CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-272

OTHER REVIEW(S)

MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 08-MAR-2010

TO: N 22272 File for OxyContin® (oxycodone hydrochloride controlled-release) Tablets

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division I, Branch II

THROUGH: Prasad Peri, Ph.D.
Acting Branch Chief
ONDQA, Division I, Branch II

SUBJECT: Review of CMC-related labeling revisions in the 24-FEB-2010, amendment of N22272

BACKGROUND: After review of the 04-FEB-2010, labeling amendment to N22272, the CMC team sent two comments to the applicant regarding the labeling. The 24-FEB-2010, amendment is a response to these comments and is the subject of this review.

EVALUATION:

Agency Comment 1
Revise the DESCRIPTION section of the labeling to state that the new OxyContin formulations (b) (4) **.**

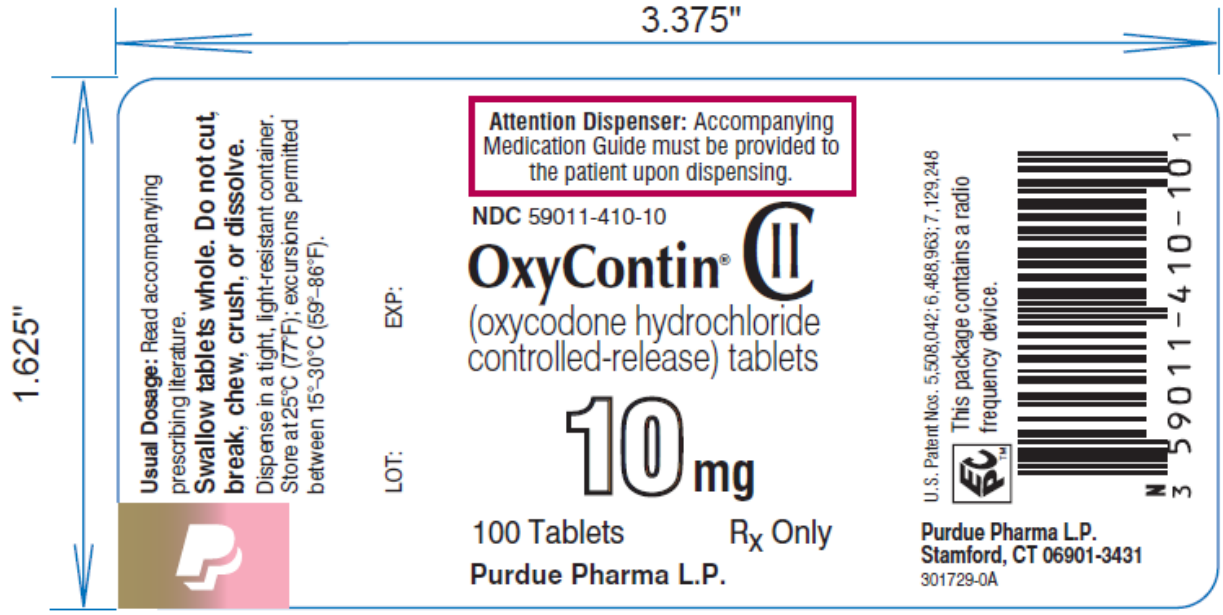
Summary of Applicant Response
The applicant has chosen the alternative and has removed the statement from the DESCRIPTION section altogether.

Evaluation: Adequate.

Agency Comment 2
For each strength of the drug product, revise and resubmit the mock-ups of the bottle labels such that it is clear where the lot number and expiration date will be located. Although the location had been clear in earlier versions of the bottle labels, it is not clear in the latest version supplied with the February 4, 2010, amendment.

Summary of Applicant Response

The location of the lot number and the expiration date are now clear on the labels. The label for the 10 mg strength is reproduced below as an example to illustrate the placement.



Evaluation: Adequate.

Recommendation

NAI. The CMC team has no further comments on the labels/labeling.

