CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201655Orig1s000

SUMMARY REVIEW

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

Summary Review for Regulatory Action

Date	December 9, 2011
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia and Addiction Products
Subject	Division Director Summary Review
NDA #	201655
Applicant Name	Endo Pharmaceuticals
Date of Submission	June 13, 2011
PDUFA Goal Date	December 13, 2011
Proprietary Name / Established (USAN) Name	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	For the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
CDTL	Ellen Fields, M.D., M.P.H.
CMC	Craig Bertha, Ph.D., Prasad Peri, Ph.D.
Clinical Pharmacology	Srikanth Nallani, Ph.D., Yun Xu, Ph.D.
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

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
OSI=Office of Scientific Investigations (previously known as the Division of Scientific Investigations or DSI)

1. Introduction

Endo Pharmaceuticals has submitted this application for a reformulated version of their approved oxymorphone ER product, Opana ER. This new formulation, developed with their partner Grünenthal GmbH, was intended to (b) (4) reduce accidental misuse and deter certain specific methods of abuse. The support for the efficacy and safety of this new product was intended to be based entirely on bioequivalence to the previously approved product. The new formulation will be dosed on the same schedule as the old formulation and will be available in the same dosage strengths.

On January 7, 2011, a Complete Response (CR) Letter was issued for the original application of NDA 201655. The current submission is the Applicant's response to the CR Letter.

2. Background

The CR Letter defined a single deficiency that resulted in the Complete Response action and three possible methods of addressing this deficiency:

> 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 deficiency by assaying back-up samples from Study EN3288-103. The data from these assays form the basis for this submission. My detailed first-cycle review and summary basis for the Complete Response action has been appended to this review. This review will only address the contents of the current submission and whether the Applicant has provided data to sufficiently address the deficiency noted above. The reader is referred to the Appendix and the primary and secondary reviews for additional detail and discussion of this application.

Of note, during the first cycle, the review team determined that the data submitted to support the (b) (4) (b) (4) (b) (4) While the new formulation has demonstrated a minimal improvement in resistance to tampering by crushing, thereby limiting the likelihood of abuse by crushing followed by ingestion, and by insufflation (snorting) to some degree, it can still be (b) (4) , cut (b) (4) rendering it readily abusable

by ingestion and intravenous injection, and possibly still by insufflation; although whether (b) (4) tablets can be snorted was not studied. Of more concern, when chewed (b) (4) the new formulation essentially dose dumps like an immediate-release formulation. While the label and MedGuide could certainly carry warnings against chewing, we remain concerned that any language in the label (b) (4)

3. CMC

The following summary of the CMC information in the current submission has been reproduced from pages 2 and 3 of Dr. Fields' review:

> 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) . 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.

I concur with the review team that there are no outstanding CMC issues that would impact approvability.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology or toxicology data were submitted with this application.

5. Clinical Pharmacology/Biopharmaceutics

The following summary of the new clinical pharmacology data in this submission has been reproduced from pages 3 and 4 of Dr. Fields' review:

> 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 Cmax 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

	Ratio of Least Squares Means (A/B)		90% Confidence Interval of the Ratio	
Parameter	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. I concur with the review team.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

No efficacy studies were submitted in this application.

8. Safety

No new safety data were included in this submission.

9. Advisory Committee Meeting

This application was not taken to an advisory committee meeting as there were no unusual concerns regarding the efficacy or safety of this reformulated opioid product.

10. Pediatrics

Pediatric studies were not required for this application as a new formulation of an approved drug is not one of the types of applications requiring pediatric data under the Pediatric Research Equity Act.

11. Other Relevant Regulatory Issues

The following discussion of the OSI re-inspection has been reproduced from page 5 of Dr. Fields' review:

> OSI conducted a re-inspection of (b) (4) in order verify the corrective actions regarding the above concerns. Following the audit of the analyitical records of the reanalyses, there were no significant adverse findings, and OSI concluded that sufficient corrective actions were implemented for the current study (b) (4) and recommended that the analytical data be accepted for Agency review.

There were no clinical studies conducted in support of this application and, therefore, no financial disclosure was required.

12. Labeling

The following summary of the key labeling issues for this application has been reproduced from page 6 of Dr. Fields' review:

> 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)

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

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approval

- Risk Benefit Assessment

  The Applicant has addressed the single deficiency noted in the CR Letter issued to the original application. This new formulation of Opana ER has been determined to be bioequivalent to the old formulation and, therefore, the application may be approved with the agreed upon product labeling and REMS.

- Required Postmarketing Risk Evaluation and Mitigation Strategy

The following summary of the review team's assessment of the Applicant's proposed REMS has been reproduced from page 8 of Dr. Fields' review:

> 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.

14 has been withheld as a duplicate copy of the "Complete Response Summary Review" dated January 7, 2011 which is located in the "Medical Review" Section of this NDA approval package.

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

/s/

BOB A RAPPAPORT
12/09/2011