

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
201655Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
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**

Addendum - Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	November 30, 2011
Reviewer(s):	Danielle Smith, PharmD, M.S., Risk Management Analyst Division of Risk Management (DRISK)
Team Leader:	Megan Moncur, M.S. DRISK
Division Director	Claudia Karwoski, PharmD DRISK
Drug Name(s):	OPANA ER (oxymorphone hydrochloride extended release)
Therapeutic Class:	Opioid Analgesic
Dosage and Route:	Oral tablets
Application Type/Number:	NDA 201655
Submission Number:	Sequence Number 0032
Applicant/sponsor:	Endo Pharmaceutical, Inc.
OSE RCM #:	2010-1527

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

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EXECUTIVE SUMMARY

The purpose of this review is to amend the Division of Risk Management's (DRISK) Final Review (Reviewer: Smith, dated October 3, 2011) of Endo Pharmaceuticals' proposed Risk Evaluation and Mitigation Strategy (REMS) for OPANA ER (oxymorphone hydrochloride extended-release (ER) tablets). The Final Review is being amended to address two additional changes proposed by the sponsor, and to document DRISK's verification that all recommended revisions have been incorporated.

The OSE, DRISK finds the revisions acceptable and recommends approval of the OPANA ER REMS, submitted 21 November 2011.

1 INTRODUCTION

1.1 BACKGROUND

OPANA ER (NDA 20-1655) is an opioid agonist, developed for the relief of moderate to severe pain in patients requiring continuous around-the-clock opioid treatment for an extended period of time.

On September 23, 2011, via email communication through Ms. Lisa Basham, Regulatory Project Manager, Endo proposed two additional revisions (described below). Since the REMS Review was in the process of being finalized and these two items required further discussion with the Office of Compliance (OC), it was decided that these proposed revisions would be addressed in the addendum to the Final REMS Review:

1. REMS document – Section II.c, Section II.e – Endo proposed the following change:

(b) (4)

To: “Endo will ensure that at least 3 weeks prior to first availability of OPANA® ER to healthcare professionals, a Dear Healthcare Professional letter will be mailed to HCPs...”

Rationale: Endo believes that for the REMS information to have maximum value, it should be delivered in a close temporal relationship to the product availability to healthcare professionals. Therefore, we are proposing this modification to the timing of the distribution of the Dear Healthcare Professional letter.

1.2 REGULATORY HISTORY

Following are highlights of key regulatory actions and communications for Opana ER, following the Final REMS Review:

03 October 2011: Final REMS Review checked into DARRTS
17 October 2011: REMS submission [via email]
28 October 2011: Interim Comments provided to Sponsor [via email]
17 November 2011: REMS submission [via email]
18 November 2011: Interim Comments provided to Sponsor [via email]
21 November 2011: Submission of final agreed-upon REMS (Seq No. 0032)

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

The following materials were reviewed:

- OPANA ER proposed REMS, REMS Supporting Document, and REMS Website Draft Screen Shots, received November 21, 2011 (Seq No. 0032), including:
 - Dear Healthcare Professional (DHCP) Letter
 - Dear Pharmacist Letter
 - Healthcare Professional (HCP) Training Guide
 - OPANA ER REMS Education Confirmation Form

The following materials were referenced:

- Opana ER proposed REMS, REMS Supporting Document, and REMS Website Draft Screen Shots, received September 7, 2011 (Seq. No. 0027) including:
 - Dear Healthcare Professional (DHCP) Letter

- Dear Pharmacist Letter
- Healthcare Professional (HCP) Training Guide
- Opana ER REMS Education Confirmation Form

2.2 ANALYSIS TECHNIQUES

Endo's proposed REMS was reviewed for conformance with Title IX, Subtitle A, Section 901 of the Food Drug Administration Amendments Act of 2007 (FDAAA), and to ensure that all comments communicated to the sponsor to date, were accurately incorporated.

A comparison of the November 21, 2011 REMS submission was made to the September 7, 2011 REMS submission to ensure that only the agreed upon revisions were made.

3 RESULTS OF REVIEW OF PROPOSED OPANA ER RISK EVALUATION AND MITIGATION STRATEGY

3.1 GOALS

The goals of the OPANA ER REMS are:

1. To inform patients and healthcare professionals about the potential for abuse, misuse, overdose and addiction associated with the use of OPANA ER
2. To inform patients and healthcare professionals about the safe use of OPANA ER

3.2 REMS ELEMENTS

3.2.1 Medication Guide

A Medication Guide will be dispensed with each OPANA ER prescription in accordance with 21 CFR 208.24.

The Medication Guide is part of the REMS and is appended.

3.2.2 Elements to Assure Safe Use

3.2.2.1 Healthcare professionals (HCPs) who prescribe OPANA ER will receive training.

- a. Endo will ensure that training will be provided to HCPs who prescribe OPANA ER. Endo will ensure that each prescriber will be provided with the OPANA ER REMS educational material.
- b. The OPANA ER REMS training includes the following:
 - i. Proper patient selection
 - ii. Appropriate OPANA ER dosing and administration

- iii. General opioid use including information about opioid abuse and how to identify patients who are at risk for addiction
 - iv. The risks of abuse, misuse, overdose, and addiction from exposure to opioids, including OPANA ER
 - v. Risks of OPANA ER, including:
 - 1. The risk of overdose caused by exposure to an essentially immediate-release form of oxymorphone by consuming broken, chewed, crushed or dissolved OPANA ER tablets
 - 2. The risk of addiction from exposure to OPANA ER
 - vi. Information to counsel patients on the need to store opioid analgesics safely out of the reach of children and household acquaintances
 - vii. The importance of providing each patient with a Medication Guide, instructing the patient to read the Medication Guide and assisting the patient in understanding the content.
- c. Endo will ensure that at least 3 weeks prior to first availability of OPANA ER to healthcare professionals, a Dear Healthcare Professional letter will be mailed to HCPs experienced in treating chronic pain with opioid agonists, including pain specialists and primary care physicians. This letter is designed to convey and reinforce the risks of abuse, misuse, overdose, and addiction of OPANA ER, as well as the need to complete the OPANA ER REMS prescriber training. The letter will be available on the OPANA ER REMS website (www.OPANAERrem.com) for 1 year from the date of mailing.
- d. The Dear Healthcare Professional letter mailing will include the following materials:
 - i. Full Prescribing Information
 - ii. Medication Guide
 - iii. OPANA ER Healthcare Professional (HCP) Training Guide
 - iv. OPANA ER REMS Education Confirmation Form
- e. Additional copies of the printed REMS materials will be available for download via the OPANA ER website (www.OPANAERrem.com) or by calling Endo's toll-free phone number 1-800-462-3636.
- f. Endo will maintain a list of all prescribers who have completed the OPANA ER REMS training.

Prescribers will be re-trained every two years or following substantial changes to the OPANA ER REMS. Substantial changes may include changed to the OPANA ER Full Prescribing Information or to the Medication Guide that require substantial modification of the REMS educational materials.

The following materials are part of the REMS and are appended:

- [Medication Guide](#)
- [Dear Healthcare Professional letter](#)
- [OPANA ER Healthcare Professional \(HCP\) Training Guide](#)
- [OPANA ER REMS Website](#)
- [OPANA ER REMS Education Confirmation Form](#)

3.2.3 Implementation System

Because OPANA ER can be approved without the Elements to Assure Safe Use described under FDCA 505-1(f)(3)(B), (C), and (D) of the Act, an Implementation System is not required.

3.2.4 Timetable for Submission of Assessments

Endo will submit REMS assessments to the FDA every 6 months for the first year from the date of approval of the REMS and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment time interval. Endo will submit each assessment so that it will be received by the FDA before or on the due date.

3.3 REMS ASSESSMENT PLAN

The following information needed for assessments is included in the REMS Supporting Document:

1. An evaluation of patients' understanding of the serious risks of OPANA ER.
2. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
3. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.
4. A report on the status of the training program for healthcare providers.
5. An evaluation of healthcare providers' awareness and understanding of the serious risks associated with OPANA ER (for example, through surveys of healthcare providers).
6. Specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that healthcare provider awareness is not adequate.
7. An analysis and summary of surveillance and monitoring activities for abuse, misuse, overdose, and addiction of OPANA ER and any intervention taken resulting from signals of abuse, misuse, overdose, and addiction.

8. With respect to the REMS goals, an assessment of the extent to which the elements to assure safe use are meeting the goals or whether the goals or such elements should be modified.

4 DISCUSSION

DRISK agreed that the timing of the distribution of the Dear Healthcare Professional Letter should be closely tied to first drug availability. However, in order to assess compliance with the REMS, and following discussion with OC, DRISK requested that the sponsor specify, in the REMS Supporting Document, a timeframe for when 'first drug availability' is to be expected. The sponsor replied by stating, "First availability of OPANA ER is anticipated to be around February 17, 2012."

(b) (4)

Further review of the proposed REMS determined that the Dear Pharmacist Letter was not a required component of the interim REMS for ER/LA opioid products. (b) (4)

5 CONCLUSION

In conclusion, Endo's proposed REMS for OPANA ER (oxymorphone hydrochloride extended-release, tablets 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg), submitted November 21, 2011, addresses the requirements stipulated by the FDA in the April 6, 2010 pre-NDA meeting via Teleconference, conforms to agency standards for other interim ER/LA opioid REMS, and incorporates all comments communicated to date. The proposed REMS includes a Medication Guide and Elements to Assure Safe Use, including a DHCP Letter, a Healthcare Professional Training Guide, an Education Confirmation Form, and REMS website.