_____

Craig M. Bertha, Ph.D.
Chemistry Reviewer

cc:
Orig. NDA 22-272
C.Bertha/ONDQA//Reviewer/3/8/10
PPeri/ONDQA/Acting Branch Chief_____
DChristodoulou/ONDQA/PAL
LBasham/DAARP/Regulatory PM

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22272	ORIG-1	PURDUE PHARMA INC	OXYCONTIN

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/s/

CRAIG M BERTHA
03/08/2010

PRASAD PERI
03/08/2010
I concur

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	September 29, 2009
To:	Bob Rappaport, MD, Director Division of Anesthesia, Analgesia and Rheumatology Products
Through:	Kristina C. Arnwine, PharmD, Team Leader Denise P. Toyer, PharmD, Deputy Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Loretta Holmes, BSN, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Container Label Review
Drug Name:	OxyContin (Oxycodone Hydrochloride Controlled-Release) Tablets 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg
Application Type/Number:	NDA 22-272
Applicant:	Purdue Pharma L.P.
OSE RCM #:	2009-717

1 INTRODUCTION

This review is written in response to a request from the Division of Anesthesia, Analgesia and Rheumatology Products for assessment of the container labels for OxyContin (Oxycodone Hydrochloride Controlled-Release Tablets).

OxyContin (NDA 20-553) was approved on December 12, 1995. Due to abuse liability similar to morphine, the Applicant has submitted a new NDA. With this new NDA (NDA 22-272), the Applicant proposes a reformulated product that is bioequivalent to the currently marketed product but more resistant to manipulations that could damage or destroy the control of Oxycodone release as compared to the currently marketed product. The reformulated tablets will replace the currently marketed OxyContin tablets. Additionally, the new product will have a REMS and Medication Guide.

2 METHODS AND MATERIALS

2.1 LABEL AND LABELING RISK ASSESSMENT

DMEPA used Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels submitted as part of the November 30, 2007 and March 29, 2009 submissions (see Appendix B).

- Container Labels
    - 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 100-count bottles, (submitted on November 30, 2007)
    - 60 mg and 80 mg, 100-count bottles, (submitted on March 29, 2009)

2.2 AERS SELECTION OF MEDICATION ERROR CASES

Since OxyContin is a currently marketed product in the U.S., DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) for medication errors associated with its use. Errors associated with the use of OxyContin should be taken into consideration when reviewing the labels and labeling for this new NDA in order to prevent such errors from occurring with these proposed labels after they are introduced into the marketplace. DMEPA searched AERS using the High Level Terms "Maladministration" and "Medication Errors", and the trade name "OxyContin" (the active ingredient name "Oxycodone" was not included in the search). The search was conducted on August 19, 2009 and retrieved a total of 485 AERS cases. Our search was further narrowed by electronically searching these cases for narratives that contained one or more of the following terms: wrong strength, look-alike, similar, labels, container, confused, or instead.

The cases identified through this narrowed search were manually reviewed to determine if medication errors occurred involving the labels/labeling of OxyContin. Those cases that did not describe a medication error were excluded from further analysis. See Appendix A for the results of the AERS search.

3 RESULTS

DMEPA identified twenty-nine (n=29) medication error cases involving wrong drug (n=16), wrong strength (n=8), and wrong technique (n=5). See Appendix A.

3.1 WRONG DRUG

The sixteen wrong drug cases involved confusion with OxyContin and the following products Oxycodone (n=9), MS Contin (n=2), Roxicodone (n=1), Percocet (1), Lexapro (n=1), Cyclobenzaprine (n=1), and Oxytocin (n=1). The wrong drug medication error cases appear to be due primarily to name confusion, overlapping product characteristics and/or similarities between the physical appearance and/or the labels and labeling of OxyContin and some of the aforementioned products. The three cases involving Lexapro, Cyclobenzaprine and Oxytocin involved reports of potential confusion (Lexapro and Cyclobenzaprine) and selection errors when using a computerized physician order entry system where the physician chose Oxytocin instead of OxyContin. Thus these three cases will not be discussed further.

