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RESEARCH**

APPLICATION NUMBER:
201655Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	30 November 2011
From	Ellen Fields, M.D., M.P.H.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	201655 Second Review Cycle, Response to CR Action
Applicant	Endo Pharmaceuticals
Date of Submission	13 June 2011
PDUFA Goal Date	13 December 2011
Proprietary Name / Established (USAN) names	Opana ER/ Oxymorphone HCl extended-release tablets
Dosage forms / Strength	Extended-release tablets/ 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg
Proposed Indication(s)	The relief of moderate-to-severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.
Recommended:	Approval

Material Reviewed/Consulted	
OND Action Package, including:	
CMC	Craig Bertha, Ph.D., Prasad Peri, Ph.D.
Clinical Pharmacology	Srikanth Nallani, Ph.D., Yun Xu, Ph.D.
DDMAC	Pending
Controlled Substance Staff	Silvia Calderon, Ph.D., Michael Klein, Ph.D.
OSI	Arindam Dasgupta, Ph.D., Xikui Chen, Ph.D., Sam Haider, Ph.D.
OSE/DMEPA	Jibril Abdus-Samad, Pharm.D., Kellie Taylor, MPH, Carol Holquist, RPh.
OSE/DRISK (patient labeling)	Steve Morin, R.N., B.S.N., O.C.N., LaShawn Griffiths, MSHS-PH, BNS, RN
OSE/DRISK (REMS)	Megan Moncur, M.S., Danielle Smith, Pharm.D., M.S., Claudia Karwoski, Pharm.D.
Project Management	Lisa Basham, M.S., Parinda Jani

1. Introduction and Background

In accordance with 21 CFR 314 and Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act, Endo Pharmaceuticals Inc. submitted an Original New Drug Application for oxymorphone hydrochloride extended-release tablets as a 505(b)(1) application on July 7, 2010. A Complete Response (CR) Action Letter was issued on January 7, 2011. The current submission is a response to the CR action.

The Applicant intended to base approval on establishing bioequivalence to OPANA ER (NDA 21-610), which was approved by the Agency on June 22, 2006, and is owned by Endo. The

proposed product is to be dosed twice daily and will be available in the same dosage strengths as OPANA ER (5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg).

The CR letter noted the following clinical deficiency regarding the bioequivalence study that was to be the basis for approval for oxymorphone extended-release tablets:

“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 cannot be relied upon to establish bioequivalence of your proposed drug product to the reference product.

This deficiency may be addressed by doing one of the following:

- 1. Provided adequate samples are available, reanalyze blood samples collected in bioequivalence study EN3288-103 and submit data establishing the bioequivalence of Oxymorphone Hydrochloride Extended-Release 40 mg tablets with OPANA ER 40 mg tablets. Ensure that the inspectional findings identified in the Agency’s audit of study EN3288-103 are properly addressed in the reanalysis of blood samples.*

OR

- 2. Conduct another pharmacokinetic study and establish the bioequivalence of Oxymorphone Hydrochloride Extended-Release 40 mg tablets with OPANA ER 40 mg tablets under fasting conditions using adequately validated analytical methodology.*

OR

- 3. Conduct a clinical development program with clinical efficacy and safety studies to support your product.”*

The Applicant chose to address the above-noted deficiency by using back-up samples from study EN3288-103 for sample reassay. In the current submission, Endo submitted results of bioequivalence study (EN3288-103) after reanalysis of all plasma samples with stability data to address various discrepancies noted by the Office of Scientific Investigations’ audit in 2010. All plasma samples were reanalyzed for oxymorphone and 6-hydroxy (OH)-oxymorphone concentrations.

The nonclinical pharmacology/toxicology portion of this NDA submission was reviewed during the first cycle, and the reader is referred to the those reviews for additional information.

2. Chemistry, Manufacturing, and Controls

The primary CMC review during both review cycles was conducted by Craig Bertha, Ph.D., with secondary concurrence by Prasad Peri, Ph.D.

There were no CMC-related issues pending at the time of the Complete Response action in January, 2011. The resubmission of June 13, 2011, included updated stability data and a proposed extension of the expiration dating period for the drug product to 36 months, with storage at controlled room temperature. In addition, update drug product stability data were provided for a single batch of 5 and 40 mg strengths (b) (4)

(b) (4) The original application had contained stability data for both 60 and 100 count bottle presentations, but the labeling had only been presented for the latter. This resubmission included bottle labels for both the 60 and 100 count bottles.

The manufacturing facilities received an overall “Acceptable” cGMP recommendation from the Office of Compliance on November 15, 2010

The information submitted was found acceptable by Dr. Bertha, who recommended approval of OPANA ER from the CMC perspective.

3. Clinical Pharmacology/Biopharmaceutics

The primary clinical pharmacology review during both review cycles was conducted by Srikanth Nallani, Ph.D., with secondary concurrence by Suresh Doddapaneni, Ph.D. during the first cycle, and Xu Yun, Ph.D. during the current review cycle.

Dr. Nallani’s current review focuses on the reanalysis of samples from study EN3288-103: A bioequivalence study of 40 mg tablets in healthy subjects under a fasted state. Details regarding review of all clinical pharmacology data submitted during the first review cycle may be found in Dr. Nallani’s prior review, dated January 6, 2011.

Bioequivalence of EN3288 to OPANA ER was established with the highest dose, 40 mg. The table below from Dr. Nallani’s review of the reanalysis shows the results of the BE studies.

Table 3: Summary Table of BE reanalyses of EN3288 40 mg compared to Opana ER 40 mg

Parameter	EN3288 40 mg	OPANA ER 40 mg
AUC _{0-t} (ng•h/mL)	31.23±10.326 (33.1)	31.51± 10.945 (34.7)
AUC _{0-inf} (ng•h/mL)	32.65±10.920 (33.4)	32.99±11.580 (35.1)
C _{max} (ng/mL)	2.42±0.941 (38.9)	2.37±1.200 (50.6)
T _{max} (h) ^a	5.0 (0.5-12.0)	3.0 (0.5-12.0)
C _t (ng/mL)	0.090±0.0552 (61.5)	0.092±0.0609 (66.0)
λ _z (1/h)	0.0754±0.02232 (29.6)	0.0736±0.01776 (24.1)
t _{1/2} (h)	9.9±2.65 (26.9)	10.0±2.55 (25.5)

Source: Dr. Nallani’s review, p. 3

Additionally, the following table from Dr. Nallani’s review compares the results of Study EN3288-103 from the original analysis and the current reanalysis. The Geometric Least Square Mean ratios and their 90% CIs of AUC and C_{max} of oxymorphone, from the original analysis and reanalysis of plasma samples from the single oral 40 mg doses administered to fasted subjects are provided in the table below. As indicated, the new formulation of oxymorphone ER is bioequivalent to the previous formulation of OPANA ER under fasting conditions according to both the original and resubmission results.

Bioequivalence Analysis of Oxymorphone Pharmacokinetic Parameters After Single Oral Doses Administered to Fasted Healthy Subjects:

Comparison of Original Submission and Resubmission

Parameter	Ratio of Least Squares Means (A/B)		90% Confidence Interval of the Ratio	
	Original Submission	Resubmission	Original Submission	Resubmission
AUC _{0-t}	0.9900	0.9942	0.9458 - 1.0363	0.9477 - 1.0430
AUC _{0-inf}	0.9874	0.9930	0.9443 - 1.0326	0.9477 - 1.0406
C _{max}	1.0383	1.0513	0.9720 - 1.1092	0.9838 - 1.1235

Source: Dr. Nallani's review, p. 4

The Clinical Pharmacology team has concluded that the results of study EN3288-103 establishing bioequivalence of OPANA ER with the new formulation are acceptable.

4. Other Relevant Regulatory Issues

Office of Scientific Investigation (OSI) Consult

During the first review cycle, OSI, (previously called DSI) was consulted to inspect the study site that conducted Study EN288-103, 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.

The clinical portion of Study EN3288-103 was conducted at SeaView Research, Inc., Miami, FL. The analytical portion was conducted at (b)(4) While the inspection of the clinical site was found acceptable OSI had concerns about the reliability of the BE/BA data generated by (b)(4)

OSI concluded that:

OSI conducted a re-inspection

(b) (4)

Following the audit of the analytical records of the reanalyses, there were no significant adverse findings, and OSI concluded that sufficient corrective actions were implemented for the current study and recommended that the analytical data be accepted for Agency review.

Risk Evaluation and Mitigation Strategies

As an extended-release Schedule II opioid, a REMS is required for the approval of this product to inform patients and providers about the potential for misuse, abuse, overdose, and addiction. The current REMS requirements for drugs in the class are a Medication Guide, an element to assure safe use (prescriber training), and a Timetable for REMS assessments. Oxymorphone ER will become part of the class-wide, long-acting opioid REMS when it ultimately takes effect.

The Applicant submitted a proposed REMS, REMS Supporting Document, and REMS Website Draft Screen Shots on September 7, 2011, including a Dear Healthcare Professional Letter, a Dear Pharmacist Letter, a Healthcare Professional Training Guide, and an OPANA ER REMS Education Confirmation Form.

As stated in the DRISK review dated September 30, 2011:

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.

The DRISK Review Team found the proposed REMS and REMS materials for OPANA ER as submitted on September 7, 2011 to be acceptable pending verification of recommended revisions. The Applicant has subsequently made the appropriate changes to the REMS. The final REMS was submitted on November 21, 2011. See the DRISK reviews dated December 9, 2010, August 31, 2011, and September 30, 2011, and November 30, 2011 for details regarding the REMS review.

5. Labeling

The Office of Surveillance and Epidemiology (OSE), Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proprietary name OPANA ER, and found it acceptable for this product. (b) (4)

However, the Applicant now intends to replace the currently marketed formulation approved under NDA 21-610 with the new formulation in NDA 201655 and therefore, proposes to continue using the OPANA ER proprietary name per agreement with the Division during an Endo/FDA teleconference held January 5, 2011.

DMEPA reviewed the carton and container labels and provided comments for the Applicant regarding differentiation from the OPANA labels, which were adequately addressed.

The Medication Guide was reviewed by the DRISK patient labeling team who provided comments to the Applicant that have been adequately addressed.

DDMAC has reviewed the label and Medication Guide and have provided comments to the Applicant that have been adequately addressed.

Due to the marked food effect associated with OPANA ER the label will state that OPANA ER must be taken on an empty stomach, at least one hour prior to or two hours after eating.

As stated in their review from the original NDA submission dated 21 December 2010, CSS recommended that the label not include language asserting that OPANA ER provides resistance to crushing (b) (4)

The Division agrees with this, as has the Applicant. (b) (4)

(b) (4) since the extended-release characteristics of the formulation are compromised by cutting, chewing or grinding.

The label will also include instructions for the patient to take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth, due to concerns regarding the potential choking and sticking resulting from the PEO in the formulation.

6. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action Approval
- Risk Benefit Assessment (taken from original submission CDTL review dated December 22, 2010)

The Applicant developed an extended-release formulation of oxymorphone HCl (b) (4) is

NDA 201655

OPANA ER (oxymorphone ER)

intended to reduce accidental misuse and to deter certain methods of intended abuse. They planned to base the approval on establishing bioequivalence to Opana ER. The proposed product is intended to be dosed twice-daily and will be available in the same dosage strengths as OPANA ER (5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg), and have the same indication.

(b) (4) was shown to be bioequivalent to Opana ER in two Phase 1 studies that demonstrated bioequivalence of the 5mg and 40 mg doses. A biowaiver was granted for the intermediate doses based on dissolution profile comparisons.

Safety data was obtained from the pharmacokinetic studies, however since most of the subjects received naltrexone blockade, the data is of minimal use. However, no new safety signals compared to those labeled for Opana ER were detected. As the Applicant relied on the Agency's previous findings of safety and efficacy for Opana ER, and (b) (4) was shown to be bioequivalent to Opana ER, no additional safety or efficacy studies were required.

Reviews of the (b) (4) abuse liability characteristics of (b) (4) by the clinical pharmacology team and the Controlled Substance Staff showed that although (b) (4) appears resistant (b) (4) the extended-release characteristics of the formulation are compromised by chewing, cutting and grinding. (b) (4)

There is a potential safety concern regarding the polyethylene oxide (PEO) in the formulation. Postmarketing adverse events that include choking and sticking have been observed with another extended-release opioid that contains PEO. These events were not observed during the development of (b) (4) however the tablets were taken under controlled conditions. The Division has determined that if the label includes patient instructions to take the tablets one at a time with sufficient water, and a postmarketing requirement of enhanced pharmacovigilance is put in place, this safety issue will not preclude approval.

A Complete Response action was taken on January 7, 2011, due to the deficiencies noted at the analytic site for the bioequivalence study that was the key factor in determining approval.

NDA 201655

OPANA ER (oxymorphone ER)

The Applicant conducted a reanalysis of the plasma samples at the site following correction of the deficiencies, and an inspection by DSI confirmed that the results of the reanalysis were acceptable for review by the Division. These results confirmed that the new formulation of OPANA ER is bioequivalent to the original formulation.

Therefore, the benefits of OPANA ER outweigh the risks at this time, with inclusion of the REMS as part of the approval.

Although there have been reports of choking and tablets sticking in the gastrointestinal tract in patients taking a different opioid product that contains polyethylene oxide (PEO), there have been none reported for OPANA ER. At this time, the Division has determined that enhanced reporting of adverse events related to the GI tract will be sufficient to monitor this potential problem. If over time, there are reports of adverse events possibly related to PEO in the formulation, additional actions may be taken. The following language will be included in the Approval letter:

“In addition to the standard reporting requirements for an approved NDA, we request that you submit as 15-day expedited reports, all post-marketing and clinical trial cases of choking, gagging, sticking, and gastrointestinal obstruction, regardless of whether these reports are classified as serious or unexpected, and that you provide analyses of clinical trial and postmarketing reports of these adverse events of special interest in your periodic safety update reports.”

- Recommendation for Postmarketing Risk Management Activities

As an extended-release opioid, a REMS is required for approval. The REMS must include a Medication Guide, an element to assure safe use (prescriber training), and a Timetable for Assessments. The Applicant has submitted a proposed REMS including the required elements, and the Division and DRISK have agreed that the REMS is acceptable with inclusion of the modifications put forth by DRISK. When the opioid class REMS is finalized, it will replace the REMS being approved with this application.

- Recommendation for other Postmarketing Study Commitments

None

- Recommended Comments to Applicant

None

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/s/

ELLEN W FIELDS
11/30/2011