

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-260

CHEMISTRY REVIEW(S)

**DIVISION OF ANESTHETICS, CRITICAL CARE AND ADDICTION
DRUG PRODUCTS
(DACCAD, HFD-170)**

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-260
CHEM.REVIEW #: 1

REVIEWED DATE: 15-MAR-2001
REVIEWER: Ravi S. Harapanhalli, Ph.D.

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	25-MAY-00	31-MAY-00	12-FEB-01
BC	30-JAN-01	21-JAN-01	12-FEB-01
BC	16-MAR-01	19-MAR-01	25-MAR-01

NAME & ADDRESS OF APPLICANT: ELAN PHARMACEUTICAL RESEARCH CORPORATION
1300 Gould Drive
Gainesville, GA, 30504
Contact name: Roger Wayne Wiley, R.Ph.
Phone #: (770) 534-8239

DRUG PRODUCT NAME

Proprietary:

Extended-Release

Capsules

Nonproprietary/USAN:

MORPHINE SULFATE Extended-Release

Capsules

Code Names/#'s:

Chemical Type/Therapeutic Class: 3S

ANDA Suitability Petition/DESI/Patent Status: N/A

N/A [if applicable]

PHARMACOLOGICAL CATEGORY/INDICATION: Opioid Analgesic for relief of chronic moderate to severe pain

DOSAGE FORM:

Capsules

STRENGTHS:

30 mg, 60 mg, 90 mg, and 120 mg

MAXIMUM DAILY DOSE:

ca. One gram

ROUTE OF ADMINISTRATION:

Oral

DISPENSED:

Rx OTC

SPECIAL PRODUCTS:

Yes No

(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

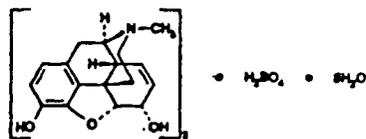
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,

MOL.WT: Morphinenan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl, (5 α , 6 α)-sulfate (2:1) (salt), pentahydrate.

7,8-Didehydro-4,5a-epoxy-17-methylmorphinan-3,6 α -diol sulfate (2:1) (salt) pentahydrate.

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

Molecular weight: 758.85



SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable): _____ (morphine sulfate)
Extended release capsules. Elan Pharmaceutical Research Corporation.

CONSULTS:

EER Consult: OC recommended "withhold" as of -3/26/2001

OPDRA-Medication Error Consult: OPDRA comments sent to applicant in a DR letter dated 01/23/01 and responses received.

Statistical consult: Not requested due to only 9 months of primary stability data.

No other consults pending.

REMARKS/COMMENTS:

See the attached list of CMC deficiencies and comments. Method validation package has not been sent due to pending review issues. Several significant degradation products were seen in the product. The product stored at accelerated temperature showed increased dissolution, indicating the instability of the product at lower relative humidity. The Elan facility is on a withhold status with potential problems of injunction. Proper target limits for the components are not identified in the manufacturing process

are inadequate to support the NDA. Information on the packaging process and in-process controls at _____ packaging site is not provided in the NDA. The primary stability data does not include the bottle configurations packaged at an alternate packaging site proposed in the NDA.

CONCLUSIONS & RECOMMENDATIONS: Elan's acceptance specifications of morphine sulfate are inadequate, since they do not specify the limits on individual impurities. The drug product composition and manufacturing process do not include target weights for each component with acceptable variations. Specifically, the

specifications. Consequently, _____ and _____ will vary from batch to batch. Since in vitro-in vivo correlation failed, this practice of adjusting the stoichiometry to meet dissolution specifications is inadequate to assure the manufacturing consistency. The process should identify targets for each component, based on the unit formula used in the pivotal studies. Several critical in-process controls need to be established or tightened to assure process consistency, since the process impacts critically on the product quality and the drug product specifications alone may not be adequate. Failure of dissolution at accelerated storage and increased dissolution at intermediate storage, and _____ at long term storage are major stability concerns in the 9-months stability data. Several other deficiencies were also noted. Elan is on withhold status from the Office of Compliance, since several critical cGMP issues were noted in the recent pre-approval inspections. From CMC perspective the NDA is "not approvable." The list of deficiencies should be forwarded to the applicant.

Ravi S. Harapanhalli, Ph.D.
Review Chemist

cc: Orig. NDA 21-260
HFD-170/NDA Division File
HFD-160/chemist/Harapanhalli
HFD-170/MO/SHertz
HFD-170/Pharmacologist/HabernyK
HFD-170/CSO/ComptonK
HFD-820/CHOiberg
R/D Init by: Dale Koble, Ph.D.
filename: c:/ddrive/mydocs/21260amar16.doc

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ON ORIGINAL**

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Q.	APPENDIX 8.	