Eleven of the OxyContin wrong drug cases involve confusion with immediate-release Oxycodone products while two cases involved confusion between OxyContin and the extended-release morphine product MS Contin. Some cases did not report causality, however, in some cases reporters indicated that name similarity contributed to the wrong drug errors. These names all share the letters 'oxy,' 'codone' or 'contin' in their proprietary names and the established name "oxycodone" (except for MS Contin which contains morphine). Additionally, all of these products are indicated for the treatment of pain and have overlapping strengths and doses which compound the potential to confuse the names.

Although not stated as a contributing factor, Purdue Pharma markets both OxyContin and MS Contin and uses a similar trade dress for both product lines. However, the proposed container labels for the reformulated OxyContin product look different from those of the currently marketed OxyContin product which may decrease the potential for selection errors between these two products.

No regulatory action is indicated at this time. However, DMEPA will continue to monitor the wrong drug cases between OxyContin and the aforementioned drugs.

3.2 WRONG STRENGTH

We identified eight wrong strength cases involving confusion within the OxyContin product line. Our review of the container labels and tablet appearance indicate that the strength on the OxyContin labels is color-coded to match the color of the corresponding tablet strength. All of the colors are different. Although some of the colors may appear similar, the differences are more apparent when compared side-by-side. Additionally, the tablet strength is embossed on the tablet. However, one case indicated that the font size of the strength presentation is small and this was a contributing factor to the medication error. Thus, we will evaluate the prominence of the strength presentation on the container labels for the reformulated OxyContin product.

3.3 WRONG TECHNIQUE

The five wrong technique cases identified involved knowledge deficits with patients, healthcare providers, and family members. These cases involved circumstances where the tablets were crushed, chewed, or cut to improve administration (e.g., via PEG tube, inability to swallow) of the drug. It appears that the providers or patients were unaware that the product should be taken whole. The current insert labeling and container labels contain the appropriate warning

statements on this issue. However, we will evaluate the prominence of the statement on the container labels for the reformulated OxyContin product.

4 RECOMMENDATIONS

We note that the Applicant did not submit for review the unit dose packaging. We recommend that those labels and labeling be submitted for review. Our evaluation of the bulk bottles noted areas where information on the container labels can be improved to minimize the potential for medication errors. We provide our recommendations for the container labels in Section 4.1 *Comments to the Applicant*. We request the recommendations in Section 4.1 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Abolade Adeolu, at 301-796-4264.

4.1 COMMENTS TO THE APPLICANT

1. The 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg statements of strength are presented in a pastel color that matches the color of the respective tablet strength. Although the strength is outlined in black, the pastel colors are not prominent and make it difficult to clearly distinguish the differences between the colors. Make the colors bolder/deeper so that they are more easily distinguished from one another. Additionally, increase the size of the strength presentation.
2. Increase the prominence of the "Swallow tablets whole. Do not cut, ..." statement on the side panel of the container label.
3. The labels do not have a Medication Guide statement. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the bottle/carton:
    a. "Dispense the enclosed Medication Guide to each patient." or
    b. "Dispense the accompanying Medication Guide to each patient."
4. Container Label 60 mg Strength Only

    Both the 60 mg strength and the tablet picture are presented in (b) (4). This (b) (4) color is also used in the triangular box on the 80 mg label. Using the same (b) (4) color prominently on the labels for both strengths minimizes the differentiation between the two strengths. We recommend you use a different color for the triangular box on the 80 mg label. Ensure that this color is not used on any of the other container labels in order to better differentiate all of the strengths.

APPENDICES

Appendix A: AERS Search Results

Wrong Drug Cases

DMEPA identified sixteen (n=16) wrong drug cases. These cases are summarized in the chart below:

# of cases	Date Report Received	Drug Prescribed	Drug Dispensed or Administered	Causality
2	09/21/2007	OxyContin	Oxycodone	Disorganized medication cabinet; lack of double check by the pharmacist
	02/26/2008			Not stated
2	05/23/2003	Oxycodone	OxyContin	Not stated
	12/20/2004			Not stated
1	02/25/1999	MS Contin	OxyContin	Not stated
1	10/03/2002	OxyContin	MS Contin	Sound-alike names
1	10/09/2008	Oxycodone IR	OxyContin	Similar names, same strength
1	03/19/2003	Roxicodone	OxyContin	Similar names, packaging, pill size and color
1	11/07/2003	Percocet	OxyContin	Not stated
# of cases	**Date Report Received**	**General or Potential Confusion**		**Causality**
4	06/07/2001	General confusion between Oxycodone immediate-release and long-acting products		Not stated
	05/12/2003			Not stated
	05/12/2003			(3 errors reported). The first five letters of the sustained release brand (Oxyco) are identical to the first five letters of the generic name for both products.
	08/14/2003			Similarity of the names. The dosage form is rarely specified in an order and the drug is ordered by its generic name.
1	08/06/2003	Potential confusion between Lexapro 10 mg tablets and OxyContin 10 mg tablets		Similar appearance, the imprint "10" to represent the strength of 10 mg.
1	02/22/2006	Physician meant to select OxyContin from the CPOE program but mistakenly selected Oxytocin		Name similarity
1	08/20/2008	Potential confusion between OxyContin 40 mg and cyclobenzaprine 10 mg (Casdista brand)		Both used for pain management, sometimes prescribed together for treatment; similar size, shape, color

Wrong Strength Cases

DMEPA identified eight (n=8) cases in which the wrong strength of OxyContin was dispensed. These cases are summarized in the chart below:

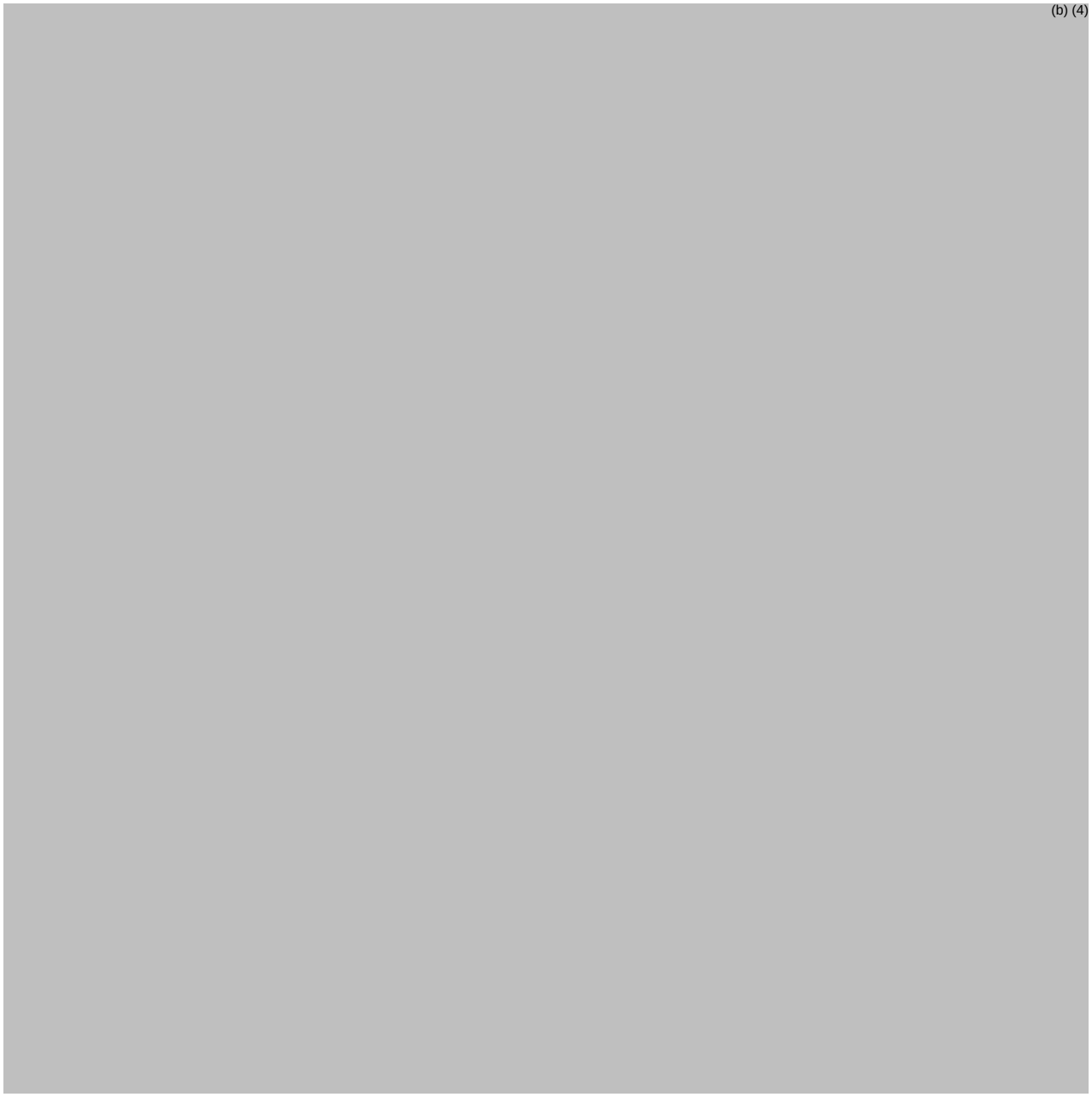
# of cases	Date Report Received	Strength Prescribed	Strength Dispensed or Administered	Causality
3	12/31/2001	OxyContin 10 mg	OxyContin 20 mg	Not stated
	06/12/2002			"Not familiar with product color of tablet or label on stock bottle"
	05/25/2004			Not stated
1	03/26/2001	OxyContin 10 mg and 20 mg tablets confused		Same size, white color
1	06/12/2001	OxyContin 10 mg	OxyContin 40 mg	Not stated
1	03/19/2003	OxyContin 10 mg	OxyContin 80 mg	Identical except for strength which is in a small font
1	01/06/2004	OxyContin 20 mg	OxyContin 80 mg	Not stated
1	01/03/2006	OxyContin 40 mg	OxyContin 80 mg	Not stated

