

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-610

21-611

CHEMISTRY REVIEW(S)

2nd Cycle



NDA 21-610

OPANA™ ER

**(Oxymorphone Hydrochloride) Extended-Release Tablets
5 mg, 10 mg, 20 mg, and 40 mg**

Endo Pharmaceuticals

Jila H. Boal, Ph.D.

Division III, ONDQA



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1. NDA # 21-610
2. REVIEW # 2
3. REVIEW DATE: May 15, 2006
4. REVIEWER: Jila H. Boal, Ph.D
5. PREVIOUS DOCUMENTS:

Previous Documents

IND 56,919
Original
Amendment
General Correspondence
Amendment
Amendment
Amendment
Amendment
Amendment
Amendment

Document Date

September 10, 1998
December 19, 2002
January 17, 2003
January 24, 2003
February 13, 2003
February 20, 2003
April 15, 2003
July 17, 2003
July 22, 2003
August 20, 2003
September 12, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

NDA Approvable Action Letter
CMC Teleconference
Post Action Letter
Meeting Minutes
Teleconference Meeting Minutes
Teleconference Meeting Minutes
Complete Response to the Approvable Action Letter
Amendment Proprietary Name Evaluation
Amendment In-vivo Study Results/ Oxymorphone
and Alcohol Co-administration
Amendment (color mock-ups of the labeling
Amendment Labeling

Document Date

October 15, 2003
December 1, 2003
February 16, 2004
March 16, 2004
May 7, 2004
July 16, 2004
December 22, 2005
February 20, 2006

March 22, 2006
March 24, 2006
March 24, 2006



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7. NAME & ADDRESS OF APPLICANT:

Name: Endo Pharmaceuticals Inc.

Address: 100 Painters Drive
Chadds Ford, PA 19317

Representative: Mary Alice Raudenbush
Vice President, Regulatory Affairs

Telephone: (610) 558-9800 Ext 4204

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: OPANA™ ER (Oxymorphone Hydrochloride) Extended Release Tablets
- b) Non-Proprietary Name (USAN): Oxymorphone Hydrochloride
- 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: 505b Application based on the following Listed Drugs:

Numorphan Injection NDA # 11,707 and
Numorphan Rectal Suppositories NDA # 11,738

10. PHARMACOL CATEGORY:

Relief of moderate to severe pain in patients requiring continuous, around the clock opioid therapy for an extended period of time.

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 5, 10, 20, and 40 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

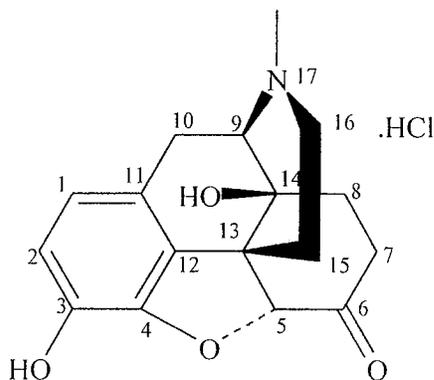
_____ SPOTS product – Form Completed

___X___ Not a SPOTS product

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

Morphinan-6-one, 4,5—epoxy-3, 14-dihydroxy-17-methyl-, hydrochloride, (5 α)-
or,
4,5 α -Epoxy-3,14-dihydroxy-17-methylmorphinan-6-one hydrochloride

C₁₇H₁₉NO₄·HCl



337.80

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	CODE ¹	STATUS ²	Date Review Completed	Comments
14502	II	Mallinckrodt Inc.	Oxycodone HCl, USP	1	Adequate	May 7, 2006	Review #2 by Jila Boal, Ph. D.
11868	IV	Penwest Pharmaceuticals Company	TIMERx [®] -N Controlled Release System	1	Adequate	April 24, 2006	Review #3 by Jila Boal, Ph. D.
	IV			Adequate	September 21, 2003	Review #3 by Jila Boal, Ph. D.	
	III			Adequate	September 15, 2000	DMF Strikeforce	



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	III	1	Adequate	September 12, 2003	Dominic Chiapperino, Ph. D.
	III	3	Adequate	March 22, 2001	Pramoda Maturu, Ph. D.
	III	3 and 4	Adequate	May 19, 2003	Donald Klein, Ph. D.
	III	3	Adequate	October 14, 2003	DMF Strikeforce
	III	3	Adequate	May 22, 2002	DMF Strikeforce Rev. # 2, p. 22, 24
	III	1	Adequate	September 19, 2003	Dominic Chiapperino, Ph. D.

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 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	56,919	Numorphan (Oxymorphone HCl) C-R Tablets
IND	58,602	Numorphan (Oxymorphone HCl) IR Tablets
NDA	21-611	Oxymorphone HCl Immediate Release Tablets
NDA	11-707	Numorphan Injection
NDA	11-738	Numorphan Rectal Suppositories

18. STATUS:

Consults / CMC Related Reviews	Recommendation	Date	Reviewer
Biometrics	Not consulted. Real time stability data for up to 48 months was submitted for the three primary stability batches for		



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	each strength and the supporting clinical batches. The proposed expiration dating of 36 months could be granted.		
EES	Except the all facilities are acceptable. However after review of the updated information in DMF amendment for TIMERx [®] -N it was determined that the facility (manufacturer of the TIMERx [®] -N excipient) does not need inspection. Requested for inspection of this facility was withdrawn from EES. An overall acceptable recommendation was then granted.	June 14, 2006	Office of Compliance Janine D. Ambrogio
Pharm/Tox	Pharm/Tox do not have any concern regarding the excipients. The non genotoxic impurity levels in the drug substance and drug product were reduced according to the relevant Guidances, and the genotoxic impurities are according to an interim acceptance criteria of (—).	June 13, 2006. As per e-mail received from Mamata De, Ph.D. the Pharm / Tox primary reviewer.	Daniel Mellon, Ph.D. Mamata De, Ph.D.
ClinicalPharm	Not Consulted		
LNC	Not consulted. Common dosage form and no issue with established naming		Jila Boal, Ph.D.
Methods Validation	Based on the ONDQA's established criteria for NDA analytical method validation (1/5/2005), none of the test methods meet the criteria for further evaluation. Except the HPLC method for the level of genotoxic impurities, will be evaluated in future once the final acceptance criteria are established. The present values are accepted on an interim bases.		Jila Boal, Ph.D.
DMETS and DDMAC	DMETS has no objections to the use of the proprietary names, Opana and Opana ER provided that only one name Opana (NDA's 21-610 and 21-611) is approved. DDMAC finds the proprietary names Opana and Opana ER acceptable from a promotional perspective.	June 12, 2006	Felicia Duffy
EA	Not applicable. Categorical	N/A	Jila Boal, Ph.D.



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	exclusion claimed and granted.		
Microbiology	Not applicable as this is solid oral dosage form and there are no apparent microbiological issues	N/A	Jila Boal, Ph.D.

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The Chemistry Review for NDA 21-610

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the standpoint of Product quality CMC, NDA 21-610 is recommended for approval. An expiration period of 36 months may be granted based on the assessment of the real time stability data.

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(s) and Drug Substance(s)

Drug Product:

Oxymorphone HCl extended release tablets are formulated in four strengths 5, 10, 20, and 40 mg. They are all octagon-shaped, convex, film-coated tablets which are distinguished by their colors and imprint: the 5 mg is pink, the 10 mg is light orange, the 20 mg is light green, and the 40 mg is yellow.

In addition to oxymorphone HCl, the formulation contains hypromellose, iron oxide black, methylparaben, propylene glycol, silicified microcrystalline cellulose, sodium stearyl fumarate, TIMERx[®]-N, titanium dioxide, and triacetin. The 5, 10 and 20 mg tablets also contain macrogol, and polysorbate 80. In addition, the 5 mg tablets contain iron oxide red. The 10 mg tablets contain FD&C yellow No. 6. The 20 mg tablets contain FD&C blue No. 1, FD&C yellow No. 6, and D&C yellow No. 10. The 40 mg tablets contain FD&C yellow No. 6, D&C yellow No. 10, and lactose monohydrate. The manufacturing process consists of _____.

The excipient TIMERx[®]-N is the primary means of controlling the drug release. It constitutes _____ of the tablet formulation. This hydrophilic matrix is a proprietary controlled-release drug delivery excipient developed by Penwest Pharmaceuticals. TIMERx[®] materials are composed of locust bean gum (LBG) and xanthan gum (XG), _____ . The CMC of TIMERx[®]-N is described in Penwest's DMF 11868 which is deemed adequate to support this NDA.

Drug Release mechanism (TIMERx®-N Control Release):

Drug substance:

Oxymorphone HCl code 0881 is manufactured, quality controlled, and packaged by Mallinckrodt Inc. described in their DMF 14502.

Oxymorphone hydrochloride is readily soluble in aqueous alkalis; moderately soluble in _____ ethanol, sparingly soluble in _____. Freely soluble in water; sparingly soluble in alcohol and ether. The favorable solubility profile of the hydrochloride salt of oxymorphone in water makes it the preferred molecular form for extended release formulation when mixed with TIMERx-N. The drug substance exists in hydrated form.

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

Oxymorphone hydrochloride is proposed for the management of moderate to severe pain where the use of an opioid is appropriate. The extended release dosage formulation of oxymorphone hydrochloride will be available as a 5 mg, 10 mg, 20 mg, and 40 mg tablet. In opioid naïve patients the recommended starting dose of the extended release dosage formulation is 5 mg taken orally every 12 hours.

These dosage formulations of oxymorphone hydrochloride have been classified as a Class II controlled substance.

Tablets are to be swallowed whole, and are not to be broken, chewed, crushed or dissolved. Taking broken, chewed, crushed or dissolved tablets leads to the rapid release and absorption of a potentially fatal dose of oxymorphone.

As with any opioid drug product, it is necessary to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience.

The marketed drug product would be packaged in several different forms. Bottles of _____ tablets with child-resistant closure. Bottles of 100 tablets with child-resistant closure. Bottles of _____ tablets with child-resistant closure. Unit-Dose package of 100 tablets (5 blister cards of 20 tablets, not child-resistant, for hospital use only).



Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

This submission is a complete response to the substantial CMC deficiencies identified in the original NDA submitted in 2002. Several post NDA Action meetings were held to streamline the approach for the resubmission of the NDA.

Since the formulation contains the drug substance in very small amounts (i.e. low dose formulations) the potential for API agglomeration or segregation within the [redacted]

[redacted] Also, [redacted] significant differences in particle size could produce a heterogeneous mixture adversely impacting the [redacted]. Therefore, the following critical quality issues were resolved during this review, paving the way for approval recommendation.

Particle size specification [redacted] was established for the drug substance to better control [redacted] the tablets. [redacted]

[redacted] Since the data demonstrate that these parameters remained consistently within narrow ranges and did not impact the [redacted] final [redacted], there was no need to specify them as [redacted] controls for routine commercial manufacture. Also, better [redacted] controls have now been established for the particle size distribution of the drug substance and TIMERx-N.

The data submitted in the resubmission indicated that [redacted] process has been well developed and validated and it met Stage I testing acceptance criteria [redacted]

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Endo committed to performing drug release testing on core tablets with samples _____ for the first three commercial batches of each strength before requesting to delete this test via a post-approval supplement. This should be reminded in the action letter.

In view of the recently identified safety concerns with dose dumping caused by alcohol, the in-vitro release of the product was assessed using hydroalcoholic media of various alcohol concentrations as the release media. The results indicated that the product was ruggedly designed as it did not dose dump. However, large quantities of ethanol consumed simultaneously with oxymorphone ER affected the pharmacokinetics of oxymorphone (i.e., increased C_{max}). The mechanism by which this occurred (enhanced absorption, decreased metabolism, etc.) is being investigated by the firm. However, based on the in-vitro data, the mechanism of the increased plasma concentrations is likely not due to dose dumping. The firm should be asked to pursue mechanistic understanding of enhanced absorption of the drug following simultaneous alcohol consumption.

Acceptance criteria for degradation products were revised according to ICH Q3 B recommendations. Adequate finished product stability data was provided for up to _____ . The analyses of stability data indicate that the assay, _____ and total degradation products remained within current specifications well beyond 36 months for all packages at 25°C/60%RH. Based on the statistical analysis results and provided real time stability data, an expiration dating period of 36 months could be granted for Oxymorphone Hydrochloride ER Tablets, 5, 10, 20 and 40 mg. The requested expiration dating of 36 months could be granted.

The drug substance specifications have been revised as per ICH Q3A recommendations. The _____



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_____ which are present as process impurities from the synthesis of the drug substance are now controlled at the _____ on an interim basis and will be tightened further based on the action taken by the DMF vendor. This should be reminded in the action letter. _____ Karl Fischer analysis is incorporated with a justified acceptance criteria of _____

In summary, the specifications for impurities in the drug substance and drug product are adequately controlled based on ICH Q3A for the drug substance and ICH Q3B for the drug product. The applicant has provided adequate response to the deficiencies identified in the NDA action letter of October 15, 2003. The manufacturing process is shown to be well understood and robust so as not to result in over-potent tablets. Properly justified in-process controls are established. Stability data confirms an expiration dating of 36 months for this product. Thus, the NDA may be approved from CMC stand point.

III. Administrative

A. Reviewer's Signature

Electronically captured in DFS

B. Endorsement Block

Electronically captured in DFS

Jila H. Boal, Ph. D, CMC Reviewer/ June 13, 2006

Ravi Harapanhalli, Ph. D, Chief, CMC Branch V (Pre-marketing)

(Anesthesia, Analgesia, Rheumatology, Medical Imaging, Hematology, and Oncology Products) Division III, ONDQA

Lisa Bascham-Cruz, Project Manager

C. CC Block

NDA 21-610

HFD-170/LBascham-Cruz/ RHarapanhalli /JBoal

71 Page(s) Withheld

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 Draft Labeling

 Deliberative Process

Withheld Track Number: Chemistry-

**This is a representation of an electronic record that was signed electronically and
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/s/

Jila Boal
6/14/2006 05:36:16 PM
CHEMIST

Ravi Harapanhalli
6/14/2006 05:44:58 PM
CHEMIST

1ST ~~2ND~~ Cycle



CHEMISTRY REVIEW



NDA 21-610

**Trademark[®] (Oxymorphone HCl) Extended-Release Tablets
5 mg, 10 mg, 20 mg, and 40 mg**

Endo Pharmaceuticals

Jila H. Boal, Ph.D.

**Division of Anesthetics, Critical Care,
and Addiction Drug Products
(HFD-170)**



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1. NDA # 21-610
2. REVIEW # 1
3. REVIEW DATE: June 10, 2003
4. REVIEWER: Jila H. Boal, Ph.D
5. PREVIOUS DOCUMENTS:

Previous Documents

IND 56,919

Document Date

September 10, 1998

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Amendment

General Correspondence

Amendment

Amendment

Amendment

Amendment

Amendment

Amendment

Amendment

Document Date

December 19, 2002

January 17, 2003

January 24, 2003

February 13, 2003

February 20, 2003

April 15, 2003

July 17, 2003

July 22, 2003

August 20, 2003

September 12, 2003

7. NAME & ADDRESS OF APPLICANT:

Name: Endo Pharmaceuticals Inc.

Address: 100 Painters Drive
Chadds Ford, PA 19317Representative: Mary Alice Raudenbush
Vice President, Regulatory Affairs



Chemistry Review Data Sheet

Telephone: (610) 558-9800 Ext 4204

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: To-be-determined (see the evaluation of the proprietary name by the Division of Medical Errors and Technical Support Office of Drug Safety, dated August 22, 2003).

b) Non-Proprietary Name (USAN): Oxymorphone HCl

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: 505B2 Application based on the following Listed Drugs:

Numorphan Injection NDA # 11,707 and
Numorphan Rectal Suppositories NDA # 11,738

10. PHARMACOL. CATEGORY: Relief of moderate to severe pain in patients requiring continuous, around the clock opioid therapy for an extended period of time.

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 5, 10, 20, and 40 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

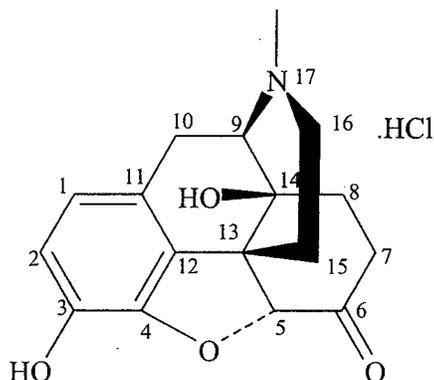
Not a SPOTS product

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

Morphinan-6-one, 4,5—epoxy-3, 14-dihydroxy-17-methyl-, hydrochloride, (5 α)-
or,
4,5 α -Epoxy-3,14-dihydroxy-17-methylmorphinan-6-one hydrochloride

Chemistry Review Data Sheet

C₁₇H₁₉NO₄·HCl
337.80



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	CODE	STATUS ²	Date Review Completed	Comments
14502	II	Mallinckrodt Inc.	Oxycodone HCl, USP	1	Deficient	August 7, 2003	Review #1 by Jila Boal, Ph. D.
11868	IV	Penwest Pharmaceuticals Company	TIMERx [®] -N Controlled Release System	1	Deficient	September 24, 2003	Review #2 by Jila Boal, Ph. D.
	IV			1	Adequate	September 21, 2003	Review #3 by Jila Boal, Ph. D.
	III			3	Adequate	September 15, 2000	DMF Strikeforce
	III			1	Adequate	September 12, 2003	Dominic Chiapperino, Ph. D.
	III			3	Adequate	March 22, 2001	Pramoda Maturu, Ph. D.
	III			3 and 4	Adequate	May 19, 2003	Donald Klein, Ph. D.
	III			3	Adequate	October 14, 2003	DMF Strikeforce
	III			3	Adequate	May 22, 2002	DMF Strikeforce Rev. # 2, p. 22, 24
	III			1	Adequate	September 19, 2003	Dominic Chiapperino, Ph. D.



Chemistry Review Data Sheet

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 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	56,919	Numorphan (Oxymorphone HCl) C-R Tablets
IND	58,602	Numorphan (Oxymorphone HCl) IR Tablets
NDA	21-611	Oxymorphone HCl Immediate Release Tablets
NDA	11-707	Numorphan Injection
NDA	11-738	Numorphan Rectal Suppositories

18. STATUS:

Consults / CMC Related Reviews	Recommendation	Date	Reviewer
Biometrics	An expiration dating of _____ may be granted. However, the data for the 5mg strength supports extrapolation to 24 months.	July 17, 2003	Dionne L. Price, Ph.D.
EES	Acceptable. However it was determined that _____ facility (manufacturer of the TIMERx [®] -N excipient) needs inspection. Request for inspection of this facility will be submitted to the Office of Compliance.	February 26, 2003	Office of Compliance Janine D. Ambrogio
Pharm/Tox	The impurities _____ as well as any other _____ (structural alerts for mutagenicity) which are identified as impurities, must be	Sep. 25, 2003	R. Daniel Mellon, Ph.D.



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	controlled to levels well below 10 or be qualified. This qualification should include a minimal genetic toxicology screen (one in vitro mutagenicity assay and one in vitro chromosome aberrations assay) testing each compound at the limit dose for the assay. Should a genetic toxicology assay yield a positive result, the specification for the impurity should be lowered to NMT 10 , or the impurity should be adequately qualified via a carcinogenicity assessment in a single species.		
Biopharm	The IVIVC studies do support the proposed acceptance criteria for the drug product dissolution.	September 23, 2003	David Lee, Ph.D.
LNC	NA		
Methods Validation	Not requested at this time since the specifications need to be revised.		
DDMAC	Recommends 10 which should be followed with an appropriate suffix to distinguish the extended release dosage formulation of this product from the immediate release dosage formulation.	August 25, 2003	Scott Dallas, R.Ph.
EA	Not applicable. Categorical exclusion claimed	N/A	N/A
Microbiology	Not applicable as this is solid oral dosage form and there are no apparent microbiological issues	N/A	N/A

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The Chemistry Review for NDA 21-610

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is approvable pending satisfactory resolution of CMC deficiencies and comments listed at the end of the review. The applicant should address all of the listed CMC deficiencies.

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

None has been made.

II. Summary of Chemistry Assessments

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

Drug Product (s):

Background

Oxymorphone hydrochloride USP, has been used as an appropriate therapeutic choice for a variety of painful conditions since 1959. Oxymorphone has a significantly higher (10 times more potent if administered parentally and 2 to 3 times more potent if administered orally) analgesic potency compared to morphine. Currently Endo Pharmaceuticals Inc. markets oxymorphone hydrochloride USP, in two formulations.

- Numorphan® (oxymorphone HCl, USP) suppositories (5 mg) under NDA 11-738.
- Numorphan® (oxymorphone HCl, USP) Injection 1mg/ml (ampule) and 1.5 mg/ml (10 ml multiple dose vials) under NDA 11-707.

This NDA for which an IND was filed on September 10, 1997, is intended to control the release of oxymorphone HCl within the gastrointestinal tract, with the result that the drug is delivered at a specific predetermined rate suitable for a twice a day dosing. The drug release rate is dependent on the diffusion of the drug from the controlled release matrix. Mechanically, the rate of drug release is controlled by the rate of water penetration into the tablet matrix to form a tight gel with a slowly eroding core.

Dosage Strengths

The oxymorphone HCl extended release tablet is formulated in four strengths 5, 10, 20, and 40 mg. They are all octagon-shaped, convex, film-coated tablets which are



Executive Summary Section

distinguished by their colors and imprint: the 5 mg is pink, the 10 mg is light orange, the 20 mg is light green, and the 40 mg is yellow.

Formulation:

Tablets contain the following inactive ingredients: hypromellose, iron oxide black, methylparaben, propylene glycol, silicified microcrystalline cellulose, sodium stearyl fumarate, TIMERx[®]-N, titanium dioxide, and triacetin. The 5, 10 and 20 mg tablets also contain macrogol, and polysorbate 80. In addition, the 5 mg tablets contain iron oxide red. The 10 mg tablets contain FD&C yellow No. 6. The 20 mg tablets contain FD&C blue No. 1, FD&C yellow No. 6, and D&C yellow No. 10. The 40 mg tablets contain FD&C yellow No. 6, D&C yellow No. 10, and lactose monohydrate.

The excipient TIMERx[®]-N is the primary means of controlling the drug release. It constitute _____ of the tablet formulation. This hydrophilic matrix is a proprietary controlled-release drug delivery excipient developed by Penwest Pharmaceuticals. TIMERx[®] materials are composed of locust bean gum and xanthan gum, _____

..... The TIMERx[®]-N is a non-compendial active excipient, therefore the CMC information is contained in DMF 11868 which is supported by Penwest Pharmaceuticals. This DMF is reviewed by me and is deficient (see Review # 2 dated September 24, 2003). The following is the major deficiency of this DMF: the particle size distribution of the TIMERx[®]-N is not sufficiently specific to assure reproducible particle size distribution in all of the TIMERx[®]-N batches. Optimal particle size distribution of all of the components of the TIMERx[®]-N formulation is critical to uniformity of the powder blend in manufacturing of these tablets. Thus, the applicant will be asked to provide a tighter particle size distribution specification for the TIMERx[®]-N, e.g., _____ distribution specification. Justification should be based on the batches used in the manufacturing of the NDA exhibit batches and biobatches.

Manufacturer and Manufacturing Sites:

Manufacturing process for Oxymorphone Hydrochloride Extended-Release Tablets is a

Executive Summary Section

- 1) _____ . This site manufactured the initial clinical study tablets. Tablet strengths manufactured at this site were 10, 20, and 40 mg. The Clinical batches manufactured at _____ are coated but unprinted tablets.
- 2) _____ . This site manufactured the following tablets:
 - Tablets that were used in late phases of clinical trials. These were 5, 10, 20, and 40 mg tablets.
 - _____ manufactured the primary stability batches. Three primary stability (exhibit) batches _____ tablets/scale of each strength were manufactured at this site. The primary stability or exhibit batches manufactured at _____ are coated and printed tablets.
 - _____ site will be responsible for commercial production of all four tablet strengths. The commercial batches are _____ times the scale of the pilot batches which is consistent with the allowance of up to a _____ increase in manufacturing scale (SUPAC-MR, scale-up, level -1).
 - In addition, _____ will be responsible for the packaging, labeling, and testing of all commercial batches.

Both _____ used the same process to manufacture these tablets and the formulation of each respective strength is the same except for the tablet coating and imprinting. Both _____ tablets were color film-coated, however for the _____ tablets the coating solution contained _____ and the tablets were imprinted with black ink.

To show that the drug products manufactured at the two sites are similar, Endo Pharmaceuticals Inc. has conducted an in-vitro drug release comparison and a bioequivalence study between the _____ manufactured batches. The bioequivalence study was conducted on 40 mg tablets manufactured at the two sites. Results of the statistical analyses of bioequivalence study indicate that the products manufactured at both sites are bioequivalent (see the Clinical Pharmacology and Biopharmaceutics review of this NDA by Dr. David Lee dated September 23, 2003).

In vitro dissolution experiments were performed in 0.1N HCl and in pH 4.5 phosphate buffer. Dissolution study demonstrates the similarity of coated and printed tablets (primary stability or exhibit batches) manufactured at _____ versus coated and unprinted tablets (Clinical batches) manufactured at _____.

The _____ are critical parameters in _____ manufacturing process, which is the manufacturing method used for these extended release tablets. In addition, the possibility for agglomeration and aggregation of the _____ should be watched closely. Therefore we will ask the applicant to perform the following tests:

Executive Summary Section

The following _____ tests should be performed on routine bases in every commercial production batch of the extended release tablets:

a) Perform the following tests on the _____ and provide the acceptance criteria:

Packaging:

Each strength of the Oxymorphone HCl ER Tablet will be packaged in two different packaging configurations. Bottles and blisters, each bottle will contain _____ 100, _____ tablets with child-resistant closure. Each blister pack will contain 100 tablets (5 blister cards of 20 tablets).

-The bottle container/closure system consists of _____ bottles supplied by _____ and is composed of the _____ the child-resistant closures from _____ with _____

-The blister package consists of _____ and _____

Specifications:

The proposed regulatory specifications and analytical methods for quality control of Oxymorphone HCl Extended- Release Tablets, 5, 10, 20 and 40 mg, includes:

Description, Identification, Assay, Degradation Products, Uniformity of Dosage Units (Content Uniformity), and Drug Release (Dissolution).

Acceptance criteria for degradation products required revision. Specifically those degradation products with _____ moiety (structural alerts for mutagenicity) arising from the drug substance should be controlled to levels well below _____ (see the Draft Deficiency List at the end of this review).

As indicated before, due to the drug release mechanism of the drug product, the _____ of the drug product should be tested and controlled on stability.

Drug release (dissolution) was studied in different dissolution media:

**Executive Summary Section****Stability:**

Amendment of July 17, 2003 contained additional stability data, which extends the stability data for as long as 24 months for the primary stability batches and up to 48 months for supportive batches. Three lots of each tablet strength packaged in the commercial packaging configurations that are mentioned above were put on stability. The primary stability data includes six months data under ICH accelerated conditions (40°C/75% RH) and up to 24-months long-term room temperature (25°C/60% RH) data. Supportive stability data on clinical trial batches at both *ICH* accelerated and room temperature conditions are also provided in this NDA. An expiration dating period of 36 months is proposed by the applicant. However, analysis of dissolution data (18 months and 24 months data) indicates a possible increase in dissolution rate on stability and thus reveals the possibility of dose dumping at 36 months. Since this NDA is approvable the applicant will be asked to provide updated drug product stability data, with statistical analysis and the expiration dating for this product will be determined at that time.

Drug substance:**Background:**

Oxymorphone (14-hydroxydihydromorphone) is a semi-synthetic opioid agonist derived from thebaine. It is a schedule II controlled substance.

Its structure is related to morphine, with the following differences:

- A ketone group substituted at the C-6 position of morphine.
- The 7-8 double bond saturation.
- Hydroxyl group substitution at C-14.

The hydrochloride salt form of Oxymorphone is a USP article. It is freely soluble in water (1 in 4).

Manufacturer and Manufacturing Sites:



Executive Summary Section

The drug substance manufacturer is Mallinckrodt Chemical Company. The CMC information supported by Mallinckrodt for oxymorphone HCl is contained in DMF # 14502. DMF 14502 is reviewed by me and was found deficient. Mallinckrodt will be informed on the deficiency of their DMF (see review of DMF 14502 by this reviewer).

The USP optical rotation test and acceptance criteria is broad and should be supported by an HPLC test. We will ask from the applicant to provide adequate information to support the stereochemical configuration and stereoisomeric purity of oxymorphone hydrochloride (i.e., the synthetically introduced chiral center).

Initial clinical trial materials were manufactured using drug substance from _____.

The _____ long-term plan was to discontinue the manufacture of oxymorphone HCl drug substance. Therefore, _____ was selected as the new drug substance supplier. All subsequent batches of drug product for clinical studies and for NDA submission were manufactured using the drug substance supplied by _____. The material from both companies exhibits comparable physical and chemical characteristics that are relevant to the manufacturing and performance of the drug product. These are, comparison of the _____, comparison of the particle size distribution, comparison of the intrinsic dissolution of the drug substance manufactured at the two sites, as well as the pH solubility profiles and the dissolution of the tablets manufactured using the drug substance from both suppliers.

Specifications:

Specifications include all USP compendial requirements, plus additional limits for related substances and residual solvents, _____. The validation of the HPLC assay and related substances method was performed by Mallinckrodt, and the data is contained in their DMF 14502. The applicant will be asked to submit the method validation for the HPLC drug substance assay and related substances (_____) in their NDA application and include this HPLC assay and related substances as the regulatory method rather than as an alternate test method. All the other methods are USP compendial and do not require validation.

The specifications for the drug substance should be modified and it will be requested from the applicant to include the followings in the drug substance specifications at release:

- Revise the specifications to establish the chromatographic method for assay and related substances as the "regulatory" methods for the NDA, replacing their designation as "alternate" methods.

Executive Summary Section

to provide a specification _____ in the drug substance using an accurate and specific method (e.g., Karl Fischer titration).

- The impurities _____, as well as any other _____ which are identified as impurities, must be controlled to levels well below (e.g., _____) the current drug substance specification of NMT _____. The applicant will be asked to coordinate with the DMF holder Mallinckrodt to submit a tightened specification acceptable to the agency, or justify the current specification based on new carcinogenicity studies. Qualifications are based upon a maximum daily dose of 1 gram.
- _____

Packaging:

This is detailed in the DMF 14502 and is found adequate.

Stability:

Stability data for the drug substance supplied by Mallinckrodt is reported in the DMF _____

_____ The stability data for _____ lots of the drug substance manufactured by _____ are reported in the NDA. Six months stability data at accelerated temperature conditions and up to 2 years data for long term storage conditions are provided. Note that the applicant is not using _____ as the future supplier of the drug substance.

Therefore the following comment will be sent to the applicant:

- Justify the proposed retest date _____ for oxymorphone hydrochloride supplied by Mallinckrodt.

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

Tablets are to be swallowed whole, and are not to be broken, chewed, crushed or dissolved. Taking broken, chewed, crushed or dissolved tablets leads to the rapid release and absorption of a potentially fatal dose of oxymorphone.

As with any opioid drug product, it is necessary to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. In the selection of the initial dose of TRADEMARK, attention should be given to the following:

1. The total daily dose, potency and specific characteristics of the opioid the patient has been taking previously;
2. The relative potency estimate used to calculate the equivalent oxymorphone dose needed;
3. The patient's degree of opioid tolerance;

**Executive Summary Section**

4. The age, general condition, and medical status of the patient;
5. Concurrent non-opioid analgesic and other medications;
6. The type and severity of the patient's pain;
7. The balance between pain control and adverse experiences.

In clinical practice, it is suggested that opioid-naïve patients being initiated on chronic around-the-clock opioid therapy be started with the lowest available dose of the ER opioid. Therefore, it is recommended that opioid-naïve patients be started with 5 mg TRADEMARK q12h and patients receiving TRADEMARK (IR) may be converted to TRADEMARK (ER) by administering half the patient's total daily oral TRADEMARK (IR) dose as TRADEMARK (ER), q12 hours. For example, a patient receiving 60 mg/day TRADEMARK (IR) may require 30 mg TRADEMARK (ER) q12h. Supplemental TRADEMARK (IR) may be required for breakthrough pain until the response to the patient's daily TRADEMARK (ER) dosage has stabilized. In clinical practice, when rescue medication is warranted, it is recommended that the supplemental breakthrough dose be calculated at approximately 10-20% of the total daily TRADEMARK (ER) dose. For example, a patient on 30mg TRADEMARK (ER) q12h would receive 5-10mg of TRADEMARK (IR) as the supplemental breakthrough dose.

C. Basis for Approvability or Not-Approval Recommendation

The CMC deficiencies are listed at the end of this review. The applicant should adequately respond to these deficiencies before the Division approves this NDA.

III. Administrative**A. Reviewer's Signature**

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B. Endorsement Block

Electronically captured in DFS

Jila H. Boal, Ph. D, CMC Reviewer/ June 10, 2003

Dale Koble, Ph. D, Chemistry Team Leader/

Lisa Bascham-Cruz, Project Manager

C. CC Block

NDA 21-610

HFD-170/LBascham-Cruz/DKoble/JBoal

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Dale Koble
10/15/03 05:32:53 PM
CHEMIST

2nd Cycle



NDA 21-611

**OPANA™
(Oxymorphone Hydrochloride) Tablets
5 mg and 10 mg**

Endo Pharmaceuticals

**Jila H. Boal, Ph.D.
Division III, ONDQA**



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Chemistry Review Data Sheet

1. NDA # 21-611
2. REVIEW # 2
3. REVIEW DATE: May 15, 2006
4. REVIEWER: Jila H. Boal, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

IND 58,602
 N 21-611-000
 N 21-611-000-BC
 N 21-611-000-BC
 N 21-611-000-BC
 N 21-611-000-BL

Document Date

July 7, 1999
 Dec. 20, 2002
 Feb. 13, 2003
 Jul. 17, 2003
 Aug. 6, 2003
 Sep. 12, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

NDA Approvable Action Letter
 CMC Teleconference
 Post Action Letter
 Meeting Minutes
 Teleconference Meeting Minutes
 Teleconference Meeting Minutes
 Complete Response to the Approvable Action Letter
 Amendment (Proprietary Name Evaluation)
 Amendment to a Complete Response—In-vivo Study
 Results/ Oxymorphone and Alcohol Co-
 administration.

Document Date

October 15, 2003
 December 1, 2003
 February 16, 2004
 March 16, 2004
 May 7, 2004
 July 16, 2004
 December 22, 2005
 February 20, 2006
 March 22, 2006

Executive Summary Section

Amendment (color mock-ups of the labeling incorporating the proposed trade name for all three products)

March 24, 2006

7. NAME & ADDRESS OF APPLICANT:

Name: Endo Pharmaceuticals
Address: 100 Painters Drive
Chadds Ford, PA 19317
Representative: Mary Alice Raudenbush
Vice President, Regulatory Affairs
Telephone: (610)-558-9800

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: OPANA™(Oxymorphone Hydrochloride) Tablets
- b) Non-Proprietary Name (USAN): Oxymorphone Hydrochloride
- c) Code Name/#: N/A
- d) Chem. Type/Submission Priority :
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

The application is filed as a 505B2 application based on the listed drugs:

Numorphan Injection, NDA# 11-707
Numorphan Rectal Suppositories, NDA# 11-738

10. PHARMACOL CATEGORY:

Management of moderate to severe pain where the use of an oral opiate is appropriate

11. DOSAGE FORM:

Immediate Release Tablet, Oral

CHEMISTRY REVIEW

Executive Summary Section

12. STRENGTH/POTENCY:

5 and 10 mg per tablet

13. ROUTE OF ADMINISTRATION:

Oral

14. Rx/OTC DISPENSED: Rx OTC

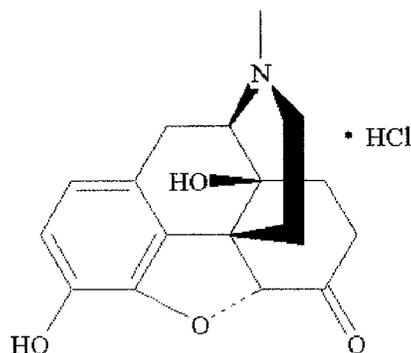
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

Morphinan-6-one, 4,5—epoxy-3, 14-dihydroxy-17-methyl-, hydrochloride, (5 α)-
or,
4,5 α -Epoxy-3,14-dihydroxy-17-methylmorphinan-6-one hydrochloride



Mol. Formula: $C_{17}H_{19}NO_4 \cdot HCl$

Mol. Weight: 337.80

17. RELATED/SUPPORTING DOCUMENTS:

CHEMISTRY REVIEW

Executive Summary Section

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
14502	II	Mallinckrodt	Oxymorphone HCl	1	Adequate	Review #2 by Jila Boal, May 7, 2006	Polymorph issues to be addressed
	III			3	Adequate	Sep. 15, 2000	Strikeforce
	III			1	Adequate	Sep. 12, 2003, by Dominic Chiapperino	
	III			1	Adequate	Sep. 12, 2003, by Dominic Chiapperino	
	III			3	Adequate	May 19, 2003, By Donald Klein, Ph.D.	
	III			3	Adequate	Oct. 14, 2003	Strikeforce
	III			3	Adequate	May 22, 2002	Strikeforce, Rev.#2, p. 22, 24
	III			1	Adequate	Sep. 19, 2003, by Dominic Chiapperino	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type I DMF

3 – Reviewed previously and no 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	56,919	Numorphan (Oxymorphone HCl) C-R Tablets
IND	58,602	Numorphan (Oxymorphone HCl) IR Tablets
NDA	21-611	Oxymorphone HCl Immediate Release Tablets

CHEMISTRY REVIEW

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NDA	11-707	Numorphan Injection
NDA	11-738	Numorphan Rectal Suppositories
NDA	21-610	Extended release formulation of oxymorphone hydrochloride tablets for oral administration.

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not consulted. Real time stability data for up to 48 months was submitted for a proposed expiration dating of 30 months.		
EES	Facilities are acceptable	Feb. 13, 2006	Janine D. Ambrogio
Pharm/Tox	Pharm/Tox do not have any concern regarding the excipients. The non genotoxic impurity levels in the drug substance and drug product were reduced according to the relevant Guidances, and the genotoxic impurities are according to an interim acceptance criteria of _____.	June 13, 2006. As per e-mail received from Mamata De, Ph.D. the Pharm / Tox primary reviewer.	Daniel Mellon, Ph.D. Mamata De, Ph.D.
ClinicalPharm	Not Consulted		
LNC	Not consulted (simple dosage form)		
Methods Validation	Based on the ONDQA's established criteria for NDA analytical method validation (1/5/2005), none of the test methods meet the criteria for further evaluation. Except the HPLC method for the level of genotoxic impurities, will be evaluated in future once the final acceptance criteria are established. The present		



CHEMISTRY REVIEW



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	values are accepted on an interim bases.		
DMETS and DDMAC	DMETS has no objections to the use of the proprietary names, Opana and Opana ER provided that only one name Opana (NDA's 21-610 and 21-611) is approved. DDMAC finds the proprietary names Opana and Opana ER acceptable from a promotional perspective.	June 12, 2006	Felicia Duffy
EA	Not applicable. Categorical exclusion claimed and granted.	As per this review	Jila H. Boal, Ph.D.
Microbiology	N/A		



The Chemistry Review for NDA 21-611

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the standpoint of Product quality CMC, NDA 21-611 is recommended for approval. An expiration period of 30 months may be granted based on the assessment of the stability data.

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(s) and Drug Substance(s)

Drug Product:

This product is manufactured using _____ procedures. Commercial batch will be manufactured at Lincoln, Nebraska, of Novartis Consumer Health, Inc. on a _____ scale. The excipients in the drug product formulation are Lactose Monohydrate (NF), Pregelatinized Starch (NF), and Magnesium Stearate (NF). The 5 mg strength tablet contains a colorant, FD&C Blue #2 Aluminum Lake, which distinguishes it from the 10 mg strength tablet containing D&C Red #30 Aluminum Lake.

The 5 mg Tablets are blue, round, convex tablets debossed with E612 over 5 on one side and plain on the other. Bottles of _____ tablets with child-resistant closure. Bottles of 100 tablets with child-resistant closure. Bottles of _____ tablets with child-resistant closure. Unit-Dose package of 100 tablets (5 blister cards of 20 tablets, not child-resistant, for hospital use only).

The 10 mg Tablets are Red, round, convex tablets debossed with E613 over 10 on one side and plain on the other. Bottles of _____ tablets with child-resistant closure. Bottles of 100 tablets with child-resistant closure. Bottles of _____ tablets with child-resistant closure. Unit-Dose package of 100 tablets (5 blister cards of 20 tablets, not child-resistant, for hospital use only).

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

Oxymorphone hydrochloride is proposed for the management of moderate to severe pain where the use of an opioid is appropriate. The immediate release dosage

Executive Summary Section

formulation of oxymorphone hydrochloride will be available as a 5 mg and 10 mg tablet. In opioid naïve patients the recommended starting dose of the immediate release dosage formulation is 5 mg taken orally every 6 — hours as needed.

These dosage formulations of oxymorphone hydrochloride have been classified as a Class II controlled substance.

C. Basis for Approvability or Not-Approval Recommendation

The NDA was submitted on December 20, 2002 under section 505(b) of the Federal Food, Drug and Cosmetic Act for Oxymorphone Hydrochloride Immediate Release (IR) Tablets. An “approvable” action was taken on October 15, 2003 to which a complete response submitted on December 22, 2005. Since there were substantial CMC deficiencies in the original NDA, Endo and the Agency were engaged in several post-action meetings to formulate strategies to address them.

The active pharmaceutical ingredient (API), oxymorphone as the hydrochloride salt, represents less than — of the overall components of the 5 mg tablet strength and less than — of the 10 mg tablet strength, as each tablet is formulated for a total weight of 220 mg. Since these are formulations in which the API is a relatively small portion of the overall formulation, and since the product are manufactured using —

The data on the bulk and tap densities — indicated that they remained unchanged in the exhibit and validation batches and were not indicative of —. Therefore, these will not be routinely monitored.

Executive Summary Section

The firm had been asked to tighten acceptance criteria for dissolution but provided data indicating that a Q of _____ is achievable at 30 minutes and this is acceptable.

The impact of alcohol on dose dumping of oxymorphone from the formulation was assessed in-vitro using hydroalcoholic media of various alcohol concentrations as the release media. Based on the results the product was shown to be rugged and it did not dose dump in 40% alcohol. However, large quantities of ethanol consumed simultaneously with oxymorphone ER effect the pharmacokinetics of oxymorphone (i.e., increased C_{max}). The mechanism by which this occurs (enhanced absorption, decreased metabolism, etc.) is unknown at present; however, based on the *in-vitro* data, the mechanism of the increased plasma concentrations is likely not due to dose dumping. This information has been captured appropriately in the package insert.

The analyses of stability data indicate that the assay, (_____) and total degradation products would remain within current specifications through 30 months for all packages at 25°C/60%RH.

Drug substance specifications have been updated to include adequate acceptance criteria for the level of impurities and degradation products. These levels are revised based on the ICHQ 3A recommendations. The _____, which are present as process impurities from the synthesis of the drug substance are controlled at _____ level on interim basis and this is consistent with the arrangements negotiated between the Agency and Mallinckrodt, the DMF holder of oxymorphone hydrochloride. The drug substance release specifications are also revised _____. Adequate justification for the _____ acceptance criteria has been provided in DMF _____.

In summary, the applicant has provided adequate response to the deficiencies identified in the NDA action letter of October 15, 2003. The manufacturing process seems to be robust. Properly justified _____ controls are established. Stability data confirms an expiration dating of 30 months for this product. Adequate finished product stability data was provided for up to 48 months. In addition, the supportive stability data confirmed the stability of this product through _____ months at long term conditions (25°C/60% RH). Hence, the requested expiration dating of 30 months could be granted.

III. Administrative

A. Reviewer's Signature

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B. Endorsement Block

Electronically captured in DFS

Jila H. Boal, Ph. D, CMC Reviewer/ June 13, 2006

Ravi Harapanhalli, Ph. D, Chief, CMC Branch V (Pre-marketing)

(Anesthesia, Analgesia, Rheumatology, Medical Imaging, Hematology, and Oncology
Products) Division III, ONDQA

Lisa Bascham-Cruz, Project Manager

C. CC Block

NDA 21-611

HFD-170/LBascham-Cruz/ RHarapanhalli /JBoal

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Ravi Harapanhalli
6/13/2006 03:32:50 PM
CHEMIST

1ST Cycle



NDA 21-611

Trademark[®] (Oxymorphone Hydrochloride) Tablets

Endo Pharmaceuticals

Dominic Chiapperino, Ph.D.
Division of Anesthetic, Critical Care and Addiction Drug
Products



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1. NDA 21-611
2. REVIEW #1
3. REVIEW DATE: September 29, 2003
4. REVIEWER: Dominic Chiapperino, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

IND 58,602

Document Date

July 7, 1999

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

N 21-611-000

N 21-611-000-BC

N 21-611-000-BC

N 21-611-000-BC

N 21-611-000-BL

Document Date

Dec. 20, 2002

Feb. 13, 2003

Jul. 17, 2003

Aug. 6, 2003

Sep. 12, 2003



Executive Summary Section

7. NAME & ADDRESS OF APPLICANT:

Name:	Endo Pharmaceuticals
Address:	100 Painters Drive Chadds Ford, PA 19317
Representative:	Mary Alice Raudenbush Vice President, Regulatory Affairs
Telephone:	(610)-558-9800

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: TRADEMARK™ Tablets
- b) Non-Proprietary Name (USAN): Oxymorphone Hydrochloride
- c) Code Name/#:
- d) Chem. Type/Submission Priority :
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

The application is filed as a 505B2 application based on the Listed drugs:

Numorphan Injection, NDA# 11-707
Numorphan Rectal Suppositories, NDA# 11-738

10. PHARMACOL. CATEGORY:

Management of moderate to severe pain where the use of an oral opiate is appropriate

11. DOSAGE FORM:

Immediate Release Tablet, Oral



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12. STRENGTH/POTENCY:

5 or 10 mg per tablet

13. ROUTE OF ADMINISTRATION:

Oral

14. Rx/OTC DISPENSED: Rx OTC

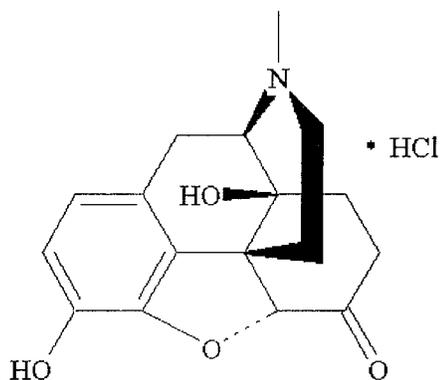
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

4,5 α -Epoxy-3,14-dihydroxy-17-methylmorphinan-6-one hydrochloride



Mol. Formula: $\text{C}_{17}\text{H}_{19}\text{NO}_4 \cdot \text{HCl}$

Mol. Weight: 337.80

17. RELATED/SUPPORTING DOCUMENTS:



CHEMISTRY REVIEW



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A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
14502	II	Mallinckrodt	Drug substance	1	Deficient	Aug. 7, 2003, by Jila Boal	
	III			3	Adequate	Sep. 15, 2000	Strikeforce
	III			1	Adequate	Sep. 12, 2003, by Dominic Chiapperino	
	III			3	Adequate	Mar. 22, 2001, by Pramoda Maturu	
	III			3	Adequate	May 19, 2003, By Donald Klein, Ph.D.	
	III			3	Adequate	Oct. 14, 2003	Strikeforce
	III			3	Adequate	May 22, 2002	Strikeforce, Rev.#2, p. 22, 24
	III			1	Adequate	Sep. 19, 2003, by Dominic Chiapperino	

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 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
Original NDA submission	N 21-610	Related NDA, extended release formulation of oxymorphone hydrochloride tablets for oral administration.



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18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Inadequate data to support _____ expiry; 30-month expiry would be acceptable based on stability data analysis	Oct. 1, 2003	Dionne Price, Ph.D.
EES	Facilities are acceptable	Feb. 26, 2003	Janine D. Ambrogio
Pharm/Tox	Inadequate qualification of degradant impurities that have specified limits above ICH guidelines	Sep. 25, 2003	Daniel Mellon, Ph.D.
Biopharm	Adequate on bioequivalency of clinical batches and exhibit batches made at different sites	Review filed in DFS Sep. 23, 2003	David Lee, Ph.D.
LNC	N/A		
Methods Validation	Will be initiated after firm response to action letter		
ODS	_____ are best proprietary names considered for the immediate release (N 21-611) and extended release (N 21-610) oxymorphone hydrochloride drug products.	Review filed in DFS Aug. 25, 2003	Scott Dallas, R.Ph.
EA	N/A		
Microbiology	N/A		

*Appears This Way
On Original*



The Chemistry Review for NDA 21-611

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is **approvable**, provided the applicant can address the deficiencies in manufacturing controls which are discussed below.

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

There are no Phase 4 (Post-Marketing) commitments, agreements, and/or risk management steps currently being negotiated with the applicant which relate to chemistry, drug manufacture, or quality controls on the drug product.

II. Summary of Chemistry Assessments

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

The drug product TRADEMARKTM Tablets, also known as Oxymorphone Hydrochloride Tablets, is an oral dosage form that is available in 5 or 10 mg strengths. The product will be marketed as a treatment for moderate to severe acute pain when the use of an oral opiate is appropriate.

The drug product is manufactured using _____ . The excipients in the drug product formulation are Lactose Monohydrate (NF), Pregelatinized Starch (NF), and Magnesium Stearate (NF). The 5 mg strength tablet contains a colorant, FD&C Blue #2 Aluminum Lake, which distinguishes it from the 10 mg strength tablet containing D&C Red #30 Aluminum Lake. There is nothing objectionable about the quality of these excipients for use in the drug product other than a somewhat loose control over particle size, which may have an impact on the uniformity of the _____ drug product.

The drug Product will be manufactured at the facility in Lincoln, Nebraska, of Novartis Consumer Health, Inc.. This site, proposed for the commercial batches to be made on a _____ scale, was also the site where the exhibit batches were manufactured on a _____ scale. The stability studies performed on these exhibit batches and on the primary clinical batches, some of which were manufactured by the contract firm _____ , show the drug product to be stable over the 24 month

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period, with minimal accumulation of degradant compounds related to the drug substance, oxymorphone.

The drug substance is the hydrochloride salt of oxymorphone, a potent analgesic in the opioid family of drug compounds. This salt is a white, or slightly off-white, odorless powder, easily soluble in water and acidic aqueous solution. The synthesis of the drug substance and much of the details of drug substance characterization and quality control are described by Mallinckrodt Chemical Company, Inc. under their DMF #14,502.

The marketed drug product would be packaged in several different forms. For both the 5 and 10 mg strength tablets, _____ bottles in _____ sizes, with child resistant caps, would be used for 100s _____ respectively. Also planned for both strengths, blister packaging containing cards with 20 tablets would be used. All of the above packaging types have been utilized in stability studies with the exhibit batches made by NCH.

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

The applicant proposes that these oxymorphone hydrochloride immediate release formulations for oral administration are intended to be used as follows:

These formulations broaden the range of therapeutic options available for the treatment of moderate to severe acute pain.

C. Basis for Approvability or Not-Approval Recommendation

There are several significant concerns, both with the drug substance and the drug product, which will need to be addressed by the applicant in order to obtain Agency approval of their NDA.

Drug Substance

With regard to the drug substance, oxymorphone hydrochloride, there are issues relating to potentially carcinogenic impurities. The improved control of these impurities by the DMF holder, Mallinckrodt Inc., or their qualification as safe by the applicant, will have to occur to alleviate concerns of the Agency on this issue. The compounds in question _____ are present as process impurities from the synthesis of the drug substance. We have been in contact with both the applicant and the DMF holder of the drug substance to determine how they can work



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toward a solution in limiting these impurities to an acceptably low level, or submitting carcinogenicity study results that would qualify the compounds as safe at the current proposed levels.

There is also the issue of inadequate characterization of the drug substance. The drug substance release specifications include a specification of NMT _____ The data imply a fairly consistent _____ of approximately _____ and the possibility of hydrate forms of the drug substance, not determined or clarified by the applicant, should be addressed. Also, the testing _____ should be specific _____, i.e. Karl Fischer analysis, where currently it is measured by loss on drying at _____

Drug Product

The proposed commercial product, an orally administered immediate-release tablet containing 5 or 10 mg of oxymorphone hydrochloride, is intended for use in cases of severe or acute pain where an opioid analgesic is appropriate. The broad concern of the Agency is that the controls proposed to insure the consistent dosage amount of this drug product are inadequate.

The active pharmaceutical ingredient (API), oxymorphone as the hydrochloride salt, represents less than _____ of the overall components of the 5 mg tablet strength and less than _____ of the 10 mg tablet strength, as each tablet is formulated for a total weight of 220 mg. Since these are formulations in which the API is a relatively small portion of the overall formulation, and since the manufacture of the tablet is performed _____ the potential for API concentration or segregation within the _____ drug product is an immediate concern.

the applicant has not described in sufficient detail the manufacturing procedures beyond batch records that would commit them to SOPs that the Agency finds acceptable.

i. There is, however, a higher than usual incidence of the need for "rescue" with naltrexone of patients in clinical studies that have been reviewed by our Medical Officers. It is not clear as to whether this high incidence was caused by inadvertent high doses attributable to heterogeneous blends of the drug product. Also, it should be noted that the applicant's proposed _____ scale-up in the manufacture of the commercial batches is as yet untested with regard to _____ optimization of parameters that may impact _____.

There are also degradant impurities controlled in the drug product which have specified limits at levels that would require qualification. We do not believe that these impurities,



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_____ have been properly qualified based on the comments of our PharmTox reviewers.

In favor of the application, the drug product has shown to be quite stable, relatively free of impurities, and fairly uniform in dosage amounts based on the content uniformity testing performed. An “Approvable” action is expected to be taken in this first review cycle with respect to the CMC portion of the application.

III. Administrative

A. Reviewer’s Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

61 Page(s) Withheld

6 Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

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

/s/

Dominic Chiapperino
10/15/03 04:32:09 PM
CHEMIST

Dale Koble
10/15/03 04:47:15 PM
CHEMIST