CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-272

SUMMARY REVIEW

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

Summary Review for Regulatory Action

Date	April 5, 2010
From	Bob A. Rappaport, M.D. Director Division of Anesthesia and Analgesia Products
Subject	Division Director Summary Review
NDA #	22-272
Applicant Name	Purdue Pharma, L.P.
Date of Submission	February 5, 2010 (Response to second CR letter)
PDUFA Goal Date	April 5, 2010
Proprietary Name / Established (USAN) Name	OxyContin® Tablets Oxycodone hydrochloride controlled-release
Dosage Forms / Strength	Extended-release tablets 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg
Proposed Indication	For the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Jin Chen, M.D., Ph.D.
Statistical Review	(CMC only) Meiyu Shen, Ph.D.; Yi Tsong, Ph.D.; Stella Machado, Ph.D.
Pharmacology Toxicology Review	Elizabeth A. Bolan, Ph.D.; R. Daniel Mellon, Ph.D.
CMC Review	Craig M. Bertha, Ph.D.; Danae D. Christodoulou, Ph.D.; Ali Al-Hakim, Ph.D.; Prasad Peri, Ph.D.
Microbiology Review	N/A
Clinical Pharmacology Review	Sayed Al Habet, R.Ph., Ph.D.; Sheetal Agarwal, Ph.D.; Suresh Doddapaneni, Ph.D.
DDMAC	Michelle Safarik, PA-C; Mathilda Fienkeng, Pharm.D.; Twyla Thompson, Pharm.D.
DSI	Jacqueline A. O'Shaughnessy, Ph.D.; C.T. Viswanathan, Ph.D.
CDTL Review	Ellen Fields, M.D.; Sharon Hertz, M.D.
CSS	James Tolliver, Ph.D.; Silvia Calderon, Ph.D.; Michael Klein, Ph.D.
OSE/DMEPA	Loretta Holmes, B.S.N., Pharm.D.; Linda Kim-Jung, Pharm.D.; Kristina Arnwine, Pharm.D.; Denise Toyer, Pharm.D.; Carol Holquist, R.Ph.
OSE/DPVII	Afrouz Nayernama, Pharm.D.
OSE/DRISK	Mary Dempsey; Jeane Perla, Ph.D.; Gita Toyserkani, Pharm.D.; Mary Willy, Ph.D.; Marcia Britt, Pharm.D.; Sharon Mills, B.S.N., R.N., C.C.R.P., Jodie Duckhorn, M.A.; Henry Francis, M.D.; Gerald Dal Pan, M.D.
DEPI	N/A
SEALD	Jeanne Delasko, RN, MS; Laurie Burke, R.Ph, M.P.H
Maternal Health Team	Richardae Araojo, Pharm.D.; Karen Feibus, M.D., Lisa Mathis, M.D.
OC/DRMS	Suzanne Barone, Ph.D; Agnes Plante, B.S.N, R.N.
Administrative Reviews/Letters	Lisa Basham, M.S.; Parinda Jani

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEDP=Division of Medication Error Prevention
DSI=Division of Scientific Investigations
DRISK= Division of Risk Management
DPVII=Division of Pharmacovigilance II
CDTL=Cross-Discipline Team Leader
DEPI= Division of Epidemiology
CSS=Controlled Substance Staff
SEALD=Study Endpoints and Labeling Development Team
OC=Office of Compliance
DRMS=Division of Risk Management and Surveillance

1. Introduction

On November 29, 2007, Purdue Pharma, L.P. submitted a new drug application for their reformulated OxyContin tablets. This reformulation was undertaken to create tablets with controlled-release features that would be less easily compromised by tampering. The sponsor submitted data from a number of studies to support the new formulation's capacity to resist compromise of the controlled-release features. Based on our review of that application and the discussion of the application by a combined meeting of the Anesthetics and Life Support and the Drug Safety and Risk Management Advisory Committees on May 5, 2008, the sponsor received a Complete Response (CR) letter. A complete discussion of the deficiencies that were included in that CR letter may be found in my review of the original application which has been appended to this review. That review and my subsequent review dated December 30, 2009, (also appended to this review) provide a complete summary of all of the details pertaining to the original application and the resubmission which is discussed in the following paragraphs.

The response to the first CR letter, submitted by Purdue on March 30, 2009, provided adequate information to address all of the deficiencies with the exception of the requirement for a Risk Evaluation and Mitigation Strategy (REMS). On December 4, 2008, the Agency issued a letter to the sponsor informing them of our current efforts to develop an opioid REMS for the entire class of long-acting and extended-release opioid products and instructing them not to submit a REMS proposal until they received further guidance from the Agency. Therefore, a REMS proposal was not included in the sponsor's response to the Agency's October 3, 2008, CR letter. A REMS was submitted during the review cycle after additional advice was forwarded to the sponsor during the review cycle. However, the sponsor's revised REMS was not received until too late in the review cycle for adequate review. A second CR letter was issued on December 30, 2009 which listed the following deficiencies:

> Because the REMS was submitted so late in the review cycle, FDA is deferring its review of the REMS to the next cycle.

In addition, the following comments regarding the need for a post-marketing study were included in the letter:

> …FDA has determined that, if NDA 22272 is approved, you will be required pursuant to section 505(o)(3) of the FDCA to conduct the following:
>
> > An epidemiological study (or studies) to address whether the changes made to the OxyContin formulation that are the subject of this application result in a decrease in misuse and abuse, and their consequences: overdose, death and addiction.
>
> We acknowledge receipt of your proposals dated November 6 and December 16, 2009, containing your proposed brief outlines of possible postmarketing studies to fulfill this requirement. Because of design and feasibility challenges that we have noted in your proposal, we are concerned that the proposed studies will not successfully capture the necessary information that will allow us to assess the impact, if any, attributable to the change in the OxyContin formulation. Therefore, additional information concerning the methodology and feasibility of the proposed potential

studies, and possibly the addition of other studies, will be needed before agreement can be reached on the design of the postmarketing epidemiology study (or studies) that will assess the risks of reformulated OxyContin.

It will be necessary for you to complete methodology and feasibility assessments for the proposed studies. In addition, you should consider other potential outcome models for use in studying the risks associated with OxyContin, including but not limited to: accidental overdose in patients, medication errors resulting in adverse events involving the actions of healthcare providers or caregivers, unintentional overdose and/or poisoning in children, accidental overdose in recreational abusers, accidental overdose in experienced abusers, and patterns of abuse.

Our interactions with the sponsor regarding their resubmission and their proposed REMS are discussed in more detail below in Section 2.

2. Background

On June 17, 2009, during the second review cycle for this application, the Agency issued a REMS Notification Letter instructing the sponsor to submit a REMS proposal that included a Medication Guide, a Communication Plan, and a Timetable for Submission of Assessments. In response, the Sponsor submitted a REMS proposal on July 24, 2009. The REMS content was under negotiation and the sponsor submitted a REMS amendment to incorporate Agency changes on September 18, 2009. Due to the timing of this submission, the PDUFA review clock was extended by three months, providing for a new PDUFA date of December 30, 2009. Upon finalization of the review of the REMS proposal, the Agency determined that the REMS requirements would be changed to include a Medication Guide, an Element to Assure Safe Use, specifically, healthcare provider training under 505-1(f)(3)(A), and a Timetable for Submission of Assessments, and issued a letter informing the sponsor of the change on December 11, 2009. The sponsor submitted their new REMS in response to this request on December 22, 2009, within a week of the action due date. With inadequate time for a thorough review of this new REMS, a CR action was taken on December 30, 2009. The sponsor submitted their revised REMS on February 5, 2010, as a response to our second CR letter. The revised REMS has been thoroughly reviewed by the clinical review team and the DRISK review staff and has been found to be acceptable to serve as the interim REMS for this product until the class-wide opioid REMS has been finalized (see discussion of “interim” and “class-wide” opioid REMS in my appended review).

3. CMC

See my previous reviews for a summary of the CMC data. I concur with the CMC review team that no additional data is necessary for approval.

4. Nonclinical Pharmacology/Toxicology

See my previous reviews for a summary of the pharmacology/toxicology data. I concur with the review team that no additional pharmacology or toxicology data is necessary for approval.

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