Wrong Technique Cases

DMEPA identified five (n=5) cases in which OxyContin was administered by the wrong technique. These cases are summarized in the chart below:

# of cases	Date Report Received	Technique Used	Causality
2	04/19/2000	OxyContin crushed	OxyContin was ordered. Patient had a PEG tube. No suffix like XR, SR, CD etc. in the name to identify the product as a controlled-release product.
	11/18/2004		Patient's sister crushed the OxyContin and mixed with applesauce because of the patient's declining ability to swallow.
2	04/22/2003	OxyContin chewed	Confusion due to disease state.
	10/29/2003		Accidental. Patient thought he was chewing a different tablet.
1	02/22/2006	OxyContin cut	Patient cut tablets in order to make the medication last longer.

Appendix B Container Labels



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/s/

LORETTA HOLMES
09/29/2009

KRISTINA C ARNWINE
09/29/2009

DENISE P TOYER
09/29/2009

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 31, 2009
To:	Bob A. Rappaport, MD, Division Director
	Division of Anesthesia, Analgesia, and Rheumatology Products
Through:	Jodi Duckhorn, MA, Team Leader
	Division of Risk Management
From:	Sharon R. Mills, BSN, RN, CCRP
	Patient Labeling Reviewer
	Division of Risk Management
Subject:	DRISK Review of Patient Labeling (Medication Guide)
Drug Name(s):	OxyContin (oxycodone hydrochloride controlled-release) Tablets
Application Type/Number:	NDA 22-272
Applicant/sponsor:	Purdue Pharma L.P.
OSE RCM #:	2009-788

1 INTRODUCTION

This review is written in response to a request by the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for OxyContin (oxycodone hydrochloride controlled-release). Please let us know if DAARP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant. The proposed REMS is being reviewed by DRISK and will be provided to DAARP under separate cover.

