CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201655Orig1s000

MEDICAL REVIEW(S)

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

Summary Review for Regulatory Action

Date	January 7, 2011
From	Bob A. Rappaport, M.D. Director Division of Anesthesia and Analgesia Products
Subject	Division Director Summary Review
NDA #	201655
Applicant Name	Endo Pharmaceuticals
Date of Submission	July 7, 2010
PDUFA Goal Date	January 7, 2011
Proprietary Name / Established (USAN) Name	(b) (4) 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:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	
Clinical Review	N/A
Statistical Review (supporting CSS)	Ling Chen, Ph.D.; Stella Machado, Ph.D.
Preclinical Review	Elizabeth Bolan, Ph.D.; Dan Mellon, Ph.D.
CMC Review	Craig Bertha, Ph.D., Prasad Peri, Ph.D.
Microbiology Review	James McVey, Ph.D.; Steven Langille, Ph.D.
Clinical Pharmacology Review	Srikanth Nallani, Ph.D., Suresh Doddapaneni, Ph.D.
Biopharmaceutics	Sandra Suarez Sharp, Ph.D.; Patrick Marroum, Ph.D.
DSI	John Kadavil, Ph.D.; Sam Haider, Ph.D.; Martin Yau, Ph.D.
CDTL Review	Ellen Fields, M.D., M.P.H.
OSE/DMEPA	Tara Turner, Pharm.D.; Jibril Abdus-Samad, Pharm.D..; Todd Bridges, R.Ph.; Zachary Oleszczuk, Pharm.D.; Denise Toyer, Pharm.D.; Carol Holquist, R.Ph.
OSE/DRISK	Steve Morin, R.N., B.S.N., O.C.N.; Barbara Fuller, R.N., M.S.N., Sharon Mills, B.S.N., R.N., C.C.R.P.; Marcia Britt, Ph.D.; Agnes Plante, B.S.N., R.N.; Megan Moncur, M.S.; Claudia Karwoski, Pharm.D.
OSE/DEPI	Rajdeep Gill, Pharm.D.; Laura Governale, Pharm.D., M.B.A.
DDMAC	Twyla Thompson; Mathilda Fienkeng
Controlled Substance Staff	James Tolliver, Ph.D.; Silvia Calderon, Ph.D.; Michael Klein, Ph.D.

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

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, (b) (4) and to thereby reduce accidental misuse and deter certain specific methods of abuse. The support for the efficacy and safety of this new product is 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.

2. Background

Based on our experience with a number of different purportedly abuse-deterrent opioid analgesic products, some approved and others still in development, and on the comments and conclusions on this topic received from the members of a joint meeting of the Anesthetic and Life Support and Drug Safety and Risk Management Advisory Committees in October of last year, we have determined that any reasonable, well-documented, even incremental change in the formulation of an abusable opioid that will possibly deter misuse and abuse is a positive step in dealing with the public health crisis of prescription opioid abuse in the United States. Both the members of the advisory committee and the Agency have also concluded that the available databases for determining whether these products actually reduce abuse in the community are inadequate to track changes over time at this point (b) (4) However, in order to provide as much information as possible regarding the advantages of these products to prescribers and patients, the labels will incorporate language describing (b) (4) of the new formulation and the routes of abuse that they are intended to deter.

Endo's product has demonstrated a minimal improvement in resistance to tampering by crushing, thereby limiting the likelihood of abuse by ingestion and by insufflation (snorting) to some degree. (b) (4) cut (b) (4) (b) (4) rendering it readily abusable by ingestion and intravenous injection, and possibly still by insufflation, although they have not tested whether the (b) (4) tablets can be snorted. Of more concern, when chewed (b) (4) (b) (4), the new formulation essentially dose dumps like an immediate-release formulation. While the label and MedGuide would certainly carry warnings against chewing, some concern exists that any language in the label noting the reduced crushability of this formulation could be misleading and result in health care practitioners or patients thinking that it is safer than the old formulation, and that it is safe to chew the product; or that it is safe to give the new product to a cognitively impaired patient who may chew the product if not adequately supervised.

This application's basis for establishing the safety and efficacy of the new formulation is entirely dependent upon two bioequivalence (BE) studies comparing the new and old formulations. Based on an inspection of the CRO site that performed those studies, the Division of Scientific Investigation (DSI) has determined that there were significant procedural flaws in the performance of Study EN3288-103 and they have recommended that the study not be accepted for use in this application. Study EN3288-103 evaluated the 40 mg strength tablets of (b) (4) compared to the 40 mg strength tablets of Opana ER in normal volunteers under fasting conditions and naltrexone blockade. DSI issued a 483 to the CRO on December 9, 2010, and DSI completed their review and final recommendations to the Division on December 20, 2010. Endo was notified of this finding by the division via teleconference on

December 27, 2010, and a Discipline Review Letter was sent to the sponsor on December 28, 2010, documenting these concerns and their possible impact on approvability. The CRO sent in a response to the 483 comments on December 29, 2010, and the response has been reviewed by DSI. Based on that review, DSI has maintained their recommendation to the division that we not use Study EN3288-103 in our assessment of the application's approvability. While Study EN3288-105, a BE study of the 5 mg tablets, also demonstrated bioequivalence to the old formulation, the Office of Clinical Pharmacology cannot make a determination of bioequivalence for the higher strength tablets based on these findings as, in a BE study, the intent is to compare the formulations for rate and extent of drug absorption after release from a given type of formulation, and this is best done with the highest strength as, over a prolonged period of time, C_{max} and AUC can be acquired with due consideration for analytical methods, duration of sampling, and duration of formulation passage in the gastrointestinal tract. Often the lowest strength formulations have plasma levels detectable for a shorter period of time, depending on the sensitivity of the analytical method.

In addition, the DSI findings raise systemic concerns about the studies performed at the CRO in question.

3. CMC

The following has been reproduced from page 8 of Dr. Bertha's review:

> For manufacturing, the formulation components are [redacted] (b) (4)

I concur with the CMC review team that there are no outstanding issues that would impact approvability. The Office of Compliance issued an overall recommendation of Acceptable in regard to the facilities inspections on November 15, 2010.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology or toxicology data was submitted with this application. The excipients used in the new formulation have either been used in approved products or have been found to be acceptable by the review team. I concur with the pharmacology/toxicology review team that there are no outstanding issues that would impact approvability.

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