upon crushing, dissolving, or chewing the pellets, morphine and naltrexone become bioavailable as in an immediate release oral dosage form. Morphine sulfate is a μ -opioid receptor agonist and naltrexone HCl, a μ -opioid receptor antagonist. Naltrexone HCl is a synthetic analog of oxymorphone approved for the treatment of alcohol dependence and blockade of the effects of exogenous opioids. This NDA is submitted electronically as a 505(b)2. The reference listed drug is Kadian® (morphine sulfate extended-release) Capsules, NDA 20-616. **The Embeda™ drug product (100 mg/4.0 mg) is bioequivalent to 100 mg Kadian®.** The applicant has requested a biowaiver for Embeda strengths below 100 mg. The biowaiver was granted (see review date 12/1/08 by Patrick Marroum, Ph.D.). The proposed drug product is indicated for the management of moderate to severe chronic pain. The container closure systems proposed are (b) (4) HDPE bottles with cotton coil and a child-resistant cap (CRC) with an induction seal. The proposed storage condition is at room temperature (20-25 °C, excursion permitted between 15 and 30 °C), and the



proposed expiry date is 24 months. The provided stability data support the proposed shelf life of 24 months when stored at room temperature conditions.

2) Drug Substance : Morphine sulfate:

The drug substance, morphine sulfate, is a previously approved drug substance, produced by chemical synthesis. All information regarding the physicochemical properties, impurities, method of synthesis and purification, process controls, control of raw materials, container closure system and stability of morphine sulfate are provided in the Drug Master Files (DMFs) (b) (4) held by (b) (4), respectively. Letters of Authorization to allow the Agency to review these DMFs are provided in the NDA. DMF (b) (4) was reviewed on 11/30/08 (Chem. Review #11 by Elsbeth Chikhale, Ph.D.) and found adequate to support this NDA. DMF (b) (4) was reviewed on 11/30/08 (Chem. Review #17 by Elsbeth Chikhale, Ph.D.) and found adequate to support this NDA.

Drug Substance : Naltrexone HCl:

The drug substance, naltrexone HCl, is a previously approved drug substance, produced by chemical synthesis. All information regarding the physicochemical properties, impurities, method of synthesis and purification, process controls, control of raw materials, container closure system and stability of morphine sulfate are provided in DMF (b) (4) held by (b) (4)t. A Letter of Authorization to allow the Agency to review this DMF is provided in the NDA. This DMF was reviewed on 11/30/08 (Chem. Review #15 by Elsbeth Chikhale, Ph.D.) and found adequate to support this NDA.

B. Description of How the Drug Product is Intended to be Used

The drug product is indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The drug product may be administered once or twice daily. Low initial doses should be used in patients who are opioid-naïve and those receiving concurrent treatment with muscle relaxants, sedatives, or other CNS-active medications. The 100 mg dose is for use in opioid-tolerant patients only. The drug product is to be swallowed whole or the contents of the capsules can be sprinkled on apple sauce. The pellets in the capsules are not to be crushed, dissolved, or chewed before swallowing. Tampering with the formulation, crushing or chewing the pellets, or other misuse and abuse, causes the rapid release and absorption of both morphine and naltrexone. The resulting morphine dose may be fatal, particularly in opioid-naïve individuals. In opioid-tolerant individuals, the absorption of naltrexone may increase the risk of precipitating withdrawal.

C. Basis for Approvability or Not-Approval Recommendation

From the CMC point of view, the application is recommended for APPROVAL, however, final labeling will be done in coordination with the clinical division.

III. Administrative

- A. **Reviewer's Signature:** in DFS
- B. **Endorsement Block:** in DFS
- C. **cc Block:** in DFS

89 pp withheld in full immed. after this page as (b)(4) CCI/TS.

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

/s/

Elsbeth Chikhale
12/8/2008 10:11:08 PM
CHEMIST

Ali Al-Hakim
12/8/2008 10:23:20 PM
CHEMIST

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 22321/000	Sponsor:	ALPHARMA PHARMS
Code:	170		1 NEW ENGLAND AVE
Priority:	4P		PISCATAWAY, NJ 08854
Stamp Date:	28-FEB-2008	Brand Name:	EMBEDA
PDUFA Date:	31-DEC-2008	Estab. Name:	
Action Goal:		Generic Name:	MORPHINE SULFATE ER W SEQUESTERED NALTRE
District Goal:	01-NOV-2008	Dosage Form:	(EXTENDED RELEASE CAPSULE)
		Strength:	20, 30, 50, 60, 80, 100
FDA Contacts:	C. HILFIGER	Project Manager	(HFD-170) 301-796-4131
	E. CHIKHALE	Review Chemist	301-796-1659
	D. CHRISTODOULOU	Team Leader	301-796-1342

Overall Recommendation: ACCEPTABLE on 08-DEC-2008 by S. FERGUSON (HFD-322) 301-796-3247

Establishment:	CFN: 2211563	FEI: 2211563	
	ACTAVIS ELIZABETH LLC 200 ELMORA AVE ELIZABETH, NJ 072021106		
DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER FINISHED DOSAGE MANUFACTURER		
Site:	CONTROL TESTING LABORATORY	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	19-AUG-2008		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		
Profile:	TABLETS, DELAYED RELEASE	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	08-DEC-2008		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:
Responsibilities: (b) (4)
Profile: OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 19-AUG-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:
Responsibilities: (b) (4)
Profile: OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 19-AUG-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: (b) (4) AADA:
Responsibilities: (b) (4)
Profile: (b) (4) OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-AUG-2008
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment:

CFN: (b) (4)

FEI: (b) (4)

(b) (4)

DMF No:

(b) (4)

ADA:

Responsibilities:

(b) (4)

Profile:

(b) (4)

OAI Status: NONE

Last Milestone:

OC RECOMMENDATION

Milestone Date:

19-AUG-2008

Decision:

ACCEPTABLE

Reason:

BASED ON PROFILE