# 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
10903 NEW HAMPSHIRE AVENUE, BLDG 22, SILVER SPRING, MARYLAND 20993

# CDTL Review

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| **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 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

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