2 MATERIAL REVIEWED

- Draft OxyContin (oxycodone hyrdrochloride controlled-release) Tablets Prescribing Information (PI) submitted March 30, 2009, revised by the Review Division throughout the current review cycle, and provided to DRISK on August 7, 2009.
- Draft OxyContin (oxycodone hyrdrochloride controlled-release) Tablets Medication Guide (MG) submitted on July 27, 2009.

3 RESULTS OF REVIEW

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- rearranged information due to PLR formatting
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
09/01/2009

JODI M DUCKHORN
09/02/2009

SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 22-272
APPLICANT	Purdue Pharma
DRUG NAME	OxyContin (oxycodone hydrochloride controlled-release)
SUBMISSION DATE	March 31, 2009
SEALD REVIEW DATE	August 13, 2009
SEALD REVIEWER(S)	Jeanne M. Delasko, RN, MS

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/s/

JEANNE M DELASKO
08/14/2009
SEALD comments sent to DARRP 8/13/09

LAURIE B BURKE
08/17/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
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Maternal Health Team (MHT) Review

Date: June 18, 2008 **Date Consulted:** March 27, 2008

From: Richardae Araojo, Pharm.D.
Regulatory Reviewer, Pediatric and Maternal Health Staff

Through: Karen Feibus, MD
Medical Team Leader, Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

To: Division of Analgesia, Anesthesia, and Rheumatology Products (DAARP)

Drug: OxyContin (oxycodone) Controlled-Release Tablets (NDA 22-272)

Subject: Pregnancy and Lactation Human Data for Oxycodone

Materials Reviewed: Relevant data submitted in NDA 22-272, Pharmacology/Toxicology Review for NDA 22-272, Reprotox, TERIS-The Teratogen Information System, Shepard's Catalog of Teratogenic Agents, and the National Library of Medicine's Drug and Lactation Database on oxycodone. Other published reports and references as cited.

Consult Questions:

1. Review of nonclinical data with oxycodone suggests that there are no clear signals for embryo-lethal or teratogenic effects supporting the current classification as Pregnancy Category B. All other opioids are designated Pregnancy Category C due to either lack of any data and/or evidence of embryo-lethal and/or teratogenic effects. Are there any data in the clinical realm that would suggest that oxycodone is safer to use during pregnancy than other opioids?

2. Are there any new clinical data for oxycodone or opioids in general that should be included in the Labor and Delivery, Nursing Mothers, or Pregnancy sections of the current oxycodone label?

3. Major malformations involving the heart or lungs have been observed in one study in a few offspring of rats treated with oxycodone during gestation. It is not clear whether these malformations are spontaneous background occurrences or if they are treatment-related. Are there any clinical data that would shed light on whether these findings in the rat are biologically relevant?

EXECUTIVE SUMMARY

The Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) is reviewing a New Drug Application for reformulated OxyContin (oxycodone hydrochloride) Controlled-Release Tablets (NDA 22-272). Oxycodone is a pure μ opioid receptor agonist and is indicated for the management of moderate to severe pain when a continuous, around-the clock analgesic is needed for an extended period of time. The new OxyContin formulation was developed by Purdue Pharma, L.P. to provide improved resistance to physical and chemical alterations (crushing and chemical extraction) of OxyContin that are considered common forms of non-medical use and abuse of the current formulation.

As part of NDA 22-272, the sponsor submitted final study reports from Segment I and Segment III reproductive toxicology studies. Data from the Segment III study revealed an unusual finding of visceral malformations involving the heart and lungs in rat offspring exposed to oxycodone during gestation. The sponsor attributed these findings to maternal toxicity and spontaneous events. Following review of these data, the DAARP Pharm/Tox review team concurred with the sponsor's conclusions that the Segment I and III studies conducted by the sponsor did not reveal an increased risk of teratogenicity or developmental abnormalities. Based on these animal findings, DAARP consulted the MHT to determine if there are human data on the fetal effects of oxycodone exposure during pregnancy and lactation.

To determine if new clinical data exists on the fetal effects of oxycodone exposure during pregnancy or nursing, the MHT performed a literature search and found that there are limited human data on the fetal effects of oxycodone exