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 [redacted] tablets can be snorted was not studied. Of more concern, when chewed [redacted] 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 [redacted]

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 [redacted]. 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.

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