

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
201655Orig1s000

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

PATIENT LABELING REVIEW

Date: October 03, 2011

To: Bob Rappaport MD, Director
Division of Anesthesia, Analgesia and Addiction Products (DAAAP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)
Barbara Fuller, RN, MSN, CWOCN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

From: Steve L. Morin, RN, BSN, OCN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name (established name): OPANA ER (oxymorphone hydrochloride)

Dosage Form and Route: Extended-Release tablets, CII

Application Type/Number: NDA 201-655

Applicant: Endo Pharmaceuticals Inc.

OSE RCM #: 2011-2447

1 INTRODUCTION

This review is written in response to a request by the Division of Anesthesia, Analgesia and Addiction Products (DAAAP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for OPANA ER (oxymorphone hydrochloride) Extended-Release tablets. The proposed indication for OPANA is for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

On July 7, 2010 Endo Pharmaceuticals submitted New Drug Application (NDA) 201-655 for (b) (4) (oxymorphone hydrochloride) Extended-Release Tablets. . DRISK completed a review of the proposed Medication Guide on December 22, 2010. On January 6 2011 Endo Pharmaceuticals (b) (4) submitted a request for the proposed proprietary tradename OPANA ER. On January 7, 2011 Endo received a Complete Response for bioequivalence study deficiencies On June 13, 2011 Endo Pharmaceuticals submitted a Class 2 Resubmission for OPANA ER (oxymorphone hydrochloride) Extended-Release Tablets.

The proposed REMS was reviewed by DRISK and submitted to DAAAP under separate cover on August 31, 2011.

2 MATERIAL REVIEWED

- Draft OPANA ER (oxymorphone hydrochloride) Extended-Release tablets Medication Guide (MG) received on June 13, 2011 and sent to DRISK on September 19, 2011.
- Draft OPANA ER (oxymorphone hydrochloride) Extended-Release tablets Prescribing Information (PI) received June 13, 2011 and sent to DRISK on September 19, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

16 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

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/s/

STEVE L MORIN
10/03/2011

LASHAWN M GRIFFITHS
10/03/2011



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 30, 2011
To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff
From: James M. Tolliver, Ph.D., Pharmacologist
Controlled Substance Staff
Subject: NDA 201-655, OPANA ER (oxymorphone HCl) Extended-Release Tablets
Indication: Relief of moderate to severe pain in patients requiring continuous around-the-clock opioid treatment for an extended period of time.
Dosages: 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg Oxymorphone HCl
Sponsor: Endo Pharmaceuticals Inc.
Materials reviewed: Label for OPANA ER (oxymorphone HCl) Extended-Release Tablets (NDA 201-655) (Module 1.14.1.3)

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I. Summary

A. Background

This memorandum is in response to a consult request dated July 5, 2011, from the Division of Anesthesia, Analgesia and Addiction Products (DAAAP) requesting that CSS review and comment on the labeling for OPANA ER (oxymorphone) Extended Release Tablets (NDA 201-655), to ensure that the current language is the same as was agreed upon during the first review cycle. CSS has reviewed the labeling with respect to abuse and dependence.

OPANA ER (Oxymorphone HCl) Extended Release Tablets are formulated to contain 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg oxymorphone HCl. The product is intended for

twice daily dosing (q12h) for treatment of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. Tablets are an (b)(4) formulation of oxymorphone HCl.

Endo Pharmaceuticals, Inc. received a CR letter January 7, 2011, regarding NDA 201-655 for (b)(4) noting a deficiency pertaining to issues with the bioequivalence analytical site. The labeling for the product was thoroughly reviewed and considered adequate during the first review cycle. The Sponsor subsequently provided a resubmission for OPANA ER (oxymorphone HCl) Extended Release Tablets addressing the deficiencies mentioned in the CR letter. (b)(4)

CSS reviewed the following sections of the OPANA ER label: Boxed Warning, section "2. DOSAGE AND ADMINISTRATION", section "5. WARNINGS AND PRECAUTIONS", and section "9. DRUG ABUSE AND DEPENDENCE."

B. Conclusions:

1. The sections of the OPANA ER label conveying information related to abuse and misuse are consistent with the sections of the label agreed during the first cycle (EDR, NDA 20655, Submission dated 1/6/2011).

C. Recommendations:

1. CSS does not recommend any additional changes to the proposed label.

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/s/

SILVIA N CALDERON
09/30/2011

MICHAEL KLEIN
09/30/2011

MEMORANDUM

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

DATE: September 19, 2011

TO: Bob A. Rappaport, M.D.
Director, Division of Anesthesia, Analgesia, and
Addiction Products (DAAAP)

FROM: Arindam Dasgupta, Ph.D. and
Xikui Chen, Ph.D.
Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: Review of EIR Covering NDA 201-655, OPANA (Oxymorphone
HCl) Extended Release Tablets, 40 mg, Sponsored by
Endo Pharmaceuticals, Inc., and

At the request of DAAAP, Division of Bioequivalence and GLP
Compliance audited the analytical portion of the following study:

Study Number: EN3288-103

Study Title: An Open-Label, Randomized, Single-Dose, Four-
Period, Replicate, Crossover Study to Determine
the Bioequivalence of EN3288 (Oxymorphone HCl
Extended-Release (b)(4) Formulation) 40
mg Compared to Opana® ER (Oxymorphone HCl
Extended-Release) 40 mg in Healthy Subjects Under
Fasted Conditions

Analytical Site: (b)(4)

The inspection was conducted to verify (b)(4) corrective
actions to concerns raised (b)(4)
(b)(4) following two previous FDA
inspections in 3 OSI had concerns about reliability of

BE/BA data generated by [REDACTED] (b) (4)
[REDACTED] for the following reasons:

[REDACTED] (b) (4)

Following the audit of the analytical records of study EN3288-103 [REDACTED] (b) (4) at [REDACTED] (b) (4) [REDACTED] (b) (4) no Form FDA-483 was issued and there were no significant adverse findings.

Conclusions:

Following the above inspection, the Division of Bioequivalence and GLP Compliance concludes that sufficient corrective actions to the concerns raised [REDACTED] (b) (4) were implemented for the current study [REDACTED] (b) (4) and recommends that the analytical data of study EN3288-103 be accepted for Agency review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Arindam Dasgupta, Ph.D.

Xikui Chen, Ph.D.

Sam H. Haidar, Ph.D., R.Ph.

Final Classification:

(b) (4) - NAI (Analytical)

cc:

CDER DSI PM TRACK

OC/Ball/Moreno

OC/OSI/DBGC/Salewski/Haidar/Dasgupta/Chen/Skelly/Dejernett

ORA/DAL-DO/Gatica

ORAORO/DDFI/NES/McClure

OND/ODEII/DAAAP/Lisa Basham

OTS/OCP/DCPII/Yun Xu

Draft: XC 9/19/2011

Edit: MFS 9/19/2011; SHH 9/19/2011

OSI: 6225; O:\BE\EIRCOVER\201655end.oxy.doc

FACTS (b) (4)

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/s/

XIKUI CHEN
09/19/2011

SAM H Haidar
09/20/2011

ARINDAM DASGUPTA
09/20/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: September 2, 2011

Reviewer(s): Jibril Abdus-Samad, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader Todd Bridges, RPh, Team Leader
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

Drug Name: Opana ER (Oxymorphone) Extended-release Tablets
5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg

Application Type/Number: NDA 201655

Applicant: Endo Pharmaceuticals Inc.

OSE RCM #: 2011-2446

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the proposed container label and insert labeling for Opana ER (NDA 201655) for areas of vulnerability that can lead to medication errors. Endo Pharmaceuticals Inc. submitted the proposed labels and labeling on June 13, 2011.

1.1 REGULATORY HISTORY

Opana ER (Oxymorphone) extended-release tablets (NDA 021610) was approved on June 22, 2006. The Applicant submitted NDA 201655 on July 7, 2010 to propose an abuse-deterrent formulation of oxymorphone extended-release tablets. The Applicant intends to replace the currently marketed formulation approved under NDA 021610 with the new formulation in NDA 201655 and therefore, proposes to continue using the Opana ER proprietary name per agreement with DAAAP during an Endo/FDA teleconference held January 5, 2011. On January 7, 2011, NDA 201655 received a Complete Response due inability to establish bioequivalence of the proposed product to the reference product (NDA 021610). The Applicant proposes to establish bioequivalence in this submission.

1.2 PRODUCT INFORMATION

Opana ER is the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. Opana ER tablets are to be swallowed whole and not to be broken, chewed, dissolved, or crushed. Opana ER is to be administered every 12 hours with the following dose recommendations:

- Opioid naive patients - 5 mg every 12 hours
- Conversion from Opana to Opana ER – half the patient's total daily oral Opana dose as Opana ER, every 12 hours.
- Conversion from parenteral - administer 10 times the patient's total daily parenteral oxymorphone dose as Opana ER in two equally divided doses [(intravenous dose x 10) divided by 2].
- Conversion from other oral opioids – follow Dose Conversion table in insert labeling.

Opana ER is available as 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg tablets in bottles of 100 tablets. Opana ER should be stored at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature]. The Applicant designed the proposed formulation to be physically harder than the referenced formulation to serve as an abuse deterrent.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted June 13, 2011 (Appendix A)
- Insert Labeling submitted June 13, 2011 (no image)

Additionally, since Opana ER is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Opana ER. The AERS search conducted on August 19, 2011 used the following search terms: active ingredient “Oxymorphone”, trade name “Opana ER”, and verbatim terms “Opana%” with selection of extended-release formulation only and “Oxymor%”. The reaction terms used were the MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues”. The time frame was limited from previous OSE Review 2010-2081 date of the AERS search, October 4, 2010, until present.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Reports excluded from the case series include those that involved intentional overdoses, drug diversion, manipulation of Opana ER for abuse, patient self-adjusting their doses or cases that did not describe a medication error.

Following exclusions, there were zero cases relevant to this review. Additionally, there were no cases involving drug name confusion.

3 DISCUSSION

The Applicant is proposing

(b) (4)

(b) (4)

Additionally, in OSE Review 2010-1651, we provided recommendations to the container label and carton labeling to minimize the potential for medication errors. The Applicant addressed DMEPA’s label and labeling recommendations from both OSE Reviews 2010-2081 and 2010-1651. However, we have identified a few other revisions that should be completed before approval.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed container labels introduce vulnerability that can lead to medication errors because the proprietary name appears as one word and the strength presentation lacks prominence. To minimize these problems, we recommend the following:

- A. Container Label
 1. Revise the presentation of the proprietary name to title case to appear as *Opana ER*. Additionally, add more space between *Opana* and *ER*. Currently, Opana ER looks like one word instead of the root name, *Opana*, and modifier, *ER*.
 2. Increase the prominence of the strength presentation, *x mg*, by increasing the font size.
 3. Submit container labels for the 100 tablet count bottle after completing the above revisions.

If you have further questions or need clarifications, please contact Danyal Chaudhry, OSE project manager, at 301-796-3813.

5 REFERENCES

1. Abdus-Samad, J. OSE Review 2010-1651: DMEPA Label and Labeling Review for [REDACTED]^{(b) (4)} December 16, 2010
2. Abdus-Samad, J. OSE Review 2010-2081: DMEPA Medication Review for Opana ER, October 28, 2010

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Appendix B: ISR numbers from AERS database search

ISR numbers	
7050431	7554055
7266095	7101147
7392010	7570107
7298687	7406346
7374265	7417569
7380552	7423561
7085797	7614396
7371730	7597904
7308176	7642520
7265643	7635541
7430159	7539693
7493851	7101898
7570108	7074543
7653585	7132425
7451714	7374233
7374061	7472735
7085145	7465132
7293485	7155803
7307408	7326356
7461562	7245419
7554056	7429307
7114246	7315115
7135428	7286095
7097735	7556608
7097736	7570929
7051382	7069251
7638090	7084165
7369577	7114569
7420174	7209107
7568946	7568954
	7623579

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/s/

JIBRIL ABDUS-SAMAD
09/02/2011

CAROL A HOLQUIST
09/02/2011

MEMORANDUM

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

DATE: January 5, 2010

TO: Bob A. Rappaport, M.D.
Director
Division of Anesthesia and Analgesia Products
(DAAP)

FROM: John A. Kadavil, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: Sam H. Haidar, Ph.D., R.Ph. _____
Acting Branch Chief,
GLP and Bioequivalence Investigation Branch
Division of Scientific Investigations

Martin K. Yau, Ph.D. _____
Acting Team Leader (Bioequivalence)
Division of Scientific Investigations (DSI)

SUBJECT: Addendum to the Review of EIRs Covering NDA 201-655, (b)(4) (Oxymorphone HCl) Extended-Release Tablets 5, 7.5, 10, 15, 20, 30, 40 mg, Sponsored by Endo Pharmaceuticals

At the request of DAAP, the Division of Scientific Investigations conducted an audit of the clinical and analytical portions of the following bioequivalence study supporting NDA 201-655:

Study Number: EN3288-103

Study Title: "An open-label, randomized, single-dose, four-period, replicate, crossover study to determine the bioequivalence of EN3288 (Oxymorphone HCl extended-release (b)(4) formulation) 40 mg compared to OPANA[®] ER (Oxymorphone HCl extended-release) 40 mg in healthy subjects under fasted conditions"

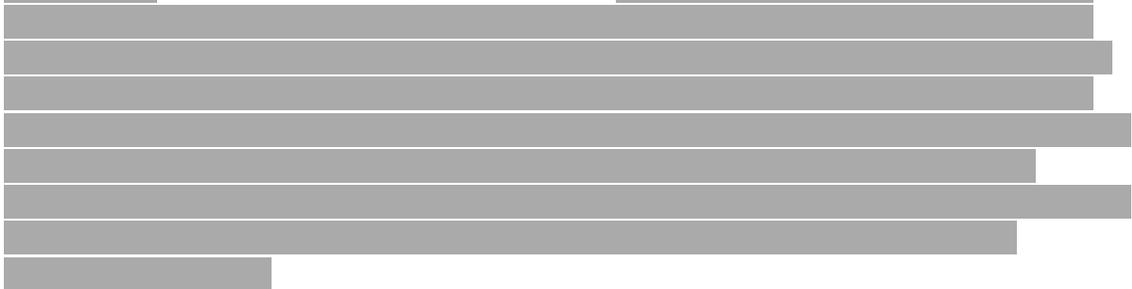
DSI inspection summary memo for the above study was sent to DAAP on (b)(4). DSI recommended that the study not be accepted for review at that time (b)(4)

On (b)(4) (analytical site) submitted their written response to the Form FDA 483. Our evaluation of the firm's written response is summarized below:



Conclusion:

Based on (1) the allegations mentioned in our cover memo submitted to you on (b)(4), (2) unsolved issues from (b)(4) previous inspection in (b)(4)



In summary, DSI's recommendation provided in the previous EIR cover memo (b)(4) remains unchanged.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

John A. Kadavil, Ph.D.
Pharmacologist

Final Classification:

(b)(4) - OAI
Seaview Research, Miami, FL - NAI

cc:

OC DSI/Ball/Haidar/Yau/Viswanathan/Kadavil/Dejernett/CF
OND ODEII DAAP/Basham
OTS OCP DCPII/Nallani
Draft: JAK 1/5/10
Edit: MKY 1/5/10
Edit: SHH 1/5/10
DSI: 6111; O:\BE\EIRCover\201655end.rev.addeundum.doc
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/s/

JOHN A KADAVIL
01/05/2011

MARTIN K YAU
01/05/2011

SAM H HAIDAR
01/05/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: December 22, 2010

To: Lisa Basham – Senior Regulatory Health Project Manager
Division of Anesthesia, and Analgesia Products (DAAP)

From: Mathilda Fienkeng – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 201655 (b)(4) (oxymorphone hydrochloride) Extended-Release
tablets C-II

DDMAC has reviewed the proposed product labeling (PI), for (b)(4) (oxymorphone hydrochloride) Extended-Release tablets C-II (b)(4) submitted for DDMAC review on July 13, 2010.

The following comments are provided using the draft PI sent via email by Lisa Basham on December 21, 2010. If you have any questions about DDMAC's comments, please do not hesitate to contact me. DDMAC will provide comments on the proposed Medication Guide under separate cover.

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/s/

MATHILDA K FIENKENG
12/22/2010

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

PATIENT LABELING REVIEW

Date: December 22, 2010

To: Bob Rappaport MD, Director
Division of Anesthesia and Analgesia Products (DAAP)

Through: Sharon Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Risk Management (DRISK)

Barbara Fuller, RN, MSN, CWOCN
Patient Labeling Reviewer
Division of Risk Management

From: Steve L. Morin, RN, BSN, OCN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name (established name): (b) (4) (Oxymorphone hydrochloride), CII

Dosage Form and Route: Extended-Release tablets

Application Type/Number: NDA 201655

Therapeutic Class: Opioid Analgesic

Applicant: Endo Pharmaceuticals Inc.

OSE RCM #: 2010-1527

1 INTRODUCTION

This review is written in response to a request by the Division of Anesthesia and Analgesia Products (DAAP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for (b) (4) (oxymorphone hydrochloride) Extended-Release tablets. The Applicant submitted New Drug Application, NDA 201655, on July 7, 2010 for (b) (4) (oxymorphone hydrochloride) Extended-Release tablets. The proposed indication for (b) (4) is for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

DRISK's review of the proposed interim REMS was sent to DAAP under separate cover dated Month December 10, 2010.

2 MATERIAL REVIEWED

- Draft (b) (4) (oxymorphone hydrochloride) Extended-Release tablets Medication Guide (MG) received on July 7, 2010, and revised by the review division throughout the review cycle, and sent to DRISK on December 14, 2010.
- Draft (b) (4) (oxymorphone hydrochloride) Extended-Release tablets prescribing information (PI) received July 7, 2010, and revised by the Review Division throughout the current review cycle, and received by DRISK on December 14, 2010.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

BARBARA A FULLER
12/22/2010

SHARON R MILLS
12/22/2010
I concur.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: December 22, 2010

To: Lisa Basham – Senior Regulatory Health Project Manager
Division of Anesthesia, and Analgesia Products (DAAP)

From: Twyla Thompson – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 201655 (b)(4) (oxymorphone hydrochloride) Extended-Release tablets C-II

DDMAC has reviewed the proposed Medication Guide, for (b)(4) (oxymorphone hydrochloride) Extended-Release tablets C-II ((b)(4) submitted for DDMAC review on July 13, 2010.

The following comments are provided using the draft Medication Guide sent via email by Lisa Basham on December 22, 2010. If you have any questions about DDMAC's comments, please do not hesitate to contact me. Comments on the proposed product labeling (PI) were provided under separate cover by Mathilda Fienkeng.

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/s/

TWYLA N THOMPSON
12/22/2010

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: December 21, 2010

To: Bob Rappaport, M.D., Director
Division of Anesthesia and Analgesia Products

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff (CSS)

From: James M. Tolliver, Ph.D., Pharmacologist
Controlled Substance Staff (CSS)

Subject: NDA 201,655 - (b)(4) (Oxymorphone HCl Extended Release)
Tablets - 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg.

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

Company: Endo Pharmaceuticals Inc.

Submission: NDA 201,655 is located in the EDR. CSS reviewed numerous documents related to abuse deterrence evaluation from the NDA (See Appendix for listing).

1. BACKGROUND

ENDO Pharmaceuticals submitted a New Drug Application (NDA 201,655) for (b)(4) (Oxymorphone HCl Extended Release) Tablets, formulated to contain 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg oxymorphone HCl. The product is intended for twice daily dosing (q12h) for treatment of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. Tablets are an (b)(4) formulation of oxymorphone HCl.

In 2008, according to SDI Vector One in the United States, only (b)(4) prescriptions for oxymorphone extended release were issued, as compared to (b)(4) prescriptions for oxycodone extended release.¹ The Addiction Severity Index-Multimedia Version

¹ Office of Surveillance and Epidemiology, August 4, 2009. Source: SDI Vector One®: National, Data Extracted 6-2009. File: VONA 2009-970 selected opioids form 06-05-09.xls

(ASI-MV) Database² for calendar year 2009 shows that the extended release oxymorphone HCl product, OPANA ER, is abused by several routes of administration: the most prominent route of abuse is by snorting, followed by swallowing whole, chewing, and injection. This database collects data from a national network of substance abuse treatment centers on substance use and abuse by adult individuals (18 years or older) entering treatment. The network has representation across the four U.S. Census Regions.³

Garside et al. (2009)⁴ documented increases in the number of deaths involving oxymorphone for North Carolina. Since the approval of OPANA ER, the following number of deaths were reported: 2 in 2000-2005; 0 in 2006; 10 in 2007; and 21 in 2008. Most deaths involved oral administration. One death was reported to involve intravenous abuse of OPANA ER, while two deaths involved abuse of OPANA ER by snorting. The Florida Department of Law Enforcement Medical Examiner's Office recently started documenting cases of deaths involving oxymorphone. In the 2009 Annual Report from the Florida Medical Examiners,⁵ 9 and 236 oxymorphone-related deaths were documented in 2008 and 2009, respectively, representing a 242 percent increase in oxymorphone-related deaths.

2. CONCLUSIONS

We reviewed the *in vitro* manipulation and chemical extraction studies, a clinical pharmacokinetic (bioavailability) study (EN3288-108), human abuse potential studies (EN3288-109), and two bench top attractiveness studies (EN3288-901 and EN3288-902), and have the following conclusions regarding (b) (4) tablets.

- (b) (4) provides limited resistance to physical and chemical manipulation for abuse. (b) (4) extended release mechanism can be overcome by cutting, chewing, or grinding. Intake of (b) (4) with food or alcohol increases blood levels of oxymorphone. (b) (4) tablets provide some resistance to crushing (b) (4)
- The Sponsor did not conduct studies to demonstrate that ground (b) (4) tablets can be abused intranasally. However, the difficulty in crushing (b) (4) tablets with (b) (4) as observed in the *in vitro* studies makes it less likely that, relative to OPANA ER, individuals will intranasally abuse (b) (4)

² Reported at the FDA Joint Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committee held October 21-22, 2010 in Gaithersburg, Maryland.

³ Butler SF, Budman SH, Licari A, Cassidy TA, Lioy K, Dickinson J, Brownstein JS, Benneyan JC, Green TC, Katz N. National addictions vigilance intervention and prevention program (NAVIPPROTM): a real-time, product-specific, public health surveillance system for monitoring prescription drug abuse. *Pharmacoepidemiology and Drug Safety*, 2008; 17: 1142-1154.

⁴ Garside D, Hargrove RL and Winecker RE (April, 2009). Concentration of oxymorphone in postmortem fluids and tissue. *Journal of Analytical Toxicology*, 33: 121-128.

⁵ 2009 Report of Drugs Identified in Deceased Persons by Florida Medical Examiners. Florida Department of Law Enforcement. June 2010.

manipulated using these tools. The bench top study (EN3288-902) demonstrated the difficulty in forming an intranasal preparation with (b) (4). However, the *in vitro* studies and study EN3288-902 did not address the grinding of (b) (4) tablets for possible abuse by intranasal administration.

- (b) (4) tablets are more difficult to cut than are OPANA ER tablets. However, Revopan tablets can be cut (b) (4) compromising the extended release properties of the product.
 - An *in vitro* study conducted by the Sponsor shows that it might be easier to prepare a solution for injection when using (b) (4) than when using OPANA ER. Exposure of a crushed (b) (4) 40 mg tablet (b) (4) of the label claim of extracted oxymorphone HCl. However, the bench top manipulation study, Study EN 3288-901, showed that both formulations behaved similarly.
 - Grinding the (b) (4) tablets severely compromises the controlled release of oxymorphone HCl, as demonstrated by the high percentages of label claim of oxymorphone HCl (b) (4). These percentages of label claim (b) (4) represent extraction levels ranging from (b) (4) of oxymorphone. Considering that at equianalgesic doses, oral oxymorphone is (b) (4) more potent than oral oxycodone when physiological opioid effects (miosis, hypotension, analgesia) are compared, the extracted amounts of oxymorphone are equivalent in its opioid effects of analgesia, miosis, and respiratory depression to (b) (4) of oral oxycodone respectively.
 - (b) (4) manipulated (b) (4) tablets or OPANA ER tablets might be difficult. (b) (4)
- (b) (4)
- Clinical abuse liability study EN3288-109 demonstrates that mastication of (b) (4) 40 mg tablets compromises the controlled release mechanism of (b) (4).
 - Based on the results of pharmacokinetic study EN3288-108 and abuse liability study EN3288-109, it is likely that the ingestion of a (b) (4) 40 mg tablet cut (b) (4) will produce substantial and statistically significant subjective reinforcing effects above those produced by the ingestion of intact (b) (4) 40 mg tablets. In addition, food increases the absorption of oxymorphone, thus increasing the likeability of oxymorphone containing products, including (b) (4).

3. RECOMMENDATIONS

Based on our review of the relevant studies concerning (b)(4) Tablets submitted under NDA 201,655 and the above conclusions, we recommend the following:

- The product label not include language asserting that Revopan provides resistance to crushing. (b)(4)
- Conduct a study to determine if (b)(4) could be administered intranasally, if such a study can be conducted safely. This study is relevant considering that the intranasal route seems to be the most prominent route of abuse of OPANA ER, followed by the oral and intravenous routes as reported by adult individuals (18 years or older) entering treatment (Addiction Severity Index-Multimedia Version (ASI-MV) 2009- Data presented at the FDA joint meeting of the Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committee held October 21-22, 2010 in Gaithersburg, Maryland).

I. APPENDIX- REVIEW

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REVIEW

1. Mechanical and Chemical Manipulation *In Vitro* Studies

(b) (4)

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3 Study EN3288-109 - Clinical Abuse Liability Study of Intact and Masticated (b) (4) 40 mg Tablets (Designated Within the Study Under the Code Name EN3288).

The objectives of study EN3288-109 were to evaluate the relative bioavailability and subjective effects produced following oral administration of intact and masticated (b) (4) 40 mg tablets (designated in this study under code name EN3288), masticated OPANA ER 40 mg tablets and intact OPANA 10 mg (4 x 10 mg) tablets to healthy nondependent, recreational oral prescription opioid users experienced in mastication of extended-release opioid formulations. This study showed that mastication of (b) (4) tablets compromised the controlled release mechanism for oxymorphone HCl. This compromise following mastication was sufficient to produce selective reinforcing subjective effects significantly higher than those produced by ingestion of intact (b) (4) 40 mg tablets and similar to the positive subjective effects found following administration of masticated OPANA ER 40 mg tablets and immediate release OPANA 10 mg (4 x 10 mg).

EN3288-109 was a randomized, double-blind, double-dummy, 4-period, single-dose, crossover study in healthy, nondependent, recreational oral prescription opioid users experienced in mastication of opioid formulations. Following a screening visit and qualification phase, 41 subjects ultimately were selected and completed the pharmacodynamic section of study. Thirty-one subjects completed the pharmacokinetic section of the study. Qualification criteria included being able to distinguish oral immediate release OPANA 30 mg (3 x 10 mg) from oral placebo on the following scales; VAS for Drug Liking, VAS of Overall Drug Liking, VAS for High, VAS of Good Effects, and a Price Value Assessment Questionnaire. Subjects were confined to the clinical research facility during each treatment phase.

The treatments included the following:

- A. (b) (4) 40 mg - Intact Tablet
- B. (b) (4) 40 mg - Tablet Ingested After Mastication
- C. OPANA ER 40 mg - Tablet Ingested After Mastication
- D. Immediate Release OPANA 40 mg (4 x 10 mg) - Intact Tablets.

Based on an assigned treatment sequence, each subject was randomly allocated to receive a single dose of the study drug over 4 periods. Each dose administration was given under fasted conditions and was separated by at least a 4 day washout period.

Blood samples were taken just before treatment and at selected times following treatment out to 48 hours. Samples were frozen and eventually analyzed for oxymorphone levels. A variety of pharmacokinetic parameters were determined. Three parameters of importance to this review were:

- $AUC_{0-\infty}$ - area under the concentration versus time curve from time 0 to infinity
- C_{max} - Observed maximum plasma concentration
- T_{max} - the time at which C_{max} is observed

At selected times following treatment a number of visual analog scales (VAS) were administered to assess positive and negative subjective responses to the treatment drug. These VAS scales included: Drug Liking, Any Drug Effects, Good Effects, Bad Effects, High Sick, Overall Drug Liking, and Take Drug Again. The Addiction Research Center Inventory (ARCI) MBG scale for euphoria was also administered. Two other VAS scales namely, Difficulty Chewing VAS and Overall Chewing Experience VAS, assessed the chewing experience by subjects. Pharmacodynamic parameters calculated included: E_{max} (peak effect), tE_{max} (time to peak effect), AUE_{0-2} (area under the effect curve to 2 hours), AUE_{0-8} hours and AUE_{0-24h} .

In response to a consult request from CSS, the FDA/CDER Office of Translational Science, Office of Biostatistics completed a statistical review and evaluation of the pharmacodynamic, but not pharmacokinetic, data from the study. This statistical review focused on just E_{max} values.

Results of the Bioavailability Section

Chewing followed by ingestion of the 40 mg (b)(4) tablet compromised the controlled release mechanism of the tablet, as evidenced by an increased C_{max} and reduced T_{max} for oxymorphone compared to that achieved from ingesting the intact (b)(4) tablet. Chewing a (b)(4) 40 mg tablet resulted in a mean C_{max} (\pm SE) of oxymorphone of 5.1604 ± 0.50975 ng/mL reached at 0.9 ± 0.077 hours (T_{max}). By contrast, ingestion of an intact 40 mg (b)(4) tablet resulted in mean C_{max} (\pm SE) of oxymorphone of 2.1682 ± 0.13902 ng/mL reached within 3.21 ± 0.384 hours (T_{max}).

Chewing a 40 mg (b)(4) tablet resulted in a C_{max} of oxymorphone (5.1604 ± 0.50975 ng/mL) that was similar to the oxymorphone C_{max} following chewing of OPANA ER (5.6659 ± 0.46908 ng/mL), but less than the oxymorphone immediate release, C_{max} (8.6884 ± 0.86696 ng/mL) OPANA 40 mg (4 x 10 mg). T_{max} remained a little longer following chewing of a 40 mg (b)(4) tablet (0.9 ± 0.77 hours) compared to the T_{max} observed following chewing of an OPANA ER tablet (0.69 ± 0.042 hours) or ingestion of immediate release OPANA 40 mg (4 x 10 mg) (0.51 ± 0.035 hours).

Pharmacodynamic Results

The pharmacodynamic results expressed as the E_{max} least square means and standard errors resulting from the different subjective measurements are provided in **Table 4 and 5**. Statistical analysis of the E_{max} least mean square differences for intact (b)(4) 40 mg versus masticated (b)(4) 40 mg, masticated (b)(4) 40 mg versus OPANA ER 40 mg masticated and masticated (b)(4) 40 mg versus immediate release OPANA 40 mg (4 x 10 mg) from the various subjective measurements are provided in **Table 5**.

Table 4. Summary of Least Square Means and Standard Errors (N = 41). (Obtained from Statistical Review and Evaluation of Study EN3288-109 Conducted by FDA/CDER Office of Translational Science, Office of Biostatistics)

Abuse Potential Measure	EN40_I		EN40_M		O40E_M		O40I_I	
	LSmean	StdErr	LSmean	StdErr	LSmean	StdErr	LSmean	StdErr
Drug Liking VAS	62.11	2.93	79.63	2.93	81.94	2.93	82.43	2.93
Any Effects VAS	49.70	3.89	77.56	3.89	87.52	3.89	89.35	3.89
Good Effects VAS	45.71	4.17	72.78	4.17	83.33	4.17	84.37	4.17
High VAS	43.80	4.10	76.37	4.10	85.89	4.10	88.55	4.10
ARCI MBG	5.05	0.79	7.97	0.79	8.59	0.79	8.29	0.79
Overall Drug Liking VAS	55.16	3.65	69.06	3.65	71.64	3.65	70.92	3.65
Take Drug Again VAS	55.80	3.79	69.40	3.79	71.61	3.79	72.70	3.79
Bad Effects VAS	15.38	4.38	22.87	4.38	24.27	4.38	25.59	4.38
Sick VAS	10.65	4.08	19.12	4.08	13.66	4.08	20.41	4.08
Difficult Chewing VAS	10.55	2.81	95.52	2.81	16.18	2.81	9.02	2.81
Overall Chewing Experience VAS	49.35	3.54	19.87	3.54	26.80	3.54	54.31	3.54

As shown in **Tables 4 and 5**, mastication of a 40 mg (b)(4) tablet caused an increase in positive reinforcing subjective effects over those produced by ingestion of an intact 40

mg (b)(4) tablet. This is in agreement with the increased oxymorphone C_{max} and decreased T_{max} following mastication of 40 mg (b)(4) compared to ingestion of an intact 40 mg (b)(4) tablet. Mastication of a 40 mg (b)(4) tablet caused a significant increase in subjective reinforcing effects over that of ingested intact 40 mg (b)(4) as shown using the Drug Like VAS, Good Effects VAS, ARCI MBG scale, Overall Drug Liking VAS, and Take Drug Again VAS. Mastication of the 40 mg (b)(4) tablet caused a reduction in the median time to E_{max} (tE_{max}). Using the Drug Liking VAS, Good Effects VAS and High VAS, the median tE_{max} was around 2 hours and 1 hour following administration of intact 40 mg (b)(4) and masticated 40 mg (b)(4) respectively. Using the ARCI MBG scale, the median tE_{max} was around 1 hour for 40 mg (b)(4) administered intact or ingested following mastication.

As reflected in the Drug Liking VAS, ARCI MBG scale, Overall Drug Liking VAS and Take Drug Again VAS, mastication of a 40 mg (b)(4) tablet produced subjective reinforcing effects statistically similar to that produced by either the mastication of a 40 mg OPANA ER tablet or by ingestion of immediate release OPANA 40 mg (4 x 10 mg) (See **Tables 4 and 5**). For example using the Drug Liking VAS scale the E_{max} least square mean score (\pm SE) with masticated (b)(4) was 79.63 ± 2.93 while the scores for masticated 40 mg OPANA ER and immediate release OPANA 40 mg (4 x 10 mg) were 81.94 ± 2.93 and 82.43 ± 3.93 , respectively.

Table 5. Statistical Analysis for Three Comparisons ($\alpha = 0.05$, N = 41). (Obtained from Statistical Review and Evaluation of Study EN3288-109 Conducted by FDA/CDER Office of Translational Science, Office of Biostatistics)*

Comparison	EN40_M vs. EN40_I			EN40_M vs. O40E_M			EN40_M vs. O40I_I		
	LSmean diff	StdErr	P-value	LSmean diff	StdErr	P-value	LSmean diff	StdErr	P-value
Drug Liking VAS	17.52	2.61	S+	-2.31	2.61	NS-	-2.80	2.61	NS-
Any Effects VAS	27.86	4.11	S+	-9.96	4.11	S-	-11.79	4.11	S-
Good Effects VAS	27.07	4.32	S+	-10.55	4.32	S-	-11.59	4.32	S-
High VAS	32.57	4.24	S+	-9.52	4.24	S-	-12.18	4.24	S-
ARCI MBG	2.92	0.54	S+	-0.62	0.54	NS-	-0.32	0.54	NS-
Overall Drug Liking VAS	13.90	3.33	S+	-2.58	3.33	NS-	-1.86	3.33	NS-
Take Drug Again VAS	13.60	3.64	S+	-2.21	3.64	NS-	-3.30	3.64	NS-
Bad Effects VAS	7.49	4.64	NS+	-1.40	4.64	NS-	-2.72	4.64	NS-
Sick VAS	8.47	4.64	NS+	5.46	4.64	NS+	-1.30	4.64	NS-
Difficult Chewing VAS	84.97	3.98	S+	79.34	3.98	S+	86.51	3.98	S+
Overall Chewing Experience VAS	-29.48	4.42	S-	-6.93	4.42	NS-	-34.44	4.42	S-

*Note: S denotes Significance at $\alpha = 0.05$, NS denotes not significant at $\alpha = 0.05$. "+" (or "-") sign denotes the least square mean in treatment 1 is larger (or smaller) than that in treatment 2.

Statistical analysis of the least square means generated from the Good Effects VAS and High VAS, reveals that masticated 40 mg (b)(4) produced statistically lower levels of subjective reinforcing effects than did masticated 40 mg OPANA ER or immediate release OPANA 40 mg (4 x 10 mg). For the Good Effects VAS, the E_{max} least square means (\pm)SE were 72.78 ± 4.7 , 83.33 ± 4.17 and 84.37 ± 4.17 , for masticated 40 mg

(b) (4) masticated 40 mg OPANA ER and intact immediate release OPANA 40 mg, respectively. In the case of the High VAS, the Emax least square means were 76.37 ± 4.10 , 85.89 ± 4.10 , and 88.55 ± 4.10 , for the three treatments, respectively. However, these differences in Emax least square mean values may underestimate the significant level of subjective reinforcing effects produced by masticated 40 mg (b) (4) tablets as determined using the Good Effects VAS and High VAS. An examination of the individual responder data show that using the Good Effects VAS, 13 out of 41 subjects scored masticated 40 mg (b) (4) at 90 or above with 10 of these subjects giving the highest positive subjective score possible, namely 100. Likewise, using the High VAS 18 of 41 subjects rated masticated 40 mg (b) (4) at above 90 with 12 subjects giving the highest positive subjective score of 100.

With respect to positive subjective reinforcing effects, mastication of 40 mg (b) (4) reduced the median tEmax to times comparable to that of masticated OPANA ER 40 mg and immediate release OPANA 40 mg (4 x 10 mg). Using the Good Effects VAS, High VAS, Drug Liking VAS and ARCI MBG scale, the median tEmax was around 1 hour for all three of these treatments.

As seen in **Table 5**, using the Difficult Chewing VAS, subjects noted that chewing a 40 mg (b) (4) tablet was much more difficult than chewing a 40 mg OPANA ER tablet. However, using the Overall Chewing Experience VAS, subjects generally expressed a dislike for chewing either a 40 mg (b) (4) tablet or a 40 mg OPANA ER tablet.

3.1 *Prediction of the Subjective Effects Produced Following Oral Administration of EN3288 40 mg Tablets Manipulated by Cutting* (b) (4)

Data from studies EN3288-108 and EN3288-109 suggest that the ingestion of a 40 mg (b) (4) tablet cut (b) (4) would be associated with positive subjective reinforcing effects as assessed by standard instruments such as the Drug Liking VAS. The Sponsor evaluated the absorption of oxymorphone from the cut (b) (4) tablets, but did not evaluate the effect of taking these manipulated forms of (b) (4) on positive subjective effects. However, it is expected that taking cut (b) (4) tablets will increase the likeability of the tablets, considering that the Cmax values (from study EN3288-108) achieved following ingestion of a cut (b) (4) (b) (4) 40 mg tablet (b) (4) (b) (4) are in the same range of the Cmax levels reached following mastication of a 40 mg (b) (4) tablet (b) (4) and knowing that these levels are associated with liking, good effects and feeling of high, as measured by "Drug Liking" VAS, "Good Effects" VAS, "High" VAS and the ARCI MBG scale (study EN3288-109)

4. Bench Top Manipulation Studies (EN3288-901 and EN3288-902)

The Sponsor conducted two bench top manipulation studies to evaluate the ability of individuals claiming to have experience in manipulating pharmaceutical opioid products to produce from 40 mg (b)(4) tablets (designated EN3288 tablets) and 40 mg OPANA ER tablets preparations suitable for intravenous injection or snorting. A limited number of subjects were found to be able to produce injectable solutions from (b)(4) and OPANA ER tablets. With respect to making a preparation suitable of snorting, 24 out of 25 subjects were successful using OPANA ER tablets but only 3 subjects out of 25 were successful using 40 mg (b)(4) tablets.

4.1 Study EN3288-901 - Ease of Preparation for Intravenous Use

The Sponsor conducted a study to compare EN3288 tablets 40 mg to OPANA ER 40 mg tablets to resist conversion into a form suitable to intravenous administration by experienced intravenous (IV) controlled-release prescription opioid abusers. Telephone interviews and on-site screening interviews were used to identify 25 individuals with experience in tampering with prescription opioids including preparation for intravenous administration.

In the laboratory, subjects were provided with either an OPANA ER tablet or EN3288 tablet in a random sequence. Tablets were designated A and B, respectively, but were identified to all subjects in the informed consent form. Subjects were instructed to use tools and chemicals to manipulate the tablets and extract active drug. Subjects were provided unlimited time and up to three additional attempts per formulation. Subjects received approved tools and solvents upon their request. Two staff members maintained close observation over the subjects during each session.

Subjects manipulated OPANA ER and EN3288 tablets for the purpose of drawing up the tablet preparation into a syringe for analysis. A solution that was able to be drawn into a syringe was considered an analyzable sample to determine the percentage yield of oxymorphone extracted from a tablet. Primary endpoints included the number of successful attempts to produce an analyzable preparation and the percentage yield of oxymorphone extracted in the preparation. Secondary endpoints included: 1) time spent in producing an analyzable i.v. preparation; 2) subject reasons for aborting attempts to make a suitable i.v. preparation; and 3) subject willingness to inject the preparation that they produced.

The most common used tools and solvents used by subjects in the study were (b)(4) (20 subjects, 80%), (b)(4) (20 subjects, 80%), (b)(4) (18 subjects, 72%), (b)(4) (17 subjects, 68%), (b)(4) (14 subjects, 56%), syringe (14 subjects, 56%), and (b)(4) (12 subjects, 48%). The mean number of tools and solvents used by subjects was similar for both formulations.

For each formulation, subjects made 28 attempts (25 first attempts and 3 second attempts) to produce a suitable intravenous preparation. Six of the attempts using EN3288 tablets resulted in preparations determined to be analyzable while seven attempts using OPANA ER tablets produced analyzable preparations. The volume, concentration and percent yield were similar between the preparations produced using OPANA ER tablets and EN3288 tablets. The lowest and highest yield for the OPANA ER preparations and EN3288 preparations were (b) (4) of the labeled API, respectively. The mean time required to produce the preparations from OPANA ER tablets and EN3288 tablets were (b) (4), respectively. Seven and five of the subjects noted that they would be willing to inject the preparation made using OPANA ER and EN3288 tablets, respectively. A majority of subjects who worked on the OPANA ER tablet stopped because "it turned to jelly/gummy substance/poor consistency." Most subjects who worked on the EN3288 tablet stopped because "it would not break up/turn into powder/bang up." Six of the 25 subjects stated that they had difficulty crushing or could not crush the EN3288 tablet compared to no subjects for the OPANA ER tablet.

4.2 Study EN3288-902 - Ease of Preparation for Snorting

The Sponsor conducted a study address the feasibility of preparing a form of (b) (4) (EN3288) suitable to intranasal administration as assessed by experienced intranasal prescription opioid abusers. Telephone interviews and on-site screening interviews were used to identify 25 individuals with experience in tampering with prescription opioids including preparation for intranasal abuse.

In the laboratory, subjects were provided with either OPANA ER tablets or EN3288 tablets in a random sequence. Tablets were designated A and B, respectively, but were identified to all subjects in the informed consent form. As such, this study was not blind to the subjects or investigators. Subjects were instructed to tamper with the tablets to form a suitable preparation for intranasal administration. Subjects were given unlimited time and three attempts. Subjects were provided with whatever tools and solvents they requested in order to complete the task. Preparations produced were subjected to particle size determination using photography and (b) (4) analysis. Subjects were maintained under constant observation by staff members.

Number of attempts and the particle size of the preparations served as the primary endpoints. Secondary endpoints included time to make a preparation for intranasal administration and answer to whether or not each subject would be willing to snort the preparation they made.

Results showed that it was more difficult to make a suitable preparation for intranasal administration using EN3288 tablets compared to using OPANA ER tablets. The most commonly used tools by subjects in the study were (b) (4) (23 subjects), (b) (4) (14 subjects), (b) (4) (9 subjects), (b) (4) (5 subjects) (b) (4) (5 subjects). Subjects made 25 attempts with the OPANA ER tablets and 28 attempts with EN3288 tablets in

order to produce a preparation suitable for intranasal use. All 25 attempts using OPANA ER tablets produced powdered material of which almost all (b)(4) contained particles (b)(4) (b)(4) in size. Of the 28 attempts using EN3288 tablets, only 8 attempts produced a preparation suitable for particle size analysis. The particle size in these eight preparations was generally larger than the particle size found in preparations using OPANA ER tablets. Out of all EN3288 samples, (b)(4) (by weight) of particles were (b)(4). Subjects spent a longer period of time attempting to manipulate EN3288 tablets (b)(4) than OPANA ER tablets (b)(4). Ninety-six percent of subjects (24) manipulating OPANA ER tablets said they would be willing to snort the preparation they made. In contrast, only 3 subjects manipulating EN3288 tablets said they would be willing to snort the preparation they made.

5. List of the Reports and Protocols Reviewed

REPORT OR PROTOCOL (MODULE IN THE NDA)	
1	Oxymorphone Hydrochloride (b)(4) Extended Release Tablets - Tamper Resistant Characteristics - <i>In Vitro</i> Studies; Preliminary Studies (3.2.P.2)
2	Grinding Trials (3.2.P.2)
3	Extraction Trials at Ambient Temperature - 5 mg Oxymorphone HCl (b)(4) Tablets (3.2.P.2)
4	Extraction Trials at Ambient Temperature - 20 mg Oxymorphone HCl (b)(4) Tablets (3.2.P.2)
5	Extraction Trials at Ambient Temperature - 40 mg Oxymorphone HCl (b)(4) Tablets (3.2.P.2)
6	Extraction Trials at Elevated Temperature - 5 mg Oxymorphone HCl (b)(4) Tablets (3.2.P.2)
7	Extraction Trials at Elevated Temperature - 40 mg Oxymorphone HCl (b)(4) Tablets (3.2.P.2)
(b)(4)	
13	SOP QKU24302 - Preparation for Snorting (3.2.P.2)
14	SOP QKU24401 - Preparation for i.v. injection (3.2.P.2)
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16	SOP QKU24601 - Extraction of Intact and Tampered Tablets in Different Media (3.2.P.2)
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18	SOP QKU24801 - Photography of Samples (3.2.P.2)
(b)(4)	
(b)(4)	
22	QKU-EB-02701 - Feasibility Study (3.2.P.2)
23	QKU-EP-03902 - Analytical Testing Outline to Challenge the Tamper-Resistant Properties (3.2.P.2)
24	OKU-VB-07401 - Report on the Validation of HPLC Method for Dissolution (3.2.P.2)
25	Excerpt from Development of a Simulated Prognosis for Dental Protheses (3.2.P.2)
26	EN3288-108 - An Open-Labeled, Randomized, Single-Dose, Six Period, Crossover Study to Evaluate the Relative Bioavailability of EN3288 40 mg Intact and After
27	Physical Tampering Using Various Methods Compared with OPANA 10 mg (4 x 10 mg) in Healthy Adult Subjects (5.3.1.2)

REPORT OR PROTOCOL (MODULE IN THE NDA)	
28	EN3288-109 - A Randomized, Single-Dose, Double-Blind, Double-Dummy, Four-Period, Crossover Study to Evaluate the Relative Bioavailability and Subjective Effects of EN3288 40 mg Administered Intact and After Mastication Compared With OPANA ER 40 mg Administered After Mastication and With OPANA 40 mg (4 X 10 mg) Administered Intact in Healthy Non-Dependent Recreational Oral Prescription Opioid Users Experienced in Mastication of Extended-Release Opioid Formulations (5.3.1.2)
29	EN3288-901 - Assessment of the Ease with Which Experienced Controlled-Release Prescription Opioid Abusers Prepare a Tamper-Resistant Formulation for Intravenous Use: Comparison Between OPANA ER and Oxymorphone Hydrochloride Extended-Release (b) (4) Tablets (5.3.5.4)
30	EN3288-902 - Assessment of the Ease with Which Experienced Controlled-Release Prescription Opioid Abusers Prepare a Tamper-Resistant Formulation for Intranasal Use: Comparison Between OPANA ER and Oxymorphone Hydrochloride Extended-Release (b) (4) Tablets (5.3.5.4)

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

/s/

SILVIA N CALDERON
12/21/2010

MICHAEL KLEIN
12/21/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 201655 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: (b)(4) (proposed) Established/Proper Name: Oxymorphone HCl Extended-Release Dosage Form: Tablets Strengths: 5, 7.5, 10, 15, 20, 30 and 40 mg		
Applicant: Endo Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: July 7, 2010 Date of Receipt: July 7, 2010 Date clock started after UN:		
PDUFA Goal Date: January 7, 2010		Action Goal Date (if different):
Filing Date: 9/5/10		Date of Filing Meeting: 8/16/10
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication: relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid analgesia for an extended period of time.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html <i>and refer to Appendix A for further information.</i>		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical	

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s):				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?																				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).																				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>																				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm If yes, please list below:																				
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		X																		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>																				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		X																		

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted).	X			
Index : Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	X			
Controlled substance/Product with abuse potential : Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff:</i>		X CII		CSS consulted 7/13/10 for abuse deterrence studies
BLAs only : Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #				

Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?				
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?	X			
<i>Forms must be signed by the APPLICANT, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)	X			
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>				
<i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	X			

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>				
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>				
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>				
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		X		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			Prop name request came in 2 weeks later on July 23, 2010 (b) (4)
Prescription Labeling	<input checked="" type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
REMS consulted to OSE/DRISK?	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	<input type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	X			

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	X			
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		X		

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>			X	
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): April 6, 2010 <i>If yes, distribute minutes before filing meeting</i>	X			Pre-IND mtg held May 22, 2009
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

¹<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 18, 2010

NDA: 201655

PROPRIETARY NAME: (b)(4) (proposed)

ESTABLISHED/PROPER NAME: Oxymorphone HCl Extended-Release

DOSAGE FORM/STRENGTH: Tablets (5, 7.5, 10, 15, 20, 30, and 40 mg)

APPLICANT: Endo Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

BACKGROUND: Reformulation of OPANA ER (NDA 021610) designed to be resistant to physical tampering (b)(4)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Lisa Basham	Y
	CPMS/TL:	Parinda Jani	N
Cross-Discipline Team Leader (CDTL)	Rob Shibuya		
Clinical	Reviewer:	Rob Shibuya (temporary)	Y
	TL:		
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Srikanth Nallani	Y
	TL:	Suresh Doddapaneni	N
Biostatistics	Reviewer:	N/A	
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Beth Bolan	Y
	TL:	Dan Mellon	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Craig Bertha	Danae Christodoulou present
	TL:	Presad Peri	N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:	Megan Moncur	N
	TL:	Gita Toyserkani	N
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		

Other reviewers: CMC Biopharm	Sandra Suarez TL: Angelica Dorantes	Y
Other reviewers: CSS Reviewers	Jim Tolliver TL: Silvia Calderon	Y

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: No clinical studies</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments: Yes. Purportedly abuse-deterrent formulation</p>	<input checked="" type="checkbox"/> YES Date if known: 12/2/10 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: Biopharm CMC: comment for 60-day letter</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: consulted to evaluate need for microbial</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments: 3 facilities acceptable, one assigned for inspection</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Bob Rappaport, MD	
21st Century Review Milestones (see attached) (optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

LISA E BASHAM
12/21/2010

PARINDA JANI
12/21/2010

MEMORANDUM

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

DATE: December 20, 2010

TO: Bob A. Rappaport, M.D.
Director
Division of Anesthesia and Analgesia Products
(DAAP)

FROM: John A. Kadavil, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: Sam H. Haidar, Ph.D., R.Ph. _____
Acting Branch Chief,
GLP and Bioequivalence Investigation Branch
Division of Scientific Investigations

Martin K. Yau, Ph.D. _____
Acting Team Leader (Bioequivalence)
Division of Scientific Investigations (DSI)

SUBJECT: Review of EIRs Covering NDA 201-655, (b)(4)
(Oxymorphone HCl) Extended-Release Tablets 5,
7.5, 10, 15, 20, 30, 40 mg, Sponsored by Endo
Pharmaceuticals

At the request of DAAP, the Division of Scientific Investigations conducted an audit of the clinical and analytical portions of the following bioequivalence study supporting NDA 201-655:

Study Number: EN3288-103

Study Title: "An open-label, randomized, single-dose, four-period, replicate, crossover study to determine the bioequivalence of EN3288 (Oxymorphone HCl extended-release (b)(4) formulation) 40 mg compared to OPANA[®] ER (Oxymorphone HCl extended-release) 40 mg in healthy subjects under fasted conditions"

Page 2 - NDA 201-655, (b)(4) (Oxymorphone HCl) Extended-Release Tablets

The clinical portion of Study EN3288-103 was conducted at SeaView Research, Inc., Miami, FL. The analytical portion was conducted at (b)(4)

Following the inspection of SeaView Research (b)(4) (b)(4) no Form FDA 483 was issued.

In addition to the subject NDA, the inspection at (b)(4) (b)(4) also included a follow-up investigation of a complaint received by the Agency in (b)(4)

(b)(4) Following the inspection at (b)(4) Form FDA 483 was issued (**Attachment 1**). As of this writing, (b)(4) response to the Form FDA 483 has not been received by DSI.

The observations and our evaluations follow:

(b)(4)



(b)(4)

(b)(4)

Conclusion:

Following DSI's evaluation of the inspectional findings, DSI recommends the following:

- Study EN3288-103 should not be accepted for review at this time (b)(4)

(b)(4) DSI is currently awaiting (b)(4) response to the Form FDA-483 to

determine what steps the firm will initiate to address the inspectional findings.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

John A. Kadavil, Ph.D.
Pharmacologist

Final Classification:

(b)(4) - OAI

cc:

OC DSI/Ball/Haidar/Yau/Viswanathan/Kadavil/Ead/CF

OND ODEII DAAP/Basham

OTS OCP DCPII/Nallani

Draft: JAK 12/14/10, 12/20/10

Edit: MKY 12/14/10

Edit: SHH 12/17/10

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/s/

JOHN A KADAVIL
12/20/2010

MARTIN K YAU
12/20/2010

SAM H HAIDAR
12/20/2010

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: December 15, 2010

Application Type/Number: NDA 201655

To: Bob Rappaport, MD, Director
Division of Anesthesia and Analgesia Products (DAAP)

Through: Todd Bridges, RPh, Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Jibril Abdus-Samad, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): (b) (4) (Oxymorphone) Extended-release Tablets,
5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg

Applicant: Endo Pharmaceuticals

OSE RCM #: 2010-1651

1 INTRODUCTION

This review responds to a request from Division of Anesthesia and Analgesia Products (DAAP) for DMEPA review of the proposed labels and labeling for (b) (4) (Oxymorphone) Extended-release Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg. DAAP requests DMEPA's assessment of the proposed labels and labeling for (b) (4) for their vulnerability to medication errors.

1.1 REGULATORY HISTORY

Opana ER (Oxymorphone) extended-release tablets were approved June 22, 2006. The Applicant submitted NDA 201655 on July 7, 2010 to propose an abuse-deterrent formulation of oxymorphone extended-release tablets.

1.2 PRODUCT INFORMATION

(b) (4) (Oxymorphone) extended-release tablets have a proposed indication for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. (b) (4) tablets are to be swallowed whole and not to be broken, chewed, dissolved, or crushed. (b) (4) is to be administered every 12 hours with the following dose recommendations:

- Opioid naive patients - 5 mg every 12 hours
- Conversion from Opana to (b) (4) - half the patient's total daily oral Opana dose as (b) (4) every 12 hours.
- Conversion from parenteral oxymorphone - administer 10 times the patient's total daily parenteral oxymorphone dose as (b) (4) in two equally divided doses [(intravenous dose x 10) divided by 2].
- Conversion from other oral opioids – follow Dose Conversion table in insert labeling.

(b) (4) is available as 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg tablets in bottles of 100 tablets and unit-dose packages of 100 tablets (b) (4) (b) (4) should be stored at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F).

2 METHODS AND MATERIALS

2.1 PREVIOUS DMEPA REVIEWS

Previous DMEPA reviews on Oxymorphone extended-release tablets were reviewed to determine if any recommendations apply to the current submission.

2.2 LABELS AND LABELING

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis¹ (FMEA) and lessons learned from post-marketing experience to evaluate the labels and labeling submitted by the Applicant on July 23, 2010.

(Appendix B; no image of insert labeling).

3 RESULTS AND DISCUSSION

The labels and labeling require revisions to minimize the risk for error. The revisions to the insert labeling are based upon conclusions from OSE Review 2010-2081, dated October 28, 2010.

3.1 CONVERSION FROM OTHER ORAL OPIOIDS TO OXYMORPHONE EXTENDED-RELEASE TABLETS

As detailed in OSE Review 2010-2081, there were 8 reported dosing errors involving conversion from other opioids to Opana ER (oxymorphone) extended-release tablets. Subsequently, DMEPA recommended revising the conversion ratio table in the Opana ER insert labeling by minimizing the text above the table and clarifying the column titles. These revisions may help minimize the medication errors involved when converting patients from other opioids to Opana ER. Because Opana ER and (b)(4) have the same dosing instructions, the recommendations for the Opana ER insert labeling apply to the (b)(4) insert labeling.

4 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation noted areas where information on the labels and labeling can be improved on to minimize the potential for medication errors. We provide comments on the insert labeling in Section 4.1, *Comments to the Division*. Section 4.2, *Comments to the Applicant* contains our recommendations for the container label and carton labeling. We request the recommendations in Section 4.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have any questions or need clarification, contact Bola Adeolu, OSE project manager, at 301-796-4264.

¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

4.1 COMMENTS TO THE DIVISION

In OSE Review 2010-2081, Opana ER (Oxymorphone) Extended-release Tablets Medication Error Review, DMEPA recommended improving the conversion ratio table in *Section 2.2 - Initiating Therapy with* (b) (4) *Conversion from Other Oral Opioids to* (b) (4) to minimize the dosing errors reported with conversion from other opioids to Opana ER.

Appendix A provides an example of how this section of the insert labeling can be revised to simplify the presentation of the information and improve readability.

4.2 COMMENTS TO THE APPLICANT

Our evaluation noted areas where information on the container labels can be improved on to minimize the potential for medication errors.

A. Container Label (All strengths)

1. Revise the presentation of the proprietary name and strength to ensure the proprietary name is the most prominent feature on the label. Currently, the colored circle that surrounds the strength makes it more prominent than the proprietary name.
2. Increase the prominence of the established name. Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
3. Increase the font size and weight of *mg* on the principal display panel.
4. Delete the light blue colored background surrounding the product strength.
5. Delete the two graphics on the left side of the proprietary name and the strength.
6. Increase the prominence of the second set of digits (product code) in the NDC number by increasing the font size so they are more prominent than the rest of the NDC number.
7. Add the word *cut* to the list of actions that must be avoided that appear on the left side panel.
8. Revise the following statements on the left side panel by changing from all uppercase letters to improve readability.
 - Swallow Tablets Whole. Tablets Are Not To Be Cut, Broken, Chewed, Crushed, or Dissolved
 - Dispense Accompanying Medication Guide To Each Patient.Note, we find it acceptable to keep these statements in bold font.
9. Decrease the font size of the *Rx only* statement.

B. Container Label (7.5 mg and 15 mg)

1. Revise the font color of the strength from white to black to provide better contrast with the background color. Currently, the presentation of the white font on both the yellow (7.5 mg tablet) and peach (15 mg tablet) background colors do not provide sufficient contrast and are difficult to read.

REFERENCES

1. OSE Review 2010-2081 Opana ER (Oxymorphone) Extended-release Tablets Medication Error Review, dated October 28, 2010
2. OSE Review 2008-43 Opana ER (Oxymorphone) Extended-release Labeling Review, dated February 27, 2008

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/s/

JIBRIL ABDUS-SAMAD
12/15/2010

TODD D BRIDGES
12/15/2010

CAROL A HOLQUIST
12/16/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: October 28, 2010

To: Bob Rappaport, MD, Director
Division of Anesthesia and Analgesia Products

Thru: Todd Bridges, RPh, Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Jibril Abdus-Samad, PharmD, Safety Evaluator
Division of Medication Error Prevention

Subject: Medication Error Review

Drug Name: Opana ER (Oxymorphone) Extended-release Tablets
5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg

Application Type/Number: NDA 021610

Applicant/sponsor: Endo Pharmaceuticals, Inc.

OSE RCM #: 2010-2081

***** Note: This review contains proprietary and confidential information that should not be released to the public.*****

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EXECUTIVE SUMMARY

This review evaluates 118 cases of manipulation and medication errors involving Opana ER (oxymorphone extended-release tablets). Fifty-six cases report some method of Opana ER manipulation prior to administration. The majority of cases were related to abuse. Fifteen of the 56 cases resulted in death following administration. The most common type of manipulation reported with abuse is crushing which led to the administration of the product by inhalation. If the proposed abuse-detering oxymorphone extended-release formulation, (b) (4) proves to provide protection against crushing it will have an impact on this type of manipulation. However, we recommend the Applicant test whether their proposed formulation can prevent other non-crushing forms of manipulation such as cutting or splitting the tablet or dissolving in liquids. Thus, the Applicant should consider whether their proposed formulation can prevent these methods of manipulation. Otherwise, these methods may become the preferred method of manipulation of Opana ER.

The remaining cases involve medication errors with Opana ER. The most frequently reported error resulted in administration of the wrong dose of Opana ER leading to over- and underdoses. Many of these cases were due to incorrect prescribing that can be addressed with provider education. The other dosing errors occurred when patients were converted from other opioids to Opana ER. However, we suspect these errors are related to the confusing dose conversion chart that appears in the Dosage and Administration section of the insert labeling. Revisions to the dosing conversion chart will minimize this type of error. We provide recommendations in Section 5 of this review.

1 BACKGROUND

1.1 INTRODUCTION

The Division of Anesthesia and Analgesia Products (DAAP) requested the Division of Pharmacovigilance II (DPV II) review abuse/dependence and death of domestic postmarketing adverse events associated with the use of Opana ER (oxymorphone extended-release tablets). DAAP requested this review for the Anesthetic and Life Support Drugs (ALSD) and Drug Safety and Risk Management (DSARM) Advisory Committee Meeting on December 3, 2010. At this meeting, an abuse-detering oxymorphone extended-release formulation, (b) (4) (NDA 201655), will be discussed.

In their review of cases, DPV II identified manipulation and medication errors involving Opana ER. DPV II contacted DMEPA, which evaluated the methods of manipulation and medication errors associated with Opana ER. These analyses will provide context to aid in the Advisory Committee's deliberations on the proposed formulation.

1.2 OPANA ER PRODUCT INFORMATION

Opana ER was approved on June 22, 2006 with the indication for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. Opana ER tablets are to be swallowed whole and not to be broken, chewed, dissolved, or crushed. Opana ER is to be administered every 12 hours with the following dose recommendations:

- Opioid naive patients - 5 mg every 12 hours
- Conversion from Opana to Opana ER – half the patient's total daily oral Opana dose as Opana ER, every 12 hours.
- Conversion from parenteral - administer 10 times the patient's total daily parenteral oxymorphone dose as Opana ER in two equally divided doses [(intravenous dose x 10) divided by 2].
- Conversion from other oral opioids – follow Dose Conversion table in insert labeling.

Opana ER is available as 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg tablets in bottles of 100 tablets and unit-dose packages of 100 tablets (b) (4). Opana ER should be stored at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].

2 METHODS AND MATERIALS

DMEPA used two data sources, the FDA Adverse Event Reporting System (AERS) and medical literature, for identification of medication errors involving Opana ER.

Reports excluded from analysis include the following criteria: intentional drug abuse (without Opana ER manipulation), non-medication error adverse drug events, suicide attempts, death that did not provide sufficient details to conclude a cause and cases that did not include Opana ER as the suspect drug.

Reports included in the analysis include the following criteria: all product manipulation cases and medication errors of any type related to Opana ER.

All reports describing medication errors or manipulation were screened for duplicates and combined into cases which were further categorized by error type and method of manipulation.

Additionally, DMEPA evaluated the labels and labeling for Opana ER for aspects that may have contributed to the reported medication errors.

2.1 AERS SEARCH STRATEGY

DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database on October 4, 2010, for medication error reports involving Opana ER tablets using the following search criteria:

Product Names: Opana ER (tradename), Opana%, with selection of extended release formulations only (verbatim)

Reaction Terms: Search was not limited to specific PT terms

2.2 MEDICAL LITERATURE SEARCH

On October 20, 2010, we searched the medical literature using PubMed with the following two search strategies:

- Opana%
- ("adverse effects "[Subheading] OR "Medication Errors"[Mesh]) AND ("oxymorphone"[MeSH Terms] OR "oxymorphone"[All Fields]) AND ("humans"[MeSH Terms])

2.3 LABELS, LABELING AND PACKAGING

For this review, DMEPA reviewed container labels, blister labels, carton labeling (see Appendix B) and insert labeling (no image).

3 RESULTS

The following sections describe the results of our AERS and literature searches and findings of the label and labeling review.

