CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201655Orig1s000

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW

NDA 201655

OPANA® ER (oxymorphone hydrochloride) Extended Release Tablets

Endo Pharmaceuticals Inc.

Craig M. Bertha, Ph.D.
Office of New Drug Quality Assessment/Division III/Branch VIII

for

Division of Anesthetics and Analgesics Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 201655

2. REVIEW #:3

3. REVIEW DATE: 18-JUL-2011

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Document Date(s)	Previous Document
07-JUL-2010	Original Submission
23-JUL-2010	Updated labeling
14-SEP-2010	Amendment (response to filing letter)
29-SEP-2010	Amendment (response to CMC DR letter)
01-OCT-2010	Amendment (stability data DP (b) (4)
06-OCT-2010	Amendment (updated package insert labeling)

6. SUBMISSION(S) BEING REVIEWED:

Document Date(s)	Submission(s) Reviewed
13-JUN-2011	Amendment (response to complete response action letter; stability update; label/labeling update)

7. NAME & ADDRESS OF APPLICANT:

Name:	Endo Pharmaceuticals Inc.
Address:	100 Endo Boulevard Chadds Ford, PA 19317
Representative:	Robert A. Barto, MBA, Vice President, Reg. Affairs

Telephone: 484-840-4262

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): oxymorphone hydrochloride
c) Code Name/# (ONDQA only): EN3288
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: analgesic; oxymorphone hydrochloride is a centrally acting opioid compound and is proposed for the relief of moderate to severe pain in patients requiring continuous opioid therapy for an extended period

11. DOSAGE FORM: extended release tablets

12. STRENGTH/POTENCY: 5, 7.5, 10, 15, 20, 30, 40 mg oxymorphone hydrochloride/tablet

13. ROUTE OF ADMINISTRATION: oral

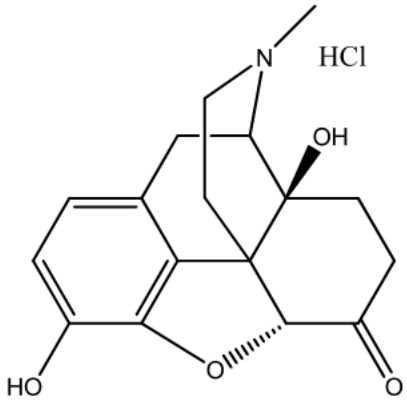
14. Rx/OTC DISPENSED: _X_Rx ___OTC

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:



oxymorphone HCl

Chemical Name: 4,5 α-epoxy-3,14-dihydroxy-17-methylmorphinan-6-one hydrochloride
Molecular formula: $C_{17}H_{19}NO_4 \cdot HCl$
Molecular Weight: 337.80 g/mol
CAS: 357-07-3

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	2	(b) (4)	(b) (4)	3	Adequate	09-APR-2010	(b) (4)
	3			1	Adequate	19-JUL-2010	
	3			4			As per policy for bottle CCSs for solid oral dosage forms
	3			3	Adequate	07-JUL-2010	
	3			7			Found adequate (b) (4)
	3			3	Adequate	03-JUN-2003	(b) (4) meets USP <661>
	3			7			Found adequate (b) (4)

Chemistry Review Data Sheet

(b) (4)	3	(b) (4)		4			(b) (4) As per policy for bottle CCSs for solid oral dosage forms
	3			3	Adequate	14-MAY-2007	Reviewed for solid oral dosage form
	2			1	Adequate	11-AUG-2010	
				1	Adequate	02-SEP-2010	
	4			1	Adequate	21-JUL-2010	
	4			3	Adequate	29-SEP-2010	
	4			1	Adequate	26-OCT-2010	

[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)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
	NDA 21611	Endo Pharmaceuticals Inc.	Opana® (oxymorphone HCl) Tablets, 5 and 10 mg
	NDA 21610	Endo	Opana® ER (oxymorphone HCl) Extended Release

		Pharmaceuticals Inc.	Tablets, 5, 10, 20, 40 mg
	IND 104250	Endo Pharmaceuticals Inc.	EN3288 (oxymorphone HCl) (b) (4) extended-release tablets

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			See p. 64 of review #1
EES		15-JUL-2010	ACCEPTABLE	OC recommendation of 15-NOV-2010
Pharm/Tox	N/A			
LNC	N/A			
Methods Validation	N/A			See evaluation of regional information section R3 in review #1
OPDRA	N/A			
EA	N/A			See p. 73 of review #1
Microbiology	lack of microbiological testing of drug product	electronic mail of 19-AUG-2010	Final/J. McVey, Ph.D. and S. Langille, Ph.D.	Acceptable, see microbiology review of 14-OCT-2010

The Chemistry Review for NDA 201655

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for **approval**.

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

None at this time.

II. Summary of Chemistry Assessments

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

The drug product, OPANA® ER (oxymorphone hydrochloride) Extended-Release Tablets is a solid dosage form with strengths 5, 7.5, 10, 15, 20, 30, and 40 mg (as the hydrochloride salt), intended for oral administration. The drug product is packaged in high-density polyethylene bottles that are fitted with child resistant closures, with each containing 60 or 100 tablets (for all strengths). The formulation for each strength consists of oxymorphone hydrochloride (b) (4) (b) (4) polyethylene oxide (b) (4) (b) (4) hypromellose (b) (4) and polyethylene glycol (b) (4) (b) (4) The formulation also contains (b) (4) of α-tocopherol (Vitamin E) (b) (4) and citric acid (b) (4) (b) (4) All of the strengths have the same tablet weight (221.5 mg) and they are all film coated with different colorants (pink, gray, orange, white, green, red, yellow) to help distinguish the strengths, along with the debossing of the numerical strengths on one side of each tablet. For manufacturing, the formulation components are (b) (4) (b) (4) (b) (4) The applicant has taken a bioequivalence approach to demonstrate a match to their already approved Opana® ER (oxymorphone hydrochloride) Extended-Release Tablets.

The drug substance is oxymorphone hydrochloride, which is a (b) (4) (b) (4) (b) (4)

[redacted] (b) (4) no additional review of the CMC information related to production of that drug substance was needed to support this application.

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

Paraphrasing the labeling, OPANA® ER is indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. The drug product is not intended for use as an as-needed analgesic and is not indicated for pain in the immediate post-operative period [redacted] (b) (4) for patients not previously taking opioids, as there is said to be a risk of oversedation and respiratory depression requiring reversal with opioid antagonists. The drug product is not indicated for pain in the post-operative period if the pain is mild or not expected to persist for an extended period of time. The expiration dating period proposed of 36 months for all strengths of the drug product (60 and 100 count bottles), with recommended storage at controlled room temperature, is supported by the data provided.

C. Basis for Approvability or Not-Approval Recommendation

N/A

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D./Chemist: 18-JUL-2011
Prasad Peri, Ph.D./Branch Chief_____

C. CC Block

DChristodoulou/CMC Lead
SPatwardhan/ONDQA PM
LBasham/OND PM

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/s/

CRAIG M BERTHA
07/18/2011

PRASAD PERI
07/19/2011
I concur

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

DATE: 16-NOV-2010

TO: N201655 File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division III, Branch VIII

THROUGH: Prasad Peri, Ph.D.
Acting Branch Chief
ONDQA, Division III, Branch VIII

SUBJECT: Update on Establishment Evaluation Request for N201655 (b) (4) (oxymorphone HCl) Extended Release Tablets; CMC recommendation

SUMMARY:

The Office of Compliance issued an overall recommendation of ACCEPTABLE for the application on 15-NOV-2010.

RECOMMENDATION: As per CMC review #2, the application was considered to be approvable, considering that there was no recommendation from the Office of Compliance. Now that the OC has put forth a recommendation of acceptable, the recommendation from the CMC team for the application is for **approval**.

Craig M. Bertha, Ph.D.
CMC Reviewer, ONDQA

cc:
OND/DAAP/LBasham
ONDQA/DIV 3/CBertha/16-NOV-2010
ONDQA/DIV 3/PPeri
ONDQA/DIV3/DChristodoulou
ONDQA/SSharp-Suarez
OND/DAAP/EFields
ONDQA/SPatwardhan

(b) (4)

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

/s/

CRAIG M BERTHA
11/16/2010

PRASAD PERI
11/16/2010
I concur

CHEMISTRY REVIEW

NDA 201655

(b) (4) **(oxymorphone hydrochloride) Extended Release Tablets**

Endo Pharmaceuticals Inc.

Craig M. Bertha, Ph.D.
Office of New Drug Quality Assessment/Division III/Branch VIII

for

Division of Anesthetics and Analgesics Products

(b) (4)

Table of Contents

Chemistry Review Data Sheet

1. NDA 201655

2. REVIEW #:2

3. REVIEW DATE: 26-OCT-2010

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Document Date(s)	Previous Document
07-JUL-2010	Original Submission
23-JUL-2010	Updated labeling

6. SUBMISSION(S) BEING REVIEWED:

Document Date(s)	Submission(s) Reviewed
14-SEP-2010	Amendment (response to filing letter)
29-SEP-2010	Amendment (response to CMC DR letter)
01-OCT-2010	Amendment (stability data DP (b) (4)
06-OCT-2010	Amendment (updated package insert labeling)

7. NAME & ADDRESS OF APPLICANT:

Name:	Endo Pharmaceuticals Inc.
Address:	100 Endo Boulevard Chadds Ford, PA 19317
Representative:	Robert A. Barto, MBA, Vice President, Reg. Affairs
Telephone:	484-840-4262

8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): oxymorphone hydrochloride
c) Code Name/# (ONDQA only): EN3288
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: analgesic; oxymorphone hydrochloride is a centrally acting opioid compound and is proposed for the relief of moderate to severe pain in patients requiring continuous opioid therapy for an extended period

11. DOSAGE FORM: extended release tablets

12. STRENGTH/POTENCY: 5, 7.5, 10, 15, 20, 30, 40 mg oxymorphone hydrochloride/tablet

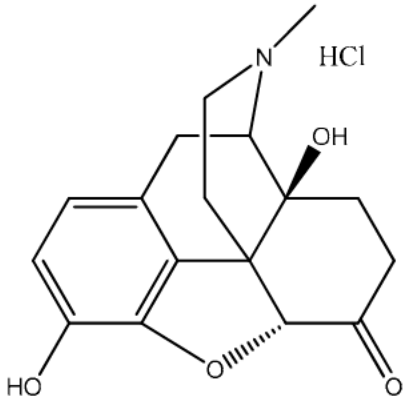
13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

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:



oxymorphone HCl

Chemical Name: 4,5 α-epoxy-3,14-dihydroxy-17-methylmorphinan-6-one hydrochloride
Molecular formula: $C_{17}H_{19}NO_4 \cdot HCl$
Molecular Weight: 337.80 g/mol
CAS: 357-07-3

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	2		(b) (4)	3	Adequate (b) (4)	09-APR-2010	(b) (4)
	3			1	Adequate	19-JUL-2010	
	3			4			As per policy for bottle CCSs for solid oral dosage forms
	3			3	Adequate	07-JUL-2010	
	3			7			Found adequate (b) (b) (4)
	3			3	Adequate	03-JUN-2003	(b) (4) (b) (4) (b) (4) meets USP <661>
	3			7			Found adequate (b) (b) (4)

Chemistry Review Data Sheet

[redacted] (b) (4)	3	[redacted] (b) (4)		4			As per policy for bottle CCSs for solid oral dosage forms
	3			3	Adequate	14-MAY-2007	Reviewed for solid oral dosage form
	2			1	Adequate	11-AUG-2010	
				1	Adequate	02-SEP-2010	
	4			1	Adequate	21-JUL-2010	
	4			3	Adequate	29-SEP-2010	
	4			1	Adequate	26-OCT-2010	

[1] Action codes for DMF Table:
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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)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
	NDA 21611	Endo Pharmaceuticals Inc.	Opana® (oxymorphone HCl) Tablets, 5 and 10 mg
	NDA 21610	Endo	Opana® ER (oxymorphone HCl) Extended Release

		Pharmaceuticals Inc.	Tablets, 5, 10, 20, 40 mg
	IND 104250	Endo Pharmaceuticals Inc.	EN3288 (oxymorphone HCl) (b) (4) extended-release tablets

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			See p. 64 of review #1
EES		15-JUL-2010	pending	
Pharm/Tox	N/A			
LNC	N/A			
Methods Validation	N/A			See evaluation of regional information section R3 in review #1
OPDRA	N/A			
EA	N/A			See p. 73 of review #1
Microbiology	lack of microbiological testing of drug product	electronic mail of 19-AUG-2010	Final/J. McVey, Ph.D. and S. Langille, Ph.D.	Acceptable, see microbiology review of 14-OCT-2010

The Chemistry Review for NDA 200533

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is considered **approvable**. The facility inspections are outstanding and the above CMC recommendation does not incorporate any potential facility inspection issues.

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

None at this time.

II. Summary of Chemistry Assessments

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

The drug product, [redacted]™ (oxymorphone hydrochloride) Extended-Release Tablets is a solid dosage form with strengths 5, 7.5, 10, 15, 20, 30, and 40 mg (as the hydrochloride salt), intended for oral administration. The drug product is packaged in high-density polyethylene bottles that are fitted with child resistant closures, with each containing 60 or 100 tablets (for all strengths). The formulation for each strength consists of oxymorphone hydrochloride [redacted] in a [redacted] of polyethylene oxide [redacted] hypromellose [redacted] and polyethylene glycol [redacted] The formulation also contains [redacted] α-tocopherol [redacted] and citric acid [redacted] for pH adjustment. All of the strengths have the same tablet weight (221.5 mg) and they are all film coated with different colorants (pink, gray, orange, white, green, red, yellow) to help distinguish the strength, along with the debossing of the numerical strength on one side of each tablet. For manufacturing, the formulation components are [redacted] The applicant is taking a bioequivalence approach to demonstrate a match to their already approved Opana® ER (oxymorphone hydrochloride) Extended-Release Tablets.

The drug substance is oxymorphone hydrochloride, [redacted] no additional review ubstance was needed to support this application.

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

Paraphrasing the labeling, [redacted]™ is indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. The drug product is not intended for use as an as-needed analgesic and is not indicated for pain in the immediate post-operative period [redacted] for patients not previously taking opioids, as there is said to be a risk of oversedation and respiratory depression requiring reversal with opioid antagonists. The drug product is not indicated for pain in the post-operative period if the pain is mild or not expected to persist for an extended period of time.

C. Basis for Approvability or Not-Approval Recommendation

The office of compliance has not issued a decision with regard to the GMP status of the application.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D./Chemistry Reviewer: 26-OCT-2010
Prasad Peri, Ph.D./Acting Branch Chief_____

C. CC Block

DChristodoulou/CMC Lead
SSuarez/Biopharm.
LBasham/PM

14 pages has been withheld in full as B(4) CCI/TS immediately following this page

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

/s/

CRAIG M BERTHA
10/26/2010

PRASAD PERI
10/27/2010
I concur

CHEMISTRY REVIEW

NDA 201655

(b) (4) (oxymorphone hydrochloride) Extended Release Tablets

Endo Pharmaceuticals Inc.

Craig M. Bertha, Ph.D.
Office of New Drug Quality Assessment/Division III/Branch VIII

for

Division of Anesthetics and Analgesics Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 201655

2. REVIEW #:1

3. REVIEW DATE: 02-SEP-2010

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
07-JUL-2010	Original
23-JUL-2010	Updated labeling

7. NAME & ADDRESS OF APPLICANT:

Name:	Endo Pharmaceuticals Inc.
Address:	100 Endo Boulevard Chadds Ford, PA 19317
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a) Proprietary Name: N/A
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- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: analgesic; oxymorphone hydrochloride is a centrally acting opioid compound and is proposed for the relief of moderate to severe pain in patients requiring continuous opioid therapy for an extended period

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12. STRENGTH/POTENCY: 5, 7.5, 10, 15, 20, 30, 40 mg oxymorphone hydrochloride/tablet

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

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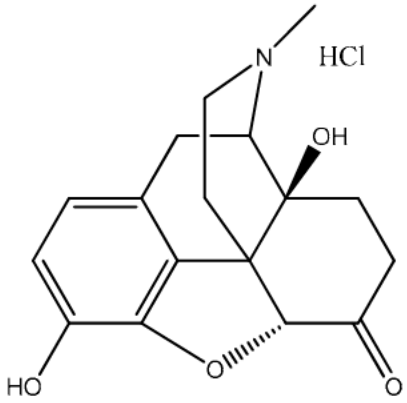

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Chemistry Review Data Sheet

							(b) (4)
(b) (4)	3		(b) (4)	4			As per policy for bottle CCSs for solid oral dosage forms
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				1	Adequate	02-SEP-2010	
	4			1	Adequate	21-JUL-2010	
	4						Have requested LOAs to allow review of the DMF for the colorants

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18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			See p. 64 of review #1
EES		15-JUL-2010	pending	
Pharm/Tox	N/A			
LNC	N/A			
Methods Validation	N/A			See evaluation of regional information section R3
OPDRA	N/A			
EA	N/A			See p. 73 of review #1
Microbiology	N/A			See P.2.5 evaluation

The Chemistry Review for NDA 200533

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is considered **approvable**. The facility inspections are outstanding and the above CMC recommendation does not incorporate any potential facility inspection issues.

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

None at this time.

II. Summary of Chemistry Assessments

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

The drug product, (b) (4)™ (oxymorphone hydrochloride) Extended-Release Tablets is a solid dosage form with strengths 5, 7.5, 10, 15, 20, 30, and 40 mg (as the hydrochloride salt), intended for oral administration. The drug product is packaged in high-density polyethylene bottles that are fitted with child resistant closures, with each containing 60 or 100 tablets (for all strengths). The formulation for each strength consists of oxymorphone hydrochloride (b) (4) (b) (4) in a (b) (4) of polyethylene oxide (b) (4) hypromellose (b) (4) and polyethylene glycol (b) (4) The formulation also contains (b) (4) α-tocopherol (b) (4) and citric acid (b) (4) for pH adjustment. All of the strengths have the same tablet weight (221.5 mg) and they are all film coated with different colorants (pink, gray, orange, white, green, red, yellow) to help distinguish the strength, along with the debossing of the numerical strength on one side of each tablet. For manufacturing, the formulation components are (b) (4) (b) (4) (b) (4) The applicant is taking a bioequivalence approach to demonstrate a match to their already approved Opana® ER (oxymorphone hydrochloride) Extended-Release Tablets.

The drug substance is oxymorphone hydrochloride, [redacted] no additional review of the CMC information related to production of that drug substance was needed to support this application.

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

Paraphrasing the labeling, [redacted]™ is indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. The drug product is not intended for use as an as-needed analgesic and is not indicated for pain in the immediate post-operative period [redacted] for patients not previously taking opioids, as there is said to be a risk of oversedation and respiratory depression requiring reversal with opioid antagonists. The drug product is not indicated for pain in the post-operative period if the pain is mild or not expected to persist for an extended period of time.

C. Basis for Approvability or Not-Approval Recommendation

CMC related issues that are currently unresolved are captured in the attached draft discipline review letter. It is expected that the applicant will be able to provide the requested information and data and revise the application such that it will be possible for the CMC team to recommend approval in the future.

It is requested that the project manager forward the comments in the attached draft letter to the applicant as a CMC discipline review letter.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D./Chemistry Reviewer: 02-SEP-2010
Prasad Peri, Ph.D./Acting Branch Chief_____

C. CC Block

DChristodoulou/CMC Lead
SSuarez/Biopharm.
LBasham/PM

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201655	ORIG-1	ENDO PHARMACEUTICALS INC	Oxymorphone HCl (b) (4) extended-release tablet

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/s/

CRAIG M BERTHA
09/02/2010

PRASAD PERI
09/08/2010
I concur

Initial Quality Assessment
Office of New Drug Quality Assessment
Division III, Branch VIII
Division of Anesthesia, Analgesia and Addiction Products

OND Division:	Anesthesia, Analgesia and Addiction
NDA:	201655
Chemical Classification	3S
Applicant:	ENDO Pharmaceuticals Inc.
Stamp date:	July 7, 2010
PDUFA Date:	January 7, 2010
Trademark:	(b) (4)
Established Name:	Oxymorphone HCl
Dosage Form:	Extended-release tablets, 5 mg, 7.5 mg, 10 mg, 20 mg, 30 mg, 40 mg
Route of Administration:	Oral
Indication:	Treatment of moderate to severe (b) (4) pain
CMC Lead:	Danae D. Christodoulou, Ph.D.

	YES	NO
ONDQA Fileability:	√	
Comments for 74-Day Letter:		√

Summary, Critical Issues and Comments

A. Summary

The application is submitted as a 505(b)(1), and aims to establishing bioequivalence to the approved product OPANA® ER (oxymorphone HCl) extended-release tablets, NDA 21-610, approved in June 22, 2006. Endo Pharmaceuticals is the owner of NDA 21-611, OPANA® (oxymorphone HCl) immediate release tablets, NDA 21-610, and the current NDA. The applicant requested a priority review (6-months review) since the new formulation is claimed to [redacted] (b) (4)

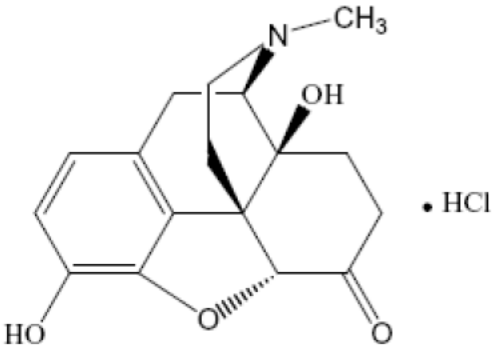
A pre-NDA meeting/agreements have been conducted with the Agency on April 6, 2010.

The proposed drug product will be available in the same seven strengths as the referenced product OPANA® ER and will be packaged in 75 cc HDPE bottles with induction sealed CR caps, countsize 60 and 100 tablets, [redacted] (b) (4)

B. Review, Comments and Recommendations

Drug Substance Oxymorphone HCl

Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight



Chemical Name(s): 4,5 α-epoxy-3,14-dihydroxy-17-methylmorphinan-6-one hydrochloride (CAS)

Molecular formula: $C_{17}H_{19}NO_4$. HCl

Molecular weight: 337.80

CAS: 357-07-3

The drug substance is manufactured by [redacted] (b) (4) and referenced to DMF [redacted] (b) (4) LoA is included in the NDA. The DMF was most recently reviewed by Julia Pinto (CMC) on 1/28/2010 and Elizabeth Bolan (non-clinical) on 7/21/2010. Dr. Pinto reviewed the [redacted] (b) (4) and Dr. Bolan the non-clinical studies, supporting the lack of genotoxic potential of the [redacted] (b) (4) impurity [redacted] (b) (4) Note that several [redacted] (b) (4) are reported as process impurities in the NDA (see Table 1 below).

[redacted] (b) (4)

The applicant stated that oxymorphone HCl, USP, [redacted] (b) (4) was used in the manufacture of development and registration batches of oxycodone [redacted] (b) (4) extended-release tablets; a newly available material, [redacted] (b) (4)

(b) (4) will be used in validation and commercial batches. Note, that in the pre-NDA meeting of April 6, 2010, the Agency requested comparative batch analysis data for drug product manufactured from the (b) (4) API, one batch each, of the lowest and highest strengths, and three-month normal and accelerated storage stability data, to be submitted for review.

Table 1. Potential (b) (4) Impurities in Oxymorphone HCl

(b) (4)

Table 2. Potential Degradation Products in Oxymorphone HCl

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/s/

DANAE D CHRISTODOULOU
08/18/2010
Initial Quality Assessment
Signing for Danae Christodoulou and Prasad Peri