

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-272

CROSS DISCIPLINE TEAM LEADER REVIEW



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

Review Date	April 5, 2010
From	Ellen Fields, M.D., M.P.H.
Subject	CDTL Review
NDA #	22-272
Applicant	Purdue Pharma
Date of Submission	February 5, 2010
PDUFA Goal Date	April 5, 2010
Proprietary Name/Established (USAN) names	Oxycontin/Controlled-Release Oxycodone
Dosage forms/Strength	Tablets 10, 15, 20, 30, 40, 60, and 80mg
Proposed Indication	For the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time
Recommendation	Approval

The focus of this review is the resubmission of NDA 22-272 submitted on February 5, 2010, by Purdue Pharma in reply to the Complete Response (CR) letter issued by the Agency on December 30, 2009. The deficiency noted in the CR letter was that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for the approval of Oxycontin, and although a REMS was submitted (on December 22, 2009), it was too late in the review cycle for adequate review, and another review cycle would be necessary. A brief summary of the regulatory history of the first two review cycles is below. For additional details the reader is referred to previously filed reviews.

Regulatory Background

NDA 22-272 for Purdue's reformulated Oxycontin tablets was initially submitted for review on November 29, 2007. According to the Applicant, the reformulation was undertaken to create tablets with controlled-release features that would be less easily compromised by tampering than the original formulation, and thereby result in a

reduction in abuse. The proposed indication was the same as the marketed Oxycontin formulation.

In accordance with section 505-1 of the FDCA, the Agency determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for OxyContin to ensure that the benefits of the drug outweigh the risks of abuse, misuse, and overdose. As the Agency is currently in the process of formulating a class-wide opioid REMS for all long-acting opioids, an “interim REMS” will be required for these products individually until the class-wide REMS is implemented.

The 2007 application included complete Chemistry, Manufacturing and Controls data, non-clinical studies, the results of a number of abuse-liability studies, and pharmacokinetic studies comparing the reformulated Oxycontin to the original formulation. This was the first submission to the Agency of an “abuse-resistant” opioid formulation, and was discussed at a joint public meeting of the Anesthesia and Life Support Drugs and the Drug Safety and Risk Management Advisory Committees on May 5, 2008. The application received a Complete Response decision on October 3, 2008, primarily because of the poor quality of the studies submitted to support the Applicant’s proposed labeling claims regarding tamper resistance, the lack of an adequate REMS to assure that the benefits of the product outweigh its risks, and the Applicant’s plan to market the 60 mg and 80 mg higher-strength tablets in the original formulation at the same time and with the same name that they marketed the lower-strength tablets in the new formulation.

The Applicant resubmitted NDA 22-272 in response to the October 3, 2008, CR letter on March 31, 2009. The submission included new detailed information on in vitro studies conducted to evaluate the tamper-resistant characteristics of the reformulated tablets, including the 60mg and 80mg strengths, with comparison to the tamper-resistant characteristics of the currently available Oxycontin.

A second joint Advisory Committee meeting was held to assess whether the studies performed by the Applicant were adequate to provide data on the abuse-deterrent characteristics of the reformulated Oxycontin product. The consensus of the committee was that the Applicant had provided adequate data. They also stated that the approval should be contingent upon a post-marketing requirement to perform an epidemiologic study to assess the impact of the reformulated Oxycontin on abuse and misuse in the community, as well as an adequate REMS. The PDUFA clock was extended from September 30, 2009, to December 30, 2009, because the Applicant submitted a REMS amendment on September 18, 2009, that represented a major amendment to the NDA.

Upon completion of the REMS proposal review, the Agency determined that a Medication Guide and Communication Plan will not be adequate to ensure adequate training of healthcare providers to address the labeled risks of Oxycontin, and to prevent the occurrence of serious adverse events associated with those risks. Therefore the REMS requirements would be changed to include a Medication Guide, 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 Applicant of this change on December 11, 2009. The Applicant 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, and review of the new REMS was planned to be conducted during our review of the Applicant's response to our December 30, 2009, Complete Response letter.

February 5, 2010 Resubmission

This submission contained the following items in response to the December 30, 2009 CR letter:

- Proposed REMS and REMS Supporting Document
- Proposed labeling
- Epidemiology Study Proposal
- Safety Update
- Inform Agency of

(b) (4)

REMS Submission

The requirements for the Oxycontin REMS as specified in the December 11, 2009, letter are as follows:

Based on our current understanding of the risks of OxyContin (oxycodone hydrochloride), we have determined that the REMS must include a Medication Guide, elements to assure safe use, specifically training for healthcare providers as described under 505-1(f)(3)(A), and a timetable for the submission of assessments of the REMS.

The Elements to Assure Safe Use must include, at a minimum, the following:

- 1) A plan to ensure that OxyContin (oxycodone hydrochloride) will only be prescribed by healthcare providers who have particular training under 505-1(f)(3)(A) about the information described below. At a minimum the plan shall require that:
 - (a) Healthcare providers are trained about:
 - (i) Proper patient selection
 - (ii) Appropriate product dosing and administration
 - (iii) General opioid use including information about opioid abuse and how to identify patients who are at risk for addiction
 - (iv) The risks of abuse, misuse, overdose, and addiction from exposure to opioids, including OxyContin (oxycodone hydrochloride)
 - (v) The risks of OxyContin (oxycodone hydrochloride) including:
 1. The risk of overdose caused by exposure to an essentially immediate-release form of oxycodone

- due to broken, chewed crushed or dissolved OxyContin (oxycodone hydrochloride)
 - 2. The risk of addiction from exposure to OxyContin (oxycodone hydrochloride)
 - 3. The risk of overdose with use of 60 mg dosages and above in non-opioid-tolerant individuals
 - (vi) Information to counsel patients on the need to store opioid analgesics safely out of reach of children and household acquaintances
 - (vii) The importance of providing each patient a Medication Guide with each prescription and instructing the patient to read it.
- (b) Healthcare providers will be retrained periodically, at a specified interval.

Information needed for assessment of the REMS may include but may not be limited to:

- a. An evaluation of patients' understanding of the serious risks of OxyContin (oxycodone hydrochloride).
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.
- d. A report on the status of the training program for healthcare providers.
- e. An evaluation of healthcare providers' awareness and understanding of the serious risks associated with OxyContin (oxycodone hydrochloride) (for example, through surveys of healthcare providers).
- f. Specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that healthcare provider awareness is not adequate.
- g. An analysis and summary of surveillance and monitoring activities for abuse, misuse and overdose, and any intervention taken resulting from signals of abuse, misuse and overdose.
- h. A claims study to evaluate OxyContin (oxycodone hydrochloride) utilization patterns including opioid-tolerant utilization patterns before and after implementation of the REMS.
- i. With respect to REMS goals, an assessment of the extent to which the elements to assure safe use are meeting the goals or whether the goals or such elements should be modified.

Each assessment must assess the extent to which the elements to assure safe use of your REMS are meeting the goals of your REMS and whether the goals or elements should be modified.

A Discipline Review Letter with REMS related comments based on review of the REMS submission of December 22, 2009, was sent to the Applicant on January 26, 2010.

On February 5, 2010, the Applicant submitted a proposed REMS that included a Medication Guide, Elements to Assure Safe Use (ETASU), and a Timetable for Submission of Assessments. The ETASU is training for healthcare providers who

prescribe Oxycontin, and the training addresses items (i) through (vii) above. Prescribers are to be re-trained very two years, and the target audience of the ETASU is healthcare providers who are likely prescribers of Oxycontin and selected healthcare professional associations for distribution to their members. Included in the REMS is a Healthcare Provider Guide, "Prescribing Oxycontin Tablets CII: A Training Guide for Healthcare Providers." The proposed Timetable for Submission of Assessments is six months and one year from the date that the REMS is approved, and annually thereafter.

The REMS has been reviewed by the Office of Safety and Epidemiology, Division of Risk Management, and the Division, and a second set of comments was sent to the Applicant on March 17, 2010 in order to bring the contents of the REMS into compliance with the requirements conveyed to the Applicant. The Applicant responded to these comments acceptably on DATE, and a final REMS has been agreed upon that satisfies the Agency's requirements.

Labeling

The name of the product will continue to be Oxycontin/oxycodone hydrochloride controlled-release tablets. Labeling changes to the current label are minimal, and include updates in the preclinical and clinical pharmacology sections.

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 Applicant:

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 Cmax 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.

A Medication Guide is included in the labeling and will be part of the REMS. There will be no information in the label regarding the physicochemical attributes of the formulation or claims regarding tamper- or abuse-resistance.

Epidemiology Study Proposal

The Applicant submitted a proposal for the conduct of seven postmarketing studies to fulfill the requirement stated in the December 30, 2009, CR letter. The proposal consisted of brief descriptions of the studies that are intended to address the outcomes requested in the CR letter, and a tentative timeline. Because of design and methodology challenges associated with the conduct of these types of studies, the Agency continues to be concerned that the proposed studies will not successfully capture the necessary information that will allow an assessment of the impact, if any, attributable to the change in the OxyContin formulation. It is likely that this issue will be brought to an Advisory

Committee in order to determine whether the Applicant's proposal is adequate to assess whether the changes made to the OxyContin formulation that are the subject of this application and which are intended to provide deterrence of misuse and abuse actually result in a decrease in the risks of misuse and abuse, and their consequences, addiction, overdose and death.

Safety Update

The Applicant submitted a safety update containing data gathered after the March 31, 2009, resubmission for NDA 022272. A total of 277 healthy subjects received doses ranging from 5 mg through 80 mg, in either the fed or fasted state, with or without naltrexone blockade. The adverse event profiles were similar for both the reformulated OxyContin and OxyContin treatments. The most common treatment-emergent adverse events reported were those known to be associated with opioids such as nausea, headache, dizziness, and vomiting. There were no unexpected safety findings. Results of laboratory tests, vital signs measurements, and SpO2 evaluations raised no safety concerns for any of the study treatments. Overall, the safety profiles of the reformulated OxyContin® as well as OxyContin® were as expected for oxycodone administered to fasted and fed, healthy, adult subjects with or without naltrexone HCl blockade.

Recommendation for Regulatory Action

Approval

The Applicant has satisfactorily responded to the deficiencies communicated in the CR letter of December 30, 2009. As stated in my CDTL reviews from the first two cycles, the safety profile of the reformulated Oxycontin appears similar to that of the original formulation. The Applicant is planning to market all strengths as the reformulated Oxycontin, and will cease marketing of the original formulation.

Recommendation for Postmarketing Risk Management Activities

The Agency has made a determination that approval of extended-release opioids should not be delayed while the development of the class-wide REMS is in progress, as long as the safety profile of the drug is not worse than the currently marketed long-acting opioids. An interim REMS that meets the Agency's requirements has been agreed upon, and will be implemented upon approval of this product. Oxycontin will become part of the class-wide opioid REMS when it is in place.

Recommendation for other Postmarketing Study Requirements

The Applicant is required to perform an epidemiologic study to address whether the changes made to the Oxycontin formulation result in a decrease in misuse and abuse, and their consequences: overdose, death, and addiction.

Since this application does not trigger PREA, there are no pediatric postmarketing study requirements.

Comments to Sponsor

Because of design and methodology challenges associated with the conduct of these types of studies, the Agency continues to be concerned that the proposed studies will not

successfully capture the necessary information that will allow an assessment of the impact, if any, attributable to the change in the OxyContin formulation. Therefore we will continue discussion of your postmarketing study proposals and will plan to engage experts in the field for their advice on the design and methodology of the proposed studies.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22272

ORIG-1

PURDUE PHARMA
INC

OXYCONTIN

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

/s/

ELLEN W FIELDS

04/05/2010