3.1 AERS DATABASE

In total, 118 cases were identified for analysis using the AERS search strategy and exclusion/inclusion criteria outlined in section 2.2. We stratified the cases into the following error types: dosage form manipulation (regardless of reason), wrong dose, wrong drug, monitoring errors, diversion, accidental exposure, and non-compliance. The cases of diversion (n=11), accidental exposure (n=1), and noncompliance (n=4) will not be discussed in this review. We describe these 102 remaining cases in the following subsections.

3.1.1 Manipulation of Dosage Form (n=56)

We identified 56 cases in which Opana ER tablets were manipulated prior to use. Appendices C and D provide a summary of the cases. These cases included manipulation of Opana ER intended for both abuse and medical reasons.

Data indicates the most common method of manipulation and administration of Opana ER is crushing followed by inhaling for abuse. We considered the terms snort and inhale interchangeable. However, there were other methods of manipulation reported that led to administration by inhalation such as: break (n=1), chop (n=4), cut (n=1), (b) (4) (n=1), (b) (4) (n=1) and unknown (n=4). These methods appear to use a sharp object to manipulate Opana ER, rather than the blunt force crushing method.

Other methods of manipulation and administration include (b) (4)

Additionally, there was one case of injecting Opana ER after crushing.

Five cases indicate the method of manipulation was related to medical use for ease of oral administration (bite and chew).

Fifteen deaths were reported with manipulation. The most common form of manipulation and administration that led to death was crushing followed by inhalation (n=9). Four deaths occurred following the splitting of the extended-release tablet. In three of the four cases, the split tablet was administered orally. In the fourth case the route was unknown. The two remaining deaths were due to biting (unknown route) and inhaling (unknown method of manipulation).

3.1.2 Wrong Dose Errors (n=38)

There were 38 medication error cases reporting prescribing, dispensing and in some cases administration of the wrong dose of Opana ER. These cases were further broken down to the following categories (overdosing of opioid naïve patients, conversion from other opioids and other).

3.1.2.1 Overdosing Opioid-Naïve Patients (n=5)

In five cases, opioid naïve patients received overdoses of Opana ER tablets. Table 1 provides a summary of the cases. The insert labeling states the initial dose for opioid naïve patients is 5 mg every 12 hours. All patients were prescribed doses at least 4 times the recommended dose for naïve patients.

Table 1: Overdosing of Opioid Naïve Patients

Date of Event	Opana ER dose patient received	Opana ER dose for Opioid Naïve patients per labeling	Age	Gender	Patient Outcome
(b) (6)	20 mg every 6 hours as needed	5 mg every 12 hours	34	Female	Emergency Room visit
3/24/10	100 mg every 12 hours	5 mg every 12 hours	50	Male	Dose reduction
(b) (6)	40 mg every 12 hours	5 mg every 12 hours	50	Male	Death
(b) (6)	30 mg every 12 hours	5 mg every 12 hours	42	Female	Hospitalized
2/9/07	40 mg every 12 hours	5 mg every 12 hours	48	Male	Unknown

3.1.2.2 Opioid Conversion Underdosing (n=4)

Four cases report an underdose with Opana ER. In the first of the four cases the physician intentionally underdosed when converting the patient from MS Contin (morphine sulfate) extended-release tablets 540 mg/day to Opana ER 20 mg twice daily. The physician intentionally started the patient on a low dose of Opana ER then titrated to a higher dose since the patient was taking a significantly large dose of MS Contin. The physician concluded the lower dose of Opana ER 20 mg twice daily was “too low” and caused the patient to experience adverse effects that led to her hospitalization.

Two of the remaining cases involve errors in which patients increased their doses without physician approval upon conversion from hydrocodone and methadone to Opana ER. The patients' final adjusted dose matched the suggested conversion dose indicated in the insert labeling of the product.

The last case involved the death of a patient that received an underdose of Opana ER when converted from Oxycontin (oxycodone) extended-release tablets. The case noted the patient had a few more tablets missing from his bottles of Opana ER and oxycodone tablets (for breakthrough pain) than expected when considering his dose. It is likely the patient may have taken extra tablets of Opana ER and oxycodone due to inadequate pain relief. It is less likely the patient intentionally overdosed because there were only a few more tablets missing as opposed to a larger amount. The details of these cases are in Table 2.

Table 2: Opioid Conversion Underdoses

Date of Event	Opioid Dose	Opana ER dose patient received	Suggested Opana ER dose, per labeling	Patient Outcome
7/07/09	Methadone 160 mg daily	Opana ER 20 mg twice daily	Opana ER 40 mg twice daily	None reported
(b) (6)	MS Contin 540 mg per day	Opana ER 20 mg twice daily	Opana ER 90 mg twice daily	Hospitalization, chest pain, nausea, vomiting
10/29/07	Vicodin 5 mg/500 mg, 8 tablets per day	Opana ER 5 mg twice daily	Opana ER 10 mg twice daily	Agitation, irritability, anger with breakthrough pain
(b) (6)	Oxycontin 80 mg three times daily	Opana ER 20 mg twice daily	Opana ER 60 mg twice daily	Death

3.1.2.3 Opioid Conversion Overdosing (n=4)

In four cases, patients received higher doses of Opana ER than what is recommended in the insert labeling when converting from other opioids. The details of these three cases are below in Table 3.

The fourth case involved a patient that was converted from Oxycodone 5 mg, 30 tablets daily (150 mg/day) to Opana ER 10 mg twice daily. The physician recommended the patient increase to Opana ER 20 mg twice daily then to 30 mg twice daily while simultaneously decreasing Oxycodone. Approximately 30 days later while taking Opana ER 30 mg twice daily and Oxycodone 105 mg to 120 mg per day, the patient experienced severe headache, vision issues, dry mouth, and nausea. Thus, the physician converted the patient from Oxycodone to Opana ER, yet kept the patient on Oxycodone.

Table 3: Opioid Conversion Overdoses

Date of Event	Opioid Dose	Opana ER dose patient received	Suggested Opana ER dose, per labeling	Patient Outcome
(b) (6)	Hydrocodone and Acetaminophen 7.5 mg/100 mg three times daily	Opana ER 30 mg twice daily	Opana ER 5 mg twice daily	Death, suicide (unrelated to error)
(b) (6)	Avinza 90 mg daily	Opana ER 60 mg twice daily	Opana ER 15 mg twice daily	Hospitalized
5/--/07	Oxycontin 40 mg twice daily	Opana ER 40 mg twice daily	Opana ER 20 mg twice daily	Severe, constipation, fever, dehydration

3.1.2.4 Other Wrong Dose Errors (n=25)

There were 25 cases of wrong dose errors related to physicians prescribing the wrong frequency of administration, inappropriate dose escalation and patients taking an extra dose or changing the frequency of administration. There was one death. However, the reporting physician did not feel that death would have occurred if the daily regimen of medications was taken as prescribed. Additionally, he did not believe it was a suicide. No information was provided in the narrative of these cases that provided insight on the root cause of these errors.

3.1.3 Wrong Drug Errors (n=5)

Five cases report confusion between Opana and Opana ER. In all cases, Opana ER was dispensed for Opana. One of the cases resulted in hospitalization of the patient and another case resulted in the patient complaining of tiredness. No outcomes were reported in the other three cases.

3.1.4 Monitoring Errors (n=3)

Three cases describe a monitoring error with Opana ER. Two of the three cases were drug-drug interactions. These cases describe two patients that died secondary to receiving multiple opioid medications. The cases did not specify whether these medications were prescribed by the same or different provider or if the prescriptions were filled at the same or different pharmacies. In one case, the physician noticed the duplicate therapy, which consisted of Opana ER, Duragesic, Opana, and Vicodin ES. The physician discontinued Duragesic, however the patient expired two days later. In the second case, the patient was taking Opana ER, methadone, fentanyl, and Vicodin. The medical examiner noted the cause of death was the combined effect of oxymorphone, methadone, and fentanyl.

The remaining monitoring error, described as a documented allergy, involves a patient suffering from allergic reaction to Opana ER. The patient had a documented angioedema to morphine, however tolerated hydrocodone.

3.1.5 Deaths (n=20)

In total, 20 deaths were reported because of medication errors or manipulation of Opana ER. Manipulation of Opana ER was the most frequent cause of death for the cases relevant to this review (n=15). Table 4 provides a summary of these cases.

Table 4: Death related to medication errors and manipulation

Cause of Death	Number of Deaths
Manipulation	15
Overdose Opioid Naive Patients	1
Opioid Conversion Underdose	1
Opioid Conversion Overdose	1
Other Wrong Dose Errors	1
Monitoring Errors	1
Total	20

3.2 MEDICAL LITERATURE

Two published manuscripts which discussed cases of oxymorphone overdose deaths.^{1,2} Garside et.al., cited one case in which a 31 year old male died secondary to oxymorphone abuse. This case was submitted to AERS as ISR 6387285-X. The specific oxymorphone product name was not provided for 2 oxymorphone fatalities in McIntyre, et.al. Both authors indicated that oxymorphone could not reliably be detected in routine laboratory screening.

3.3 CONTRIBUTING FACTORS OF ERRORS IDENTIFIED FROM THE LABEL AND LABELING

Our review of the labels and labeling indicates that the opioid conversion ration table in the Dosage and Administration section of the insert labeling may be contributing to the medication errors relating to dosing errors evaluated in this review (see Appendix E).

4 DISCUSSION

Evaluation of the cases revealed the following three broad categories of concern with Opana ER, which are discussed below: (1) manipulation for abuse; (2) wrong dose errors with Opana ER; and (3) confusion between Opana and Opana ER.

4.1 MANIPULATION CASES (N=56)

Opana ER is manipulated several ways prior to administration. Most of these manipulations are related to abuse. Eight of the 56 cases reported patient manipulation of Opana ER for non-abuse and describe chewing or sucking Opana ER to obtain greater pain relief, increase duration of action, or misunderstood the administration instructions.

The most common method of manipulation reported with abuse is crushing which led to the administration of the product by inhalation. This type of manipulation led to death in nine cases. If the proposed formulation proves to provide protection against crushing it will have an impact on this type of manipulation. However, other methods of manipulation that resulted in fatalities (n=4) report biting, chopping, and splitting of the tablet prior to inhalation or oral administration. Additionally, other forms of manipulation included breaking, cutting, scraping, and (b) (4) the tablet prior to inhalation. In these cases, a sharp object was used to manipulate the Opana ER tablet rather than blunt force crushing seen in the other cases.

The Applicant should consider whether their proposed formulation could prevent the cutting, (b) (4) biting or chewing of the tablet.

4.2 WRONG DOSE ERRORS (N=38)

Numerous wrong dose errors reported physicians prescribing the wrong frequency of administration, inappropriate dose escalation and patients taking extra doses or changing the frequency of administration. There were also a number of cases in which opioid naïve patients received overdoses. The Dosage and Administration section of the insert labeling clearly instructs prescribers to dose Opana ER every 12 hours and provides dose titration at increments of 5 mg to 10 mg every 12 hours every 3 to 7 days. The labeling also clearly states the dosing for opioid naïve patients. Therefore, these errors may be related to a provider knowledge deficit and require educational measures to address.

Other wrong dose errors relate to erroneous conversions between Opana ER and other opioids, which led to over- and underdosing. With the exception of one case, none of the case narratives provided detail as to why these doses were prescribed. We suspect based on the dose described in one of the cases that the total daily dose of Opana ER was not equally divided into 2 doses as recommended in the approved product labeling. Within the insert labeling, the text above the dosing conversion table instructs practitioners to administer half of the calculated total daily dose of Opana ER in two divided doses, every 12 hours. The manner in which the information is presented in the chart is confusing and does not easily illustrate the steps required for appropriate dose conversion from other oral opioids to Opana ER. The text above the table can be minimized and the columns can be clarified. Modifications to this table may minimize these types of wrong dose errors.

4.3 WRONG DRUG ERRORS (N=5)

A small number (n=5) of wrong drug errors involve confusion between Opana, the immediate release formulation, and Opana ER, the extended release formulation. This type of confusion is common among product line extensions at the time the new formulation is introduced into the market especially when the products share overlapping strengths. All of the wrong drug cases occurred with the shared 5 mg and 10 mg strengths. A couple of additional contributing factors were noted in the case narratives such as pharmacy computer systems only having one product, Opana ER, listed in their system and providers prescribing the immediate release formulation by the name *Opana IR* rather than Opana. Although, the prescriptions included different frequencies of administration (every 4 to 6 hours or 3 times daily) this was not sufficient to prevent these errors. Thus, the similarity of the names and overlapping strengths for both Opana and Opana ER contributed to these errors. The container labels and carton labeling for Opana and Opana ER provide differentiation to help minimize confusion at the point of product selection from the shelf. However, if the prescription is misinterpreted at the

point of data entry these label/labeling visual distinctions are not helpful in minimizing these types of error. Although we have seen a decline over time with this type of error, we will continue to monitor postmarketing reports of this type to determine if other measures are needed to address this issue.

5 CONCLUSIONS AND RECOMMENDATIONS

The Applicants proposal to market oxymorphone extended-release tablets with an abuse deterrent to prevent manipulation by crushing will address the majority of manipulations reported to date with Opana ER. However, we recommend the Applicant test whether their proposed formulation can prevent other non-crushing forms of manipulation such as cutting or splitting the tablet or dissolving in liquids.

Additionally, we recommend the conversion ratio table in the insert labeling be improved by minimizing the text above the table and clarifying the column titles to minimize the dosing errors reported with conversion from other opioids to Opana ER.

If you have further questions or need clarifications, please contact, OSE Project Manager, Bola Adeolu at 301-796-4264.

6 APPENDICES

Appendix A:

Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

Appendix B: Opana ER Labels and Labeling

(b) (4)



3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

6 pages of draft labeling have been withheld in full as B(4) CCI/TS immediately following this page

Appendix E: Conversion instructions from other Oral Opioids to Opana ER

Conversion from Other Oral Opioids to OPANA ER For conversion from other opioids to OPANA ER, physicians and other healthcare professionals are advised to refer to published relative potency information, keeping in mind that conversion ratios are only approximate. In general, it is safest to start the OPANA ER therapy by administering half of the calculated total daily dose of OPANA ER (see conversion ratio table below) in 2 divided doses, every 12 hours. Gradually adjust the initial dose of OPANA ER until adequate pain relief and acceptable side effects have been achieved.

The following table provides approximate equivalent doses, which may be used as a guideline for conversion. **The conversion ratios and approximate equivalent doses in this conversion table are only to be used for the conversion from current opioid therapy to OPANA ER.** (b) (4)



CONVERSION RATIOS TO OPANA ER	
Opioid	Oral Conversion Ratio ^a
Oxymorphone	1
Hydrocodone	0.5
Oxycodone	0.5
Methadone b	0.5
Morphine	0.333

^aRatio for conversion of oral opioid dose to approximate oxymorphone equivalent dose. Select opioid and multiply the dose by the conversion ratio to calculate the approximate oral oxymorphone equivalent.

- **The conversion ratios and approximate equivalent doses in this conversion table are only to be used for the conversion from current opioid therapy to OPANA ER.**
- Sum the total daily dose for the opioid and multiply by the conversion ratio to calculate the oxymorphone total daily dose.
- For patients on a regimen of mixed opioids, calculate the approximate oral oxymorphone dose for each opioid and sum the totals to estimate the total daily oxymorphone dose.
- The dose of OPANA ER can be gradually adjusted, preferably at increments of 10 mg every 12 hours every (b) (4) days, until adequate pain relief and acceptable side effects have been achieved [see *Dosage and Administration (2.1)*].

b It is extremely important to monitor all patients closely when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and tends to accumulate in the plasma.

Appendix F: ISR Numbers

Category	ISR Number	MFR Control Number
ACCID CHILD	5442009	2007EN000202
CONVERT LO	5582914	(b) (4)
CONVERT LO	5606483	2007EN000307
CONVERT LO	5727853	OPER20080080
CONVERT LO	6293631	OPER20090137
CONVERT OD	5195818	2006EN000025
CONVERT OD	5875344	OPIR20080025
		(b) (4)
CONVERT OD	5382755	
	5421712	USA_2007_0028151
	5421735	; 2007EN000171
	6337049	OPER20090077;
CONVERT OD	6157589	190213USA; US-
	6159987	(b) (4)
DIVERSION	5483492	2007EN000238
DIVERSION	5484277	2007EN000249
DIVERSION	5484341	2007EN000243
DIVERSION	5677901	OPER20080045
DIVERSION	5695447	OPER20080059
DIVERSION	5695448	OPER20080058
DIVERSION	5744641	OPER20080096
DIVERSION	5875345	OPER20080166
DIVERSION	5892543	OPER20080180
DIVERSION	6156515	OPER20090050
DIVERSION	6746026	OPER20100091
MANIP	5195811	2006EN000053
MANIP	5257257	2007EN000072
MANIP	5397931	2007EN000185
MANIP	5472382	2007EN000233
MANIP	5484240	2007EN000242
MANIP	5484274	2007EN000246
MANIP	5484289	2007EN000247
MANIP	5484328	2007EN000248
MANIP	5484338	2007EN000245
MANIP	5506767	2007EN000262
MANIP	5580383	2007EN000298
MANIP	5580384	2007EN000299
MANIP	5580396	2007EN000297
MANIP	5580398	2007EN000296
MANIP	5603810	2007EN000286
MANIP	5631527	OPER20080020
MANIP	5654427	OPER20080037
MANIP	5676113	OPER20080023
MANIP	5677902	OPER20080042
MANIP	5677933	OPER20080046
MANIP	5695445	OPER20080052
MANIP	5706533	OPER20080066
MANIP	5744635	OPER20080092
MANIP	5760632	OPER20080094
MANIP	5760646	OPER20080095
MANIP	5796785	OPER20080123
MANIP	5828001	OPER20080114

MANIP	5835328	OPER20080145
MANIP	5875713	OPER20080168
MANIP	6155388	OPER20090061
MANIP	6155413	OPER20090065
MANIP	6155755	OPER20090066
MANIP	6156324	OPER20090067
MANIP	6156325	OPER20090063
MANIP	6156521	OPER20090043
MANIP	6156570	OPER20090020
MANIP	6156619	OPER20080228
MANIP	6191017	OPER20090096
MANIP	6198036	OPER20090099
MANIP	6199228	OPER20090062
MANIP	6202136	OPER20090100
MANIP	6215446	OPER20090107
MANIP	6239917	OPER20090118
MANIP	6312494	OPER20090003
MANIP	6326252	OPER20090059
MANIP	6416790	OPER20090184
MANIP	6568523	OPER20100017
MANIP	6685879	OPER20100056
MANIP	6820017	OPER20100094
MANIP	6861413	OPER20100124
MANIP	6916539	US-ENDO PHARMACEUTICAL S INC.- OPER20100137
MANIP	6918592	US-ENDO PHARMACEUTICAL S INC.- OPER20100138
MANIP	6918593	US-ENDO PHARMACEUTICAL S INC.- OPER20100135
MANIP	5261711 5261713	2007EN000074
MANIP	6326255 6636947	OPER20090060, 090814-0000911 OPER20100087;
MANIP	6784101 6931507	US-ENDO PHARMACEUTICAL S INC.- OPER20100087
MONITORING	5833682	OPER20080136
MONITORING	5348691 5701504 5717007 5719906 5730509 5747200 5756701 5772798	2007EN000154; 2007EN000147: US- (b) (4)
MONITORING	6179906 6182135	(b) (4)
NAÏVE OD	5285478	(b) (4)

NAÏVE OD	5735770	(b) (4)
NAÏVE OD	6105091	(b) (4)
NAÏVE OD	6544321	(b) (4)
NAÏVE OD	6973950	US-ENDO PHARMACEUTICAL S INC.- OPER20100156
NONCOMPLIAN CE	5603780	2007EN000269
NONCOMPLIAN CE	6066719	(b) (4)
NONCOMPLIAN CE	6156495	OPER20080198
NONCOMPLIAN CE	6587748	OPER20100019
WRG DOSE OTHER	5318536	2007EN000123
WRG DOSE OTHER	5453447	2007EN000218
WRG DOSE OTHER	5606485	OPER20080004
WRG DOSE OTHER	5677062	OPER20080041
WRG DOSE OTHER	5677898	OPER20080040
WRG DOSE OTHER	5695446	OPER20080034
WRG DOSE OTHER	5712265	OPER20080073
WRG DOSE OTHER	5736879	OPER20080088
WRG DOSE OTHER	5812614	OPER20080134
WRG DOSE OTHER	5853238	OPER20080157
WRG DOSE OTHER	5863847	OPER20080067
WRG DOSE OTHER	6156323	OPER20090068
WRG DOSE OTHER	6156491	OPER20080215
WRG DOSE OTHER	6156500	OPER20080191
WRG DOSE OTHER	6156585	OPER20090006
WRG DOSE OTHER	6335694	OPER20090156
WRG DOSE OTHER	6523007	OPER20090225
WRG DOSE OTHER	6745669	OPER20100089
WRG DOSE OTHER	6913664	US-ENDO PHARMACEUTICAL S INC.- OPER20100136
WRG DOSE OTHER	6913921	US-ENDO PHARMACEUTICAL S INC.- OPER20100139
WRG DOSE OTHER	7009211	US-ENDO PHARMACEUTICAL S INC.- OPER20100167
WRG DOSE OTHER	5421706	2007EN000116;
WRG DOSE OTHER	5421716	2007EN000115
WRG DOSE OTHER	5442011	2007EN000127
WRG DOSE OTHER	5442017	2007EN000128

WRG DOSE	6155427	
OTHER	6127682	OPER20090054
	6126774	
		(b) (4)
	6395412	
WRG DOSE	6398802	
OTHER	6396458	
	6399876	
WRONG DRUG	5139541	2006EN000006
WRONG DRUG	5279117	(b) (4)
WRONG DRUG	5427206	
WRONG DRUG	5637773	OPER20080021
		US-ENDO
WRONG DRUG	6964641	PHARMACEUTICAL
		S INC.-
		OPER20100147

7 REFERENCES

¹ Garside D, Hargrove RL, Winecker RE. Concentration of oxymorphone in postmortem fluids and tissue. *J Anal Toxicol* 2009; 33: 121 – 128.

² McIntyre IM, Sherrard JL, Nelson CL. Oxymorphone-involved fatalities: a report of two cases. *J Anal Toxicol* 2009; 33: 615 – 619.

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/s/

JIBRIL ABDUS-SAMAD
10/28/2010

DENISE P TOYER on behalf of CAROL A HOLQUIST
10/28/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: October 26, 2010

To: Ellen Fields, MD
Medical Officer
Division of Anesthesia, and Analgesia Products (DAAP)
Office of New Drugs

Through: Laura Governale, PharmD, MBA
Drug Utilization Data Analysis Team Leader
Division of Epidemiology
Office of Surveillance and Epidemiology

From: Rajdeep Gill, PharmD
Drug Utilization Data Analyst
Division of Epidemiology
Office of Surveillance and Epidemiology

Subject: Oxymorphone Drug Utilization Review

Drug Name(s): Opana® ER and Opana®

Application Type/Number: NDA 201655

Applicant/sponsor: Endo Pharmaceuticals Inc.

OSE RCM #: 2010-2081

EXECUTIVE SUMMARY

The Division of Anesthesia and Analgesia Products (DAAP) requested drug utilization data for Opana® ER (oxymorphone extended-release tablets) and Opana® (oxymorphone immediate-release tablets) in support of the upcoming Anesthetic and Life Support Drugs Advisory Committee meeting to be held on December 2, 2010. The focus of this meeting is to discuss the new drug application (NDA) (b) (4)™ (oxymorphone HCl (b) (4) extended-release tablets) and its safety for the proposed indication of relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. This analysis provides the utilization trends for Opana® ER and Opana® from drug approval in June 2006 through year-to-date August 2010.

Summary of the findings:

- In the pain market, oxymorphone extended-release tablets accounted for approximately (b) (4) of the total extended-release opioid prescriptions dispensed through U.S. outpatient retail pharmacies in year 2009
- Opana® ER accounted for approximately (b) (4) of total oxymorphone prescriptions (b) (4) and Opana® accounted for (b) (4) of total oxymorphone prescriptions in an aggregate time period from June 2006 through August 2010
- Total dispensed prescriptions of Opana® ER increased from approximately (b) (4) in year 2007 to approximately (b) (4) in year 2009 accounting for approximately (b) (4)
- Opana® ER 20 mg was the most commonly dispensed strength accounting for approximately (b) (4) of total Opana® ER dispensed prescriptions closely followed by 40 mg (b) (4) and 10 mg (b) (4)
- Total number of unique patients receiving prescription of Opana® ER and Opana® in outpatient retail pharmacies increased from approximately (b) (4) patients in year 2007 to (b) (4) patients in year 2009 accounting for approximately (b) (4)
- “Anesthesiologist” was the top prescribing specialty group for Opana® and Opana® ER followed by “Physical Medicine and Rehabilitation” and “General Practice/Family Medicine/Osteopathy”
- “Lumbosacral Neuritis NOS” (ICD-9 724.4) and “Postlaminectomy Syndrome” (ICD-9 722.8) and “Lumbago” (ICD-9 724.2) were the top three diagnosis codes associated with oxymorphone use
- Approximately 65% of the diagnosis codes recorded were associated with “diseases of musculoskeletal system and connective tissue” (ICD-9 codes 710-739) which include chronic pain conditions such as arthritis and back pain
- In year 2009, approximately (b) (4) of the total prescriptions for both Opana® ER and Opana® were dispensed to patients who did not have a prior opioid/narcotic prescription in the previous one month period.
- Opana® ER was most commonly switched/added to and from Hydrocodone/acetaminophen therapy in year 2009

1 INTRODUCTION

The Division of Anesthesia and Analgesia Products is conducting an Advisory Committee Meeting on December 2, 2010, to discuss the new drug application (NDA) (b) (4)™ (oxymorphone HCl (b) (4) extended-release tablets) and its safety for the proposed indication of relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. The extended-release characteristics of this formulation are purportedly less easily defeated than other formulations of controlled-release oxymorphone. In support of the review of this new drug application, the Division of Epidemiology has been requested to provide drug utilization patterns of Opana ER® and Opana®. Using the currently available proprietary drug use databases licensed by the Agency, this review provides overall sales data, use by indication, prescriber specialty and switch/add-on analysis from July 2006 through year-to-date August 2010.

2 BACKGROUND

Opana® ER (oxymorphone extended-release) was initially approved (NDA- 021610) in June 2006 for the management of moderate to severe pain when a continuous, around-the-clock opioid (b) (4) is needed for an extended period of time.¹ Opana® ER is currently available as 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg and 40 mg extended-release tablets. Opana® was also approved (NDA 021611) in June 2006 for relief of moderate to severe acute pain, with currently available strengths of 5 mg and 10 mg. The sponsor has submitted a new drug application to the FDA for a (b) (4) formulation for oxymorphone extended-release tablets under NDA 201655 for (b) (4) (oxymorphone HCl (b) (4) extended-release). To understand the utilization patterns of oxymorphone, this drug utilization review provides the outpatient trends of both Opana® ER and Opana® from July 2006 through year-to-date August 2010.

3 METHODS AND MATERIAL

3.1 DETERMINING SETTINGS OF CARE

IMS Health, IMS National Sales Perspectives™ (*see Appendix 2 for detailed database descriptions*) was used to determine the various retail and non-retail channels of distribution for Opana® ER and Opana®. Sales data for year 2009 indicated that approximately (b) (4) of Opana® ER and Opana® bottles and packages (b) (4) were distributed to outpatient retail pharmacies for both products; (b) (4) were to non-retail settings; and (b) (4) were to mail order pharmacies.² As a result, outpatient retail utilization patterns were examined. Neither mail order nor non-retail settings data were included in this analysis.

3.2 DATA SOURCES

Proprietary drug use databases licensed by the Agency were used to conduct this analysis (see Appendix 1 for full data description).

¹Opana® ER(oxymorphone ER) label-
http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021610s006lbl.pdf

²IMS Health, IMS Nationals Sales Perspectives™, Data extracted 10/10. Source File: 1010opan.DVR

SDI, Vector One®: National (VONA) was used to obtain estimates of the number of outpatient dispensed prescriptions for Opana® ER and Opana® from June 2006 to August 2010. We also obtained switch/add-on analysis and the number of dispensed prescriptions stratified by the prescribing specialties for an aggregate time period from June 2006 to August 2010. SDI, Vector One®: Total Patient Tracker (TPT) was used to obtain estimates of the number of patients receiving a dispensed prescription for Opana® ER and Opana®, in the outpatient settings from June 2006 to August 2010. Diagnoses associated with the use of Opana® ER and Opana® were obtained from the SDI, Physician Drug and Diagnosis Audit™ (PDDA) from July 2006 through August 2010.

4 RESULTS

4.1 OUTPATIENT DISPENSED PRESCRIPTIONS OF OXYMORPHONE EXTENDED RELEASE TABLETS

Outpatient dispensed prescriptions of Opana® ER (oxymorphone extended-release tablets) through U.S. outpatient retail pharmacies accounted for approximately (b) (4) of total opioid extended-release prescriptions dispensed in year 2009. The prescription share of Opana® ER in opioid extended-release market is small, but has gradually increased from approval in June 2006. (Table 1 in Appendix 1)



4.2 OUTPATIENT DISPENSED PRESCRIPTIONS FOR OPANA® ER AND OPANA®

Table 1 and Figure 2 display the total number of projected dispensed prescriptions of Opana® ER and Opana® through outpatient retail pharmacies from approval in June 2006 through year-to-date August

2010. Opana® ER prescriptions increased from approximately (b) (4) prescriptions in year 2007 to approximately (b) (4) prescriptions in year 2009 accounting for approximately (b) (4). A total of about (b) (4) prescriptions of Opana® ER were dispensed through U.S. outpatient retail pharmacies in a cumulative period from approval time in June 2006 through August 2010. Opana® ER 20 mg, 40 mg and 10 mg were the most commonly prescribed strengths in the study period.

Opana® prescriptions increased from approximately (b) (4) prescriptions in year 2007 to (b) (4) prescriptions in year 2009; the 10 mg strength was the most commonly prescribed strength of Opana® through U.S. outpatient retail pharmacies. A total of approximately (b) (4) prescriptions of Opana® were dispensed in a cumulative period from approval time in June 2006 through August 2010.

(b) (4)

4.3 PATIENTS RECEIVING PRESCRIPTIONS FOR OPANA® ER AND OPANA®

Table 2 and Figure 3 displays the total number of projected unique patients receiving a dispensed prescription of oxymorphone from U.S. outpatient retail pharmacies from June 2006 through August 2010. In an aggregate time period from approval in June 2006 through August 2010, approximately (b) (4) unique patients received a prescription for Opana® ER and approximately (b) (4) unique patients received Opana®. Patients receiving prescription for Opana® ER increased from approximately (b) (4) patients in year 2007 to approximately (b) (4) patients in year 2009, nearly a (b) (4). Similarly, patients receiving prescription for Opana® increased from approximately (b) (4) patients in year 2007 to approximately (b) (4) patients in year 2009.

4.4 DISPENSED PRESCRIPTIONS OF OXYMORPHONE BY PRESCRIBER SPECIALTY

Figure 4 shows the number of dispensed prescriptions of oxymorphone by top prescribing specialties for an aggregate time period from approval in June 2006 through August 2010. “Anesthesiologist” (b) (4) was the top prescribing specialty followed by “Physical Medicine and Rehabilitation Specialist” (b) (4), “General Practice/Family Medicine/Osteopathy” (b) (4) and “Internal Medicine” (b) (4).

“Nurse Practitioners” (b) (4), “Physician Assistants” (b) (4), “Neurologist” (b) (4), “Rheumatologists” (b) (4) and “Orthopedic Surgeons” (b) (4) were also in the group of top ten prescribers.

4.5 DIAGNOSES ASSOCIATED WITH THE USE OF OXYMORPHONE

Table 3 displays the diagnosis (ICD-9) associated with the use of oxymorphone for an aggregate time period from approval time in June 2006 through August 2010. According to the office-based physician practices in the U.S., “Lumbosacral Neuritis NOS” (ICD-9 724.4) was the top diagnosis code with (b) (4) of the total uses followed by “Postlaminectomy Syndrome” (ICD-9 722.8) with approximately (b) (4) of the total uses and “Lumbago” (ICD-9 724.2) with approximately (b) (4) of total oxymorphone uses.

When grouping ICD-9 diagnosis codes, approximately (b) (4) of the diagnosis codes were associated with “diseases of musculoskeletal system and connective tissue” (ICD-9 codes 710-739) which includes chronic pain conditions such as arthritis and back pain, and approximately (b) (4) of the diagnosis codes were associated with “headaches and nerve pain” (ICD-9 codes 337-359) which includes chronic pain syndrome and chronic pain.

4.6 NEW, CONTINUING, SWITCH/ADD-ON PATIENT PRESCRIPTIONS FOR OXYMORPHONE

We analyzed dispensed prescriptions of Opana® ER and Opana® in year 2009 to evaluate which of those were being dispensed to new patients, continuing patients, or switch/add-on patients. Prescriptions were classified as *new patient prescriptions* if no opioid/narcotic³ prescription was dispensed to a patient within the previous one month look-back period. Prescriptions were classified as *continuing patient prescriptions* if an opioid prescription was dispensed to a patient within the last one month period. Lastly, prescriptions were classified as *switch/add-on patient prescriptions* if an opioid prescription was dispensed to a patient in the previous one month; these prescriptions were either added on to current oxymorphone therapy or switched from one therapy to another.

Of the approximately (b) (4) prescriptions dispensed for Opana® ER by retail pharmacies during year 2009, the majority of prescriptions dispensed ((b) (4)) were from patients who were continuing on a prior prescription opioid/narcotic therapy, and approximately (b) (4) of the prescriptions were from patients who had switched from another opioid/narcotic prescription or added on therapy to Opana® ER within the last one month. Approximately (b) (4) of the total patients receiving prescription for Opana® ER were new to prescription opioid/narcotic therapy.

In case of Opana®, there were approximately (b) (4) prescriptions dispensed by retail pharmacies in year 2009. Approximately (b) (4) of the Opana® prescriptions were from patients who were continuing on a prior prescription opioid/narcotic, approximately (b) (4) of the prescriptions were from patients who had switched from another prescription or added on therapy within the last one month. Approximately (b) (4) of the total patients receiving a prescription for Opana® were new to prescription opioid/narcotic therapy.

³ Opioid/narcotic prescriptions include the following drug classes from the pain market: synthetic narcotic analgesics injectable (USC 02211), propoxyphenes (USC 02212), synthetic narcotic unknown form (USC 02213), synthetic narcotic non-injectable (USC 02214), morphine and opium injectable (USC 02221), morphine and opium non-injectable (USC 02222), morphine and opium unknown form (USC 02223), codeine and combination injectable (USC 02231), codeine and combination non-injectable (USC 02232), codeine and combination unknown form (USC 02233),

4.7 SWITCH/ADD-ON- ANALYSIS

Table 5 summarizes the information on the top ten drug products dispensed from the pain market one month prior or one month after receiving a new prescription for Opana® ER in year 2009.

One month prior therapy analysis: In year 2009, switch/add-on-analyses indicate Opana® ER therapy was *switched/added from* hydrocodone/acetaminophen approximately (b) (4) of the times followed by oxycodone (b) (4) and oxycodone/acetaminophen (b) (4). In other words, of the approximately (b) (4) new Opana® ER prescriptions dispensed in year 2009, approximately (b) (4) of Opana® ER prescriptions came from patients who had been previously prescribed hydrocodone/ acetaminophen in the previous one month period.

One month after therapy analysis: Opana® ER therapy was *switched/added to* hydrocodone/acetaminophen approximately (b) (4) of the times followed by oxycodone/acetaminophen (b) (4) and Opana® (b) (4). In other words, of the nearly (b) (4) Opana® ER prescriptions dispensed in year 2009, approximately (b) (4) of Opana® ER prescriptions were lost to hydrocodone/acetaminophen prescriptions in the next one month period.

5 DISCUSSION

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that Opana® ER and Opana® are distributed primarily to the retail outpatient setting based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these outpatient retail pharmacy channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

This review analyzed data from the outpatient retail pharmacy setting only, which accounts for approximately (b) (4) of the total distribution volume of the selected sales market. Up to (b) (4) of the total distribution volume going into mail order and non-retail settings was not analyzed.

SDI uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

Indications for use were obtained using SDI's PDDA, a monthly survey of (b) (4) office based physicians. Although PDDA data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, PDDA data are best used to identify the typical uses for the products in clinical practice, and the VONA outpatient prescription data to evaluate trends over time.

Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

6 CONCLUSIONS

Although the oxymorphone has a very small market share in the pain market, the number of prescriptions and patients receiving Opana® ER and Opana® have been gradually increasing since market approval in June 2006 to August 2010. “Anesthesiologist” was the top prescribing specialty group for oxymorphone followed by “Physical Medicine and Rehabilitation” and “General Practice/Family Medicine/Osteopathy”. Approximately (b) (4) of the diagnosis codes associated with oxymorphone use were associated with “diseases of musculoskeletal system and connective tissue” (ICD-9 codes 710-739) which includes chronic pain conditions such as arthritis and back pain. Nearly (b) (4) of Opana® ER and Opana® prescriptions were dispensed to patients who did not have a prior opioid/narcotic prescription in the previous one month period.

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APPENDIX 2: DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

SDI Vector One®: National (VONA)

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

SDI Vector One®: Total Patient Tracker (TPT)

SDI's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

SDI Physician Drug & Diagnosis Audit (PDDA) with Pain Panel

SDI's Physician Drug & Diagnosis Audit (PDDA) with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

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/s/

RAJDEEP K GILL
11/01/2010

LAURA A GOVERNALE
11/01/2010
drug use data cleared by data vendors

DSI CONSULT
Request for Biopharmaceutical Inspections

DATE: 8/16/10

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: Suresh Doddapaneni, Ph.D.
Team Leader and Deputy Division Director, DCP2, Office of Clinical Pharmacology

FROM: Lisa Basham, Senior Regulatory Health Project Manager, Division of Anesthesia and Analgesia Products, HFD-170

SUBJECT: Request for Biopharmaceutical Inspections
NDA 201655
(b) (4) (Oxymorphone HCl) Extended-Release Tablets, 5, 7.5, 10, 15, 20, 30, and 40 mg.
Endo Pharmaceuticals, Inc.

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
EN3288-103	Axel Juan, MD SeaView Research, Inc. 3898 NW 7 th Street Miami, FL 33126	Facility for Bioanalytical Analyses (b) (4)

International Inspections:

(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)

We have requested an international inspection because:

_____ There is a lack of domestic data that solely supports approval;

_____ Other (please explain):

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by (b) (4). We intend to issue an action letter on this application by **January 7, 2011**.

Should you require any additional information, please contact Lisa Basham, Senior Regulatory Health Project Manager, at 301-796-1175.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-201655

ORIG-1

ENDO
PHARMACEUTICA
LS INC

Oxymorphone HCl (b) (4)
extended-release tablet

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/s/

LISA E BASHAM
08/25/2010