The OPANA ER REMS is acceptable to the Office of Surveillance and Epidemiology, the Division of Risk Management.

6 RECOMMENDATIONS

The OSE, DRISK recommends approval of the OPANA ER REMS (submitted 21 November 2011; Seq No. 0032).

ATTACHMENTS

REMS Document

Dear Healthcare Professional Letter

Healthcare Professional Training Guide

OPANA ER REMS Website

OPANA ER REMS Education Confirmation Form

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/s/

DANIELLE SMITH
11/30/2011

CLAUDIA B KARWOSKI
11/30/2011
concur

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

DRISK REMS REVIEW

Date: September 30, 2011

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

Through: Claudia Karwoski, Pharm.D, Director
Division of Risk Management (DRISK)

From: Danielle Smith, Pharm.D, M.S.
Risk Management Analyst (RMA), DRISK

Review Team: Megan Moncur, MS
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Regulatory Review Officer
Division of Drug Marketing, Advertising and
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Marcia Britt Williams
Consumer Safety Officer,
Division of Risk Management and Surveillance
Office of Compliance

Subject: Review of Proposed Risk Evaluation and Mitigation
Strategies (REMS)

Drug Name (Established Name): Opana® ER (Oxymorphone Hydrochloride, Extended-Release Tablets)

Application Type/Number: NDA 201655

Applicant: Endo Pharmaceuticals Inc.

OSE RCM #: 2010-1527

1 PURPOSE

This purpose of this review, performed at the request of the Division of Analgesia, Anesthesia and Addiction Products (DAAAP), is to evaluate Endo Pharmaceuticals' proposed Risk Evaluation and Mitigation Strategy (REMS) for Opana ER (oxymorphone hydrochloride (HCl) extended-release (ER) tablets), submitted 07 September 2011.

2 INTRODUCTION

Opana ER (NDA 20-1655) is an opioid agonist, developed for the relief of moderate to severe pain in patients requiring continuous around-the-clock opioid treatment for an extended period of time. It is formulated as a hard tablet designed to withstand crushing. In standardized studies, oxymorphone HCl ER was shown to resist crushing forces in excess of (b) (4) however the clinical significance of this property and the impact on abuse liability has not been established.

This product contains the same drug substance found in the immediate-release (IR; OPANA®, NDA 21-611) oral formulation of oxymorphone HCl, which was approved by the Food and Drug Administration (FDA) on June 22, 2006.

In pre-NDA meeting communications (teleconference, 06 April 2010), FDA confirmed for Endo that an interim REMS would be required, pending approval of the class-wide Opioid REMS, to inform patients and providers about the potential for misuse, abuse, overdose, and addiction. Endo was informed that the REMS must include a Medication Guide and Elements to Assure Safe Use.

On 07 July 2010, Endo submitted an Original NDA for Opana ER; the REMS included in this submission was consistent with the requirements conveyed by FDA.

On December 10, 2010, comments from the first review of the proposed REMS and REMS materials [Interim REMS Review: Comment Set #1] were sent to the Sponsor. On December 17, 2010, the sponsor submitted the revised REMS documents incorporating the Agency's comments. On December 30, 2010, additional REMS comments were provided to the sponsor via email correspondence through Ms. Lisa Basham, FDA Senior Regulatory Health Project Manager. The sponsor submitted the revised REMS document and REMS Supporting Document on January 6, 2011 (Seq. No. 0021).

Subsequently, an audit performed by the Agency of the bioequivalence study EN3288-103 identified deficiencies in the methods used at the analytical site. Because of these deficiencies, the bioequivalence study could not be relied upon to establish bioequivalence of the proposed drug product. Therefore, NDA 201655 received a Complete Response (CR) Action Letter from the Agency on January 7, 2011. Due to the CR Action Letter, no comments were provided to the Sponsor on the REMS amendment submitted on January 6, 2011.

In April 2011, the sponsors of all extended-release and long-acting (ER/LA) opioid products received a Pre-Approval REMS notification letter that stated in the interest of

public health, and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs, a single, shared system should be used to implement the REMS for all members of the class of ER/LA opioid products. The Agency is currently working with all sponsors of ER/LA opioids to develop the single shared system. Endo, and other sponsors with pending approvals, have been instructed to each develop an interim REMS that will conform with agency standards for approved interim REMS for other ER/LA opioid products.

On June 13, 2011 (Seq. No. 0025), the sponsor submitted a Complete Response to the January 7, 2011 Action Letter. On August 31, 2011, comments on the proposed REMS were sent to the sponsor via email correspondence through Ms. Lisa Basham. On September 7, 2011, the sponsor submitted an amendment to the proposed REMS document and REMS Supporting Document (Seq. No. 0027). The proposed REMS, submitted on July 7, 2010 and amended on January 6, 2011, June 13, 2011, and September 7, 2011, is the subject of this review.

2 MATERIALS REVIEWED OR REFERENCED

The materials reviewed included:

- Opana ER proposed REMS, REMS Supporting Document, and REMS Website Draft Screen Shots, received September 7, 2011 (Seq. No. 0027), including:
 - Dear Healthcare Professional (DHCP) Letter
 - Dear Pharmacist Letter
 - Healthcare Professional (HCP) Training Guide
 - Opana ER REMS Education Confirmation Form

The materials referenced included:

- DRISK Interim REMS Review: Comment Set #2. Reviewer: Smith, D., dated August 31, 2011.
- Opana ER REMS Website Draft Screen Shots, received June 13, 2011 (Seq. No. 0025)
- Pre-Approval REMS Notification Letter, dated April 18, 2011.
- Opana ER proposed REMS and REMS Supporting Document, received January 06, 2011 (Seq. No. 0021), including:
 - Dear Healthcare Professional (DHCP) Letter
 - Dear Pharmacist Letter
 - Healthcare Professional (HCP) Training Guide
 - Opana ER REMS Education Confirmation Form
- DRISK Interim REMS Review: Comment Set #1. Reviewer: Moncur, M., dated December 9, 2010

- Oxymorphone HCl ER proposed REMS and REMS Supporting Document, received July 07, 2010 (Seq. No. 0000), including:
 - Dear Healthcare Professional (DHCP) Letter,
 - Dear Pharmacist Letter,
 - Healthcare Professional (HCP) Training Guide
- Opana ER proposed Prescribing Information, received June 13, 2011 (Seq. No. 0025)
- REMS Memorandum, dated January 10, 2011.
- Opana ER proposed Prescribing Information and Medication Guide, received January 06, 2011 (Seq. No. 0021)
- OxyContin REMS (Initial Approval 04/2010; Most Recent Modification 11/2010) and Prescribing Information
- Exalgo REMS (Initial Approval 03/01/2010; Most Recent Modification 03/24/2010)

3 REVIEW OF PROPOSED REMS

Following is a list of the documents reviewed and an overview of the proposed Opana ER REMS:

- Opana ER REMS document
- Opana ER REMS Supporting Document
- Dear Healthcare Professional (DHCP) Letter
- Dear Pharmacist Letter
- Healthcare Professional (HCP) Training Guide
- REMS Website Screen Shots

3.1 Goals

1. To inform patients and healthcare professionals about the potential for abuse, misuse, overdose and addiction associated with the use of OPANA ER
2. To inform patients and healthcare professionals about the safe use of OPANA ER

3.2 REMS Elements

3.2.1 Medication Guide

A Medication Guide will be dispensed with each OPANA ER prescription in accordance with 21 CFR 208.24.

3.2.2 Elements to Assure Safe Use

1. Healthcare professionals (HCP) who prescribe OPANA ER will receive training.

- a. Endo will ensure that training will be provided to HCPs who prescribe OPANA ER. Endo will ensure that each prescriber will be provided with the OPANA ER REMS educational material.
- b. The OPANA ER REMS training includes the following:
 - i. Proper patient selection
 - ii. Appropriate OPANA ER dosing and administration
 - iii. General opioid use including information about opioid abuse and how to identify patients who are at risk for addiction
 - iv. The risks of abuse, misuse, overdose, and addiction from exposure to opioids, including OPANA ER
 - v. Risk of OPANA ER, including:
 1. The risk of overdose caused by exposure to an essentially immediate-release form of oxymorphone by consuming broken, chewed, crushed or dissolved OPANA ER tablets
 2. The risk of addiction from exposure to OPANA ER
 - vi. Information to counsel patients on the need to store opioid analgesics safely out of the reach of children and household acquaintances
 - vii. The importance of providing each patient with a Medication Guide, instructing the patient to read the Medication Guide and assisting the patient in understanding the content.
- c. Endo will ensure that (b) (4), a Dear Healthcare Professional letter will be mailed to HCPs experienced in treating chronic pain with opioid agonists, including pain specialists and primary care physicians. This letter is designed to convey and reinforce the risks of abuse, misuse, overdose, and addiction of OPANA ER, as well as the need to complete the OPANA ER REMS prescriber training. The letter will be available on the OPANA ER REMS website (www.OPANAERREMS.com) for 1 year from the date of mailing.
- d. The Dear Healthcare Professional letter mailing will include the following materials:
 - i. Full Prescribing Information
 - ii. Medication Guide
 - iii. OPANA ER Healthcare Professional (HCP) Training Guide
 - iv. OPANA ER REMS Education Confirmation Form
- e. (b) (4)

- f. Additional copies of the printed REMS materials will be available for download via the OPANA ER website (www.OPANAERrems.com) or by calling Endo's toll-free phone number 1-800-462-3636.
- g. Endo will maintain a list of all prescribers who have completed the OPANA ER REMS training.

Prescribers will be re-trained every two years or following substantial changes to the OPANA ER REMS. Substantial changes may include changed to the OPANA ER Full Prescribing Information or to the Medication Guide that require substantial modification of the REMS educational materials.

The following materials are part of the REMS and are appended:

- [Medication Guide](#)
- [Dear Healthcare Professional letter](#)
- [OPANA ER Healthcare Professional \(HCP\) Training Guide](#)

(b) (4)

- [OPANA ER REMS Website](#)
- [OPANA ER REMS Education Confirmation Form](#)

3.3 REMS Assessment Plan

Endo will submit REMS assessments to the FDA every 6 months for the first year from the date of approval of the REMS and annually thereafter.

The following information needed for assessments is included in the REMS Supporting Document:

1. An evaluation of patients' understanding of the serious risks of OPANA ER.
2. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
3. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.
4. A report on the status of the training program for healthcare providers.
5. An evaluation of healthcare providers' awareness and understanding of the serious risks associated with OPANA ER (for example, through surveys of healthcare providers).
6. Specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that healthcare provider awareness is not adequate.

7. An analysis and summary of surveillance and monitoring activities for abuse, misuse, overdose, and addiction of OPANA ER and any intervention taken resulting from signals of abuse, misuse, overdose, and addiction.
8. With respect to the REMS goals, an assessment of the extent to which the elements to assure safe use are meeting the goals or whether the goals or such elements should be modified.

4 DISCUSSION AND RECOMMENDATIONS

Endo's proposed REMS for OPANA ER (submitted Sept. 7, 2011) addresses the requirements stipulated by the FDA in the April 6, 2010 pre-NDA meeting via teleconference and conforms to agency standards for other interim ER/LA opioid REMS. The proposed REMS includes a Medication Guide and Elements to Assure Safe Use, including a DHCP Letter, a Dear Pharmacist Letter, a Healthcare Professional Training Guide, an Education Confirmation Form, and REMS website.

One additional recommendation was communicated to the sponsor via email correspondence on Sept. 21, 2011 (through the Regulatory Project Manager, Ms. Lisa Basham), and is described below:

- Please modify the goals of your REMS to read as follows:

I. GOAL(S):

The goals of the OPANA ER REMS are:

1. To inform patients and healthcare professionals about the potential for abuse, misuse, overdose and addiction associated with the use of OPANA ER
2. To inform patients and healthcare professionals about the safe use of OPANA ER

5 CONCLUSION

The DRISK Review Team finds the proposed REMS and REMS materials for OPANA ER, as submitted September 7, 2011 (and appended to this review) to be acceptable (pending DRISK's verification of the recommended revisions).

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/s/

DANIELLE SMITH
09/30/2011

CLAUDIA B KARWOSKI
10/03/2011
concur

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

DRISK INTERIM REMS REVIEW

Date: August 31, 2011

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

Through: Claudia Karwoski, Pharm.D, Director
Division of Risk Management (DRISK)

From: Danielle Smith, Pharm.D, M.S.
Risk Management Analyst (RMA), DRISK

Review Team: Megan Moncur, MS
Team Leader, Risk Management Analyst (RMA), DRISK

Kate Heinrich
Health Communications Analyst, DRISK

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

Agnes Plante, BSN, RN
Consumer Safety Officer,
Division of Risk Management and Surveillance
Office of Compliance

Subject: Interim REMS Review **Comment Set # 2**

Drug Name (Established Name): Opana® ER (Oxymorphone Hydrochloride, Extended-Release Tablets)

Application Type/Number: NDA 201655

Applicant: Endo Pharmaceuticals

OSE RCM #: 2010-1527

1 INTRODUCTION

The purpose of this interim review is to provide recommendations on Endo's proposed REMS for Opana ER (Oxymorphone Hydrochloride (HCl) Extended-Release (ER) tablets), submitted 06 January 2011. The review includes recommendations to the review division and letter-ready comments for the applicant.

2 MATERIALS REVIEWED OR REFERENCED

The materials reviewed included:

- Opana ER REMS Website Draft Screen Shots, received June 13, 2011 (Seq. No. 0025)
- Opana ER proposed REMS and REMS Supporting Document, received January 06, 2011 (Seq. No. 0021), including:
 - Dear Healthcare Professional (DHCP) Letter,
 - Dear Pharmacist Letter,
 - Healthcare Professional (HCP) Training Guide
 - Opana ER REMS Education Confirmation Form

The materials referenced included:

- DRISK Interim REMS Review: Comment Set #1. Reviewer: Moncur, M., dated December 9, 2010
- DDMAC Internal Consult for Opana ER REMS Materials, received August 10, 2011. Reviewer: Mathilda Fienkeng
- Oxymorphone HCl ER proposed REMS and REMS Supporting Document, received July 07, 2010 (Seq. No. 0000), including:
 - Dear Healthcare Professional (DHCP) Letter,
 - Dear Pharmacist Letter,
 - Healthcare Professional (HCP) Training Guide
- Opana ER proposed Prescribing Information, received June 13, 2011 (Seq. No. 0025)
- Opana ER proposed Prescribing Information and Medication Guide, received January 06, 2011 (Seq. No. 0021)
- OxyContin REMS (Initial Approval 04/2010; Most Recent Modification 11/2010) and Prescribing Information

- Exalgo REMS (Initial Approval 03/01/2010; Most Recent Modification 03/24/2010)

3 BACKGROUND

Opana ER (NDA 20-1655) is an opioid agonist, developed for the relief of moderate to severe pain in patients requiring continuous around-the-clock opioid treatment for an extended period of time. It is formulated as a hard tablet designed to withstand crushing. In standardized studies, oxymorphone HCl ER was shown to resist crushing forces in (b) (4); however the clinical significance of this property and the impact on abuse liability has not been established.

This product contains the same drug substance found in the immediate-release (IR; OPANA®, NDA 21-611) oral formulation of oxymorphone HCl, which was approved by the Food and Drug Administration (FDA) on June 22, 2006.

An audit performed by the Agency of the bioequivalence study EN3288-103 identified deficiencies in the methods used at the analytical site. Because of these deficiencies, the bioequivalence study could not be relied upon to establish bioequivalence of the proposed drug product. Therefore, NDA 20-1655 received a Complete Response (CR) Action letter from the Agency on January 7, 2011.

On June 13, 2011, NDA 20-1655 was resubmitted.

4 REMS SUMMARY

In pre-NDA meeting communications (teleconference, 06 April 2010), FDA confirmed for Endo that an interim REMS would be required, pending approval of the class-wide opioid REMS, to inform patients and providers about the potential for misuse, abuse, overdose, and addiction. Endo was informed that the REMS must include a Medication Guide and an element to assure safe use, prescriber training.

The applicant's proposed REMS, included in their 07 July 2010 NDA submission, was consistent with requirements conveyed.

On December 10, 2010, comments from the first review of the proposed REMS and REMS materials [Interim REMS Review: Comment Set #1] were sent to the Sponsor. On December 17, 2010, the sponsor submitted the revised REMS documents incorporating the Division's comments. On December 30, 2010, additional REMS comments were provided to the sponsor via email correspondence through Ms. Lisa Basham, FDA Senior Regulatory Health Project Manager. The sponsor submitted an amendment to the proposed REMS document and REMS Supporting Document on January 6, 2011 (Seq. No. 0021).

On April 18, 2011, the sponsor received a Pre-Approval REMS notification that stated in the interest of public health, and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs a single, shared system should be

used to implement the REMS for all members of the class of extended-release and long-acting (ER/LA) opioid products. The Agency is currently working with all sponsors of ER/LA opioids to develop the single shared system. Sponsors with pending approvals have been instructed to develop an interim REMS that will conform with agency standards for the other interim REMS for ER/LA opioids.

On June 13, 2011, the sponsor submitted an amendment (NDA RESUBMISSION) to NDA 20-1655 to provide a CR to the January 7, 2011 Action Letter (the CR did not include a complete REMS submission, but instead amended the January 6, 2011 (Seq. No. 0021) submission to include the requested REMS Website screen shots.

5 RECOMMENDATIONS FOR THE REVIEW DIVISION

Please provide the following recommendations on the Opana ER REMS to the applicant as soon as possible. In addition to the recommendations in Section 5 below, the materials in Appendix A and Appendix B, which include our tracked changes, should be sent to the applicant.

Please copy DRISK on the communication sent to the applicant. If there are questions, concerns, or disagreement with our recommendations, please contact DRISK to discuss. Please request that the applicant respond to these comments as soon as possible to facilitate further review in order to meet the action date for this NDA.

6 RECOMMENDATIONS FOR THE APPLICANT

Following are FDA's comments on your proposed REMS, appended materials and Supporting Document, submitted to NDA 20-1655, on January 6, 2011 and June 13, 2011. Please incorporate the changes and submit all revised materials within 1 week.

The comments provided are based on the draft Product Labeling. Your REMS document and all REMS materials will need to be updated to be consistent with the final agreed upon PI.

1. REMS Document

See attached document for tracked changes and comments of the proposed REMS document.

2. Other REMS Materials

a. Website Screen Shots

- i. Append screen shots of the REMS website to your REMS document
- ii. See edits/comments provided in the attached document.

b. DHCP Letter, Dear Pharmacist Letter, and Healthcare Professional (HCP) Training Guide

- i. See edits/comments provided in the attached document

- c. *Healthcare Professional (HCP) Training Guide*
 - i. See edits/comments provided in the attached document

3. REMS Supporting Document

Make the minor edits to the document as noted in the tracked changes and revise the REMS Supporting Document to be consistent with all changes made to the REMS document.

4. Re-submission Requirements and Instructions

- a. Submit the revised proposed REMS with all appended materials and the REMS Supporting Document.
- b. Formatting requirements:
 - i. Provide a WORD document with tracked changes and a clean WORD version of all revised materials and documents.
 - ii. Submit the REMS and the REMS Supporting Document as two separate WORD documents. It is preferable that the entire REMS document and attached materials be in a single WORD document.
 - iii. Date and paginate all REMS documents to facilitate review and document control.

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/s/

DANIELLE SMITH
08/31/2011

MEGAN M MONCUR
08/31/2011
I concur



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

M E M O R A N D U M

DATE: January 10, 2011

TO: NDA 201-655, (b) (4)

From: Ellen Fields, M.D., M.P.H.
Clinical Team Leader

Through: Bob Rappaport, M.D.
Division Director

RE: Risk Evaluation and Mitigation Strategy (REMS) Requirements

Title IX, Subtitle A, Section 901 of FDAAA amends the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if the Secretary determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits of (b) (4) (Oxymorphone extended-release tablets) outweigh its risks. In reaching this determination we considered the following:

- A. The proposed indication could result in use of the product in a population of millions of patients with chronic pain.
- B. The patients for this product are patients with moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. This is a serious condition, particularly for those patients who have chronic pain due to etiologies that are unlikely to improve.
- C. The expected benefit of the drug to patients is that patients respond differently to different opioid drug substances and some patients develop tolerance to an opioid after chronic exposure. Having different opioids available as modified-release formulations provides important options for these patients.
- D. The expected duration of treatment with the drug will be from weeks to months or longer.
- E. The most serious of the known adverse events are death, respiratory depression, CNS depression and addiction. Oxymorphone has also been associated with severe hypotension, gastrointestinal tract reactions such as nausea, vomiting and diminutive effects on the propulsive peristaltic waves, and the known potential to elevate intracranial pressure and biliary tract pressure. Patients must not consume alcoholic beverages or medication containing alcohol while taking (b) (4) as the co-ingestion of alcohol with (b) (4) may result in increased plasma levels and a potentially fatal overdose of oxymorphone.
- F. (b) (4) contains the active drug substance oxymorphone and is not a new molecular entity.

In addition, based on the clear risk of abuse, overdose and addiction associated with marketed potent opioid analgesics, and pursuant to 21 CFR Part 208, FDA has determined that (b) (4) an opioid analgesic, poses a serious and significant public health concern requiring the distribution of a Medication Guide, and elements to ensure safe use. The Medication Guide and elements to ensure safe use are necessary for patients' safe and effective use of (b) (4)

The elements of the REMS will be a Medication Guide, elements to ensure safe use, and a timetable for submission of assessments of the REMS.

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

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/s/

ELLEN W FIELDS
01/10/2011

BOB A RAPPAPORT
01/10/2011

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

DRISK INTERIM REMS REVIEW

Date: December 10, 2010

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

Through: Claudia Karwoski, Pharm.D, Director
Division of Risk Management (DRISK)

From: Megan Moncur, M.S.
Acting Team Leader, Risk Management Analyst (RMA)
DRISK

Review Team Marcia Britt, PhD,
Regulatory Health Specialist,
DRISK

Agnes Plante, BSN, RN
Consumer Safety Officer,
Office of Compliance Division of Risk Management and
Surveillance

Subject: Interim REMS Review **Comment Set # 1**

Drug Name (Established Name): Oxymorphone Hydrochloride, Extended-Release Tablets

Application Type/Number: NDA 201655

Applicant: Endo Pharmaceuticals

OSE RCM #: 2010-1527

1 INTRODUCTION

The purpose of this interim review is to provide recommendations on Endo's proposed REMS for Oxymorphone Hydrochloride (HCl) Extended-Release (ER) Tablets, submitted 07 July 2010. The review includes recommendations to the review division and letter-ready comments for the applicant.

2 MATERIALS REVIEWED OR REFERENCED

- Oxymorphone HCl ER proposed REMS and REMS Supporting Document, received July 07, 2010 (Seq. No. 0000), including:
 - Dear Healthcare Professional (DHCP) Letter,
 - Dear Pharmacist Letter,
 - Healthcare Professional (HCP) Training Guide
- Oxymorphone HCl ER proposed Prescribing Information and Medication Guide, received 27 October 2010 (Seq. No. 0012)
- OxyContin REMS (Initial Approval 04/2010; Most Recent Modification 11/2010) and Prescribing Information
- Exalgo REMS (Initial Approval 03/01/2010; Most Recent Modification 03/24/2010)

3 BACKGROUND

Oxymorphone HCl ER (NDA 20-1655) is an opioid agonist, developed for the relief of moderate to severe pain in patients requiring continuous around-the-clock opioid treatment for an extended period of time. It is formulated as a hard tablet designed to withstand crushing. In standardized studies, oxymorphone HCl ER was shown to resist crushing forces (b) (4); however the clinical significance of this property and the impact on abuse liability has not been established

This product contains the same drug substance found in immediate-release (IR; OPANA®, NDA 21-611) and extended-release (ER; OPANA® ER, NDA 21-610) oral formulations of oxymorphone HCl, which were both approved by the Food and Drug Administration (FDA) on June 22, 2006.

4 REMS SUMMARY

4.1 Required REMS

In pre-NDA meeting communications (teleconference, 06 April 2010), FDA confirmed for Endo that an interim REMS would be required, pending approval of the class-wide opioid REMS, to inform patients and providers about the potential for misuse, abuse, overdose, and addiction. Endo was informed that the REMS must include a Medication Guide and an element to assure safe use, prescriber training.

The applicant's proposed REMS, included in their 07 July 2010 NDA submission, was consistent with requirements conveyed.

5 RECOMMENDATIONS FOR THE REVIEW DIVISION

Please provide the following recommendations on the oxymorphone HCl ER REMS to the applicant as soon as possible. In addition to the recommendations in Section 5 below, the materials in Appendix A and Appendix B, which include our tracked changes, should be sent to the applicant.

Please copy DRISK on the communication sent to the applicant. If there are questions, concerns, or disagreement with our recommendations, please contact DRISK to discuss.

Please request that the applicant respond to these comments as soon as possible to facilitate further review in order to meet the action date for this NDA/BLA .

6 RECOMMENDATIONS FOR THE APPLICANT

The following comments are on the proposed REMS, appended materials and Supporting Document submitted to NDA 20-1655, on 07 July 2010. Please incorporate the changes and submit all revised materials within 1 week.

The comments provided are based on the draft Product Labeling. Your REMS document and all REMS materials will need to be updated to be consistent with the final agreed upon PI.

1. REMS Document

See **Appendix A** for tracked changes and clean versions of the REMS document.

2. Medication Guide

Specific comments on the content of the Medication Guide will be provided under separate cover.

3. Other REMS Materials

- a. Add an 'education confirmation' form to your REMS (see **Appendix A**, tracked changes version of the REMS).

The purpose of the form is to confirm and track HCPs' completion of the REMS training program, and confirm their understanding of the key safety messages. Instruct HCPs to complete the form and return it to you, Endo, after the HCP has reviewed the Training Guide. Inform HCPs that completion of the form will not affect their ability to prescribe oxymorphone HCl ER.

- b. Append screen shots of the REMS website to your REMS document. Since your REMS materials will be maintained on a website (as referenced in your REMS

document), the website has been included as part of the REMS (see **Appendix A**, tracked changes version of the REMS). Specific website recommendations are included below.

- i. We recommend a stand-alone, REMS-dedicated website.
 - ii. We recommend that you include a prominent link on the product website's homepage for REMS materials. We remind you that any component of a REMS proposal must be reviewed and approved by the FDA, including any post-approval modifications. Because of this requirement, we recommend creating a single-click, prominent direct link off the main website that includes REMS-specific materials. This link will direct users to a separate webpage that describes the REMS program and lists only approved REMS materials. The REMS-related webpage(s) should not be a means to promote oxymorphone HCl ER or any other Endo product. Only the separate webpage(s) and /or link will be considered a component of the REMS.
 - iii. The landing page of the separate REMS link should contain background information on the REMS, as well as safety information, the REMS goals, along with links to the REMS materials.
 - iv. This page should include a prominent header to communicate the risks associated with oxymorphone HCl ER and addressed through the REMS.
- c. Revisions were made to the following documents:
- Dear Healthcare Professional Letter
 - Dear Pharmacist Letter
 - TRADEMARK Healthcare Professional Training Guide
- See **Appendix B** for tracked changes versions of these documents

4. Supporting Document

Revise the REMS Supporting Document to be consistent with all changes made to the REMS document.

5. Re-submission Requirements and Instructions

- a. Submit the revised proposed REMS with all appended materials and the REMS Supporting Document.
- b. Formatting requirements:
 - i. Provide a WORD document with tracked changes and a clean WORD version of all revised materials and documents.
 - ii. Submit the REMS and the REMS Supporting Document as two separate WORD documents. It is preferable that the entire REMS document and attached materials be in a single WORD document.
 - iii. Date and paginate all REMS documents, to facilitate review and document control.

APPENDICES

Appendix A: Tracked changes and clean versions of the REMS

Appendix B: Redline versions of REMS Materials

- DHCP Letter
- Dear Pharmacist Letter
- TRADEMARK Healthcare Professional (HCP) Training Guide

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/s/

MEGAN M MONCUR
12/09/2010

CLAUDIA B KARWOSKI
12/09/2010
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