

**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.

5. Clinical Pharmacology/Biopharmaceutics

While there were no clinical pharmacology or biopharmaceutics deficiencies noted in the second CR letter, additional information regarding potential drug-drug interactions that could affect patients taking OxyContin became available in the medical literature during this review cycle. The following language was added to the product label by the review team and its inclusion was agreed to by the sponsor:

CYP450 inducers, such as rifampin, carbamazepine, and phenytoin, may induce the metabolism of oxycodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone. A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone (oral) AUC and C_{max} by 86% and 63%, respectively. If co-administration with OxyContin is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP3A4 inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved.

I concur with the clinical team that no additional clinical pharmacology data are necessary to support approval

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

No new efficacy data was required for or submitted with this response.

8. Safety

No new safety data was required for this response. However, the sponsor did submit a safety update which was reviewed by Dr. Fields. A total of 277 healthy subjects received doses of the new formulation ranging from 5 mg to 80 mg, some with and some without naltrexone blockade. The adverse event profile was similar to that seen with the original formulation with the most common adverse events being nausea, headache, dizziness and vomiting. There were no unexpected safety findings.

9. Advisory Committee Meeting

Discussion regarding the two advisory committee meetings held to discuss this application may be found in my earlier reviews for the CR actions.

10. Pediatrics

Pediatric data was not submitted in this application and the application does not fall under the authority granted to FDA by PREA.

11. Other Relevant Regulatory Issues

Discussion regarding additional regulatory issues related to the abuse liability of OxyContin and this new formulation may found in my two earlier reviews for the CR actions.

12. Labeling

Final labeling, including the package insert, Medication Guide and package and container labels, has been agreed upon by both the review team and the sponsor.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action
Approval
- Risk Benefit Assessment

As stated in my review of December 30, 2009:

I concur with the review team and the advisory committee members that the sponsor has provided adequate data to demonstrate that their reformulated OxyContin product will potentially be more tamper-resistant based on changes to the controlled-release formulation, less likely to result in overdose when tampered with and ingested, and less likely to be insufflatable or syringeable/injectable. While this certainly does not solve the many problems associated with the misuse and abuse of OxyContin, it is an important incremental change. However, to fully support this approval, I again agree with the review team and the advisory committee members that the sponsor should be required to perform a post-marketing study to assess the impact of the new formulation in the community. This study should be undertaken as a Post-Marketing Requirement under the authorities granted the Agency in the Food and Drugs Administration Amendments Act.

The sponsor has now provided an acceptable interim REMS and, therefore, there are no further impediments to approving this application. It is important to add, however, that all communications regarding this new formulation of OxyContin must include the following key points:

- The changes to the OxyContin formulation appear to provide some degree of increased resistance to manipulation of the controlled-release features making the new product less easy to

chew, crush or dissolve. These incremental improvements in the formulation will, hopefully, reduce the incidence of overdose due to abuse and misuse by ingestion or administration (e.g., via a nasogastric tube) of crushed or chewed OxyContin, which, due to the manipulation, would act as an immediate-release, high-dose oxycodone formulation. The formulation changes will also likely reduce overdose and abuse associated with insufflation or parenteral injection.

- Nevertheless, the product is not completely tamper-resistant and those intent on abusing this new formulation will likely find a means to do so.
 - In addition, the product can still be misused or abused and result in overdose by simply administering or ingesting larger than recommended oral doses.
 - The REMS approved for this product will, hopefully, mitigate to some degree the continued risks associated with OxyContin.
 - While the improvements in tamper resistance produced by this new formulation will not provide a completely safe version of OxyContin, even incremental changes that increase the product's resistance to tampering may reduce the misuse and abuse of OxyContin to some degree. The sponsor's required post-marketing epidemiological study should help us determine whether this actually happens when the new formulation becomes the only one available on the market.
- Required Postmarketing Studies

With the February 5, 2010 resubmission, the sponsor submitted seven study proposals to address the requirement for a post-marketing epidemiological study to assess the impact of the new OxyContin formulation on abuse and misuse, but the review team felt that, even on face, these proposed studies would be unlikely to provide the necessary data for this assessment. We plan to have ongoing discussions with the sponsor regarding the design of this study(ies) and to have a public discussion of the final proposed study design at an advisory committee meeting. The following language has been included in the approval letter:

We acknowledge receipt of your proposal, included in your February 5, 2010, resubmission to this application, that contains brief descriptions of possible postmarketing studies to fulfill this requirement. Because of design and methodology challenges, we continue to be 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

(Oxycodone Hydrochloride Controlled-Release) Tablets formulation. Therefore, we will continue discussion of your postmarketing study proposals at an advisory committee meeting in the fall of 2010 on the design and methodology of the proposed studies.

For the study to be conducted first, you must submit the final protocol and the timetable for completion of the study by January 31, 2011. Likewise, for the study to be conducted last, you must submit the final protocol and timetable for completion of the study by March 1, 2011.

- Required Postmarketing Risk Evaluation and Mitigation Strategy

A final REMS, including a MedGuide, required prescriber educational materials and a timetable for submission of assessments was submitted during this cycle and has been reviewed by the clinical review team and the DRISK review team. The following comments on this plan have been reproduced from page 9 of Dr. Perla's review:

The REMS Supporting Document outlines the information that the Sponsor will use to assess the effectiveness of the REMS in meeting the goals. The Sponsor did not submit the patient and prescriber survey instruments or methodologies; however, this information does not need to be submitted for FDA review prior to approval of the REMS. The DR letter of March 18, 2010 indicated that the Sponsor must submit for review the detailed plans that will be used to evaluate patients', prescribers', and pharmacists' understanding about the risks associated with and safe use of OxyContin[®] at least 90 days before the evaluation will be conducted. Please convey to the Sponsor that a pharmacist survey will not be necessary...

Based on our current understanding of the risks of OxyContin[®], DRISK believes that a REMS comprised of these components is appropriate until a class-wide opioid REMS is established.

A summary of the prescriber education program, submitted as an Element to Assure Safe Use, has been reproduced from pages 5 through 7 of Dr. Perla's review:

3.2.3. Elements to Assure Safe Use

1. Healthcare providers who prescribe OxyContin[®] will receive training.
 - a. Purdue will ensure that training will be provided to healthcare providers who prescribe OxyContin[®]. To become trained, each prescriber will be provided with the OxyContin[®] Educational materials.

The Training includes the following:

- i) Proper patient selection;
- ii) Appropriate OxyContin[®] dosing and administration;

- iii) General principles of safe opioid use, including information about opioid abuse and how to identify patients who are at risk for addiction;
 - iv) Potential abuse, misuse, overdose and addiction from exposure to opioids, including OxyContin[®];
 - v) Risks of OxyContin[®], including:
 - 1. The risk of overdose caused by exposure to an essentially immediate-release form of oxycodone by consuming broken, chewed, crushed or dissolved OxyContin[®] tablets;
 - 2. The risk of addiction from exposure to OxyContin[®]; and
 - 3. The risk of overdose in patients who have not developed tolerance to the sedating or respiratory-depressant effects of opioids from exposure to a single dose of OxyContin greater than 40 mg;
 - vi) Information to counsel patients and caregivers on the need to store opioid analgesics safely out of reach of children and household acquaintances and the need to properly dispose of unused drugs when no longer needed by the patient; and
 - vii) Importance of providing each patient a Medication Guide with each prescription and instructing the patient to read the Medication Guide.
- b. Purdue will ensure that at least 3 weeks prior to first availability of OxyContin[®] to healthcare professionals, a Dear Healthcare Professional letter will be mailed to prescribers most experienced in treating chronic pain with opioid agonists, including pain specialists, psychiatrists, and primary care physicians. This letter is designed to convey and reinforce the risks of abuse, misuse, overdose and addiction of OxyContin[®] as well as the need to complete the OxyContin[®] REMS Educational Program. This letter will be available on the Purdue website (www.OxyContinrems.com) for 1 year from the date of mailing.
- c. The mailings will include the following OxyContin[®] REMS Educational Program materials:
- i) OxyContin[®] Medication Guide
 - ii) Prescribing OxyContin[®] Tablets CII: A Guide for Healthcare Providers
 - iii) OxyContin[®] Education Confirmation Form
- d. Additional printed educational material will be available through field-force distribution and by calling the toll-free number at Purdue (1-888-726-7535).

- e. The educational material will also be available for download at www.OxyContinrems.com.
- f. Purdue will maintain a list of all prescribers who have completed the OxyContin[®] REMS Educational Program.

Prescribers will be re-trained every two years or following substantial changes to the OxyContin[®] REMS. Substantial changes may include changes in the OxyContin[®] Full Prescribing Information, OxyContin[®] Medication Guide, or OxyContin[®] REMS that require substantial modification of the educational materials.

The following materials are part of the REMS and are appended:

- o Dear Healthcare Professional Letter
- o Medication Guide
- o The Healthcare Provider Guide, “Prescribing OxyContin[®] Tablets CII: A Training Guide for Healthcare Providers”
- o OxyContin[®] Education Confirmation Form

FIRST AND SECOND REVIEWS RESULTING IN COMPLETE RESPONSE ACTIONS

2 Complete Response Summary Reviews (consisting of 26 pages) dated September 30, 2008 and December 30, 2009 from Bob Rappaport, M.D. has been removed immediately following this page and has been relocated to the Medical Review section of this NDA approval package.