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146 Pages redacted in full

✓ (b)(4) CCI TS

(b)(5)

(b)(6)



NDA 21-260

Elan Pharmaceuticals Research Corporation

Ravi S. Harapanhalli, Ph.D.
Division of Anesthetics, Critical Care, and Addiction Drug
Products (DACCADP)- HFD-170

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Chemistry Review Data Sheet

1. NDA 21-260

2. REVIEW #: 2

3. REVIEW DATE: March 11, 2002

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4. REVIEWER: Ravi S. Harapanhalli, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Original NDA 000
BC
BC

Document Date

May 25, 2000
January 30, 2001
March 16, 2001

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
AC (NDA Resubmission)

Document Date

July 26, 2001

7. NAME & ADDRESS OF APPLICANT:

Name:	Elan Pharmaceuticals Research Corporation
Address:	1300 Gould Drive Gainesville, GA 30504
Representative:	Roger Wayne Wiley, R.Ph. Director, North America Regulatory Affairs
Telephone:	770-534-8239

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: _____
 b) Non-Proprietary Name (USAN): Morphine sulfate ER Capsules
 c) Code Name/# (ONDC only): N/A
 d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Resubmission of NDA is response to the "AE" letter dated March 30, 2001.

10. PHARMACOL. CATEGORY: Opioid Analgesic

11. DOSAGE FORM: Capsule

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12. STRENGTH/POTENCY: 30-mg, 60-mg, 90-mg, and 120-mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

SPOTS product – Form Completed

Not a SPOTS product

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

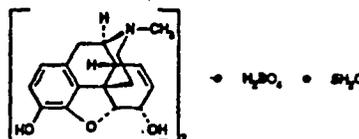
Morphinenan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl, (5 α , 6 α)-sulfate (2:1) (salt), pentahydrate.

7,8-Didehydro-4,5 α -epoxy-17-methylmorphinan-3,6 α -diol

sulfate (2:1) (salt) pentahydrate.

Molecular formula: (C₁₇H₁₉NO₃)₂ · H₂SO₄ · 5 H₂O;

Molecular weight: 758.85



17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
-------	------	--------	-----------------	-------------------	---------------------	-----------------------	----------

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND	Morphine sulfate Extended-release capsules

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not consulted since		



CHEMISTRY REVIEW



Chemistry Review Data Sheet

	specifications were not finalized.		
EES	Acceptable	03/01/02	Office of Compliance
Pharm/Tox	Qualification threshold for	03/06/02 and 03/11/02	Kathy Haberny, Ph.D.
Biopharm	Acceptable for in vitro stability of beads mixed with applesauce. Also concurred with Chemist's recommendations for dissolution specifications.	10/17/01 and 02/26/02	Suliman Alfayoumi, Ph.D.
LNC	Refer to OPDRA		
Methods Validation	Inadequate	02/12/02	DPA Laboratories, St. Louis, MO
OPDRA	Acceptable tradename "Avinza"		
EA	Exclusion from EA	03/05/01	R. S. Harapanhalli, Ph.D.
Microbiology	N/A		
Medical	Pending from Dr. Sharon Hertz: Acceptability of non-child-resistant blister configuration for hospitals		

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The Chemistry Review for NDA 21-260

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable pending satisfactory resolution of CMC deficiencies and comments listed at the end of the review.

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

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

_____ ^M contains morphine sulfate, an opioid analgesic and is indicated for the relief of chronic moderate to severe pain. _____ ^M Extended-release capsule is a multiparticulate bead formulation of morphine sulfate, which utilizes Elan's SODAS™ (Spheroidal Oral Drug Absorption System) technology. The technology is based on initially coating sugar spheres with morphine sulfate, fumaric acid, talc, sodium lauryl sulfate and povidone to form immediate release (IR) beads. A series of subsequent coatings of the IR beads with sustained release (SR) coating solution of _____ and filler talc produces the SR beads with the outer rate-controlling membrane. The IR and SR beads are blended in a definite ratio and are encapsulated to produce the final dosage form. Within the gastrointestinal tract, due to the permeability of the _____ of the beads, fluid enters the beads and solubilizes the drug. This is mediated by fumaric acid, which acts as an osmotic agent and a local pH modifier, and the resultant solution then diffuses out gradually. Thus, the immediate release portion of the dose allows for the rapid onset of absorption and attainment of therapeutic blood levels, and the SR component releases the drug in a predetermined fashion over the 24-h period. Therefore, the product is designed for a 24-h dosing interval as opposed to two previously approved regimen, namely a six-times a day oral solution formulation and a twice a day MS Contin formulation.

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

A once a day oral capsule formulation

C. Basis for Approvability or Not-Approval Recommendation

The NDA was beset with several deficiencies in all areas of CMC and deficiencies were conveyed to the applicant in the "Approvable" letter dated March 30, 2001. The applicant submitted complete response to the deficiency letter on July 26, 2001 and addressed the CMC

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

R. S. Harapanhalli, Ph.D./March 11, 2002
Dale Koble, Ph.D./March 11, 2002
Kim Compton/March 11, 2002

C. CC Block

cc: Orig. NDA 21-260, HFD-170/NDA Division File
HFD-170/chemist/Harapanhalli, HFD-170/MO/Shertz,
HFD-170/Pharmacologist/HabernyK, HFD-170/CSO/ComptonK
R/D Init by: Dale Koble, Ph.D.
filename: c:/ddrive/mydocs/21260review2agrp.doc

81 Pages redacted in full

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NDA 21-260

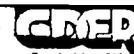
Elan Pharmaceuticals Research Corporation

**Ravi S. Harapanhalli, Ph.D.
Division of Anesthetics, Critical Care, and Addiction Drug
Products (DACCADP)- HFD-170**

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Chemistry Review Data Sheet

1. NDA 21-260

2. REVIEW #: 3

3. REVIEW DATE: March 18, 2002

4. REVIEWER: Ravi S. Harapanhalli, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Original NDA 000

BC

BC

AC (NDA Resubmission)

Document Date

May 25, 2000

January 30, 2001

March 16, 2001

July 26, 2001

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

AC (Volume 12 containing package insert only)

BC

BC

BC

BC

BC

BC

BC

Document Date*

July 26, 2001

September 17, 2001

March 7, 2002

March 12, 2002

March 13, 2002

March 14, 2002

March 15, 2002

March 18, 2002

*The review was written based on some of the faxed submissions and therefore the reviewer did not check whether the above submissions are in DSS/COMIS. However, the firm stated that they would follow up each faxed submission with a hard copy to the NDA and therefore the submissions would bear the same date as indicated above. The Project Manager should check to make sure all the above submissions are entered in the DSS.

7. NAME & ADDRESS OF APPLICANT:



Chemistry Review Data Sheet

Name: Elan Pharmaceuticals Research Corporation
Address: 1300 Gould Drive
Gainesville, GA 30504
Representative: Roger Wayne Wiley, R.Ph.
Director, North America Regulatory Affairs
Telephone: 770-534-8239

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: _____
b) Non-Proprietary Name (USAN): Morphine sulfate ER Capsules
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Resubmission of NDA is response to the "AE" letter dated March 30, 2001.

10. PHARMACOL. CATEGORY: Opioid Analgesic

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 30-mg, 60-mg, 90-mg, and 120-mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

SPOTS product – Form Completed

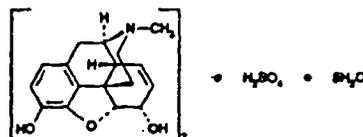
Not a SPOTS product

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Chemistry Review Data Sheet

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

Morphinenan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl, (5 α , 6 α)-sulfate (2:1) (salt), pentahydrate.
 7,8-Didehydro-4,5a-epoxy-17-methylmorphinan-3,6 α -diol sulfate (2:1) (salt) pentahydrate.
 Molecular formula: (C₁₇H₁₉NO₃)₂ · H₂SO₄ · 5 H₂O;
 Molecular weight: 758.85



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
				1	Adequate	03/17/02	Dr. Maturu
				3	Adequate	9/22/99	Dr. SZeka
				2	Type 1	N/A	
				3	Adequate	12/19/00	Dr. Kline
				3	Adequate	12/19/00	Dr. Kline
				3	Adequate	1/5/00	Dr. Rosencrance
				3	Adequate	1/5/00	Dr. Rosencrance
				3	Adequate	1/5/00	Dr. Rosencrance
				3	Adequate	12/19/00	Dr. Kline
				1, 4	Adequate	2/21/02	Dr. Maturu
				1, 4	Adequate	2/21/02	Dr. Maturu
				1, 4	Adequate	2/27/02	Dr. Maturu
				3	Adequate	1/8/01	Dr. Oliver
				4	Adequate	3/9/01	Dr. Maturu

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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**CHEMISTRY REVIEW**

Chemistry Review Data Sheet

IND	IND	Morphine sulfate Extended-release capsules

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not consulted formally. Results of analysis by Cynthia Liu are incorporated into this review.	March 18, 2002	Cynthia Liu, Ph.D. (She computed the expiration dating for the 30-mg bottle configurations based on statistical analysis of linear regression with 95% CI.
EES	Acceptable	03/01/02	Office of Compliance
Pharm/Tox	Qualification threshold for Pseudomorphine and 10-oxomorphine	03/06/02 and 03/11/02	Kathy Haberny, Ph.D.
Biopharm	Acceptable for in vitro stability of beads mixed with applesauce. Also concurred with Chemist's recommendations for dissolution specifications.	10/17/01 and 02/26/02	Suliman Alfayoumi, Ph.D.
OPDRA	Not acceptable for carton/container labels Acceptable for Tradename	03/15/02	Alina Mahmud
Methods Validation	Method validation report was received from _____ and the relevant comments will be forwarded to the firm shortly. The _____ will be also be sent to a second FDA laboratory for verification. Since additional validation data on 10-hydroxymorphine, 10-oxomorphine and normorphine was submitted recently, the firm should be asked to submit updated _____ including all methods and revised specifications.	02/12/02	
OPDRA	Acceptable tradename "Avinza"		
EA	Categorical Exclusion from EA	03/05/01	See CMC review # 1
Microbiology	N/A		
Medical	Pending from Dr. Sharon Hertz: Acceptability of non-child-resistant blister configuration for hospitals		

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/s/

Ravi Harapanhalli

3/30/01 06:15:33 PM

CHEMIST

Please sign off

The review version is the same as the one we discussed today. I ahve i
ncluded the latest corrections.

Dale Koble

3/30/01 06:19:46 PM

CHEMIST

**APPEARS THIS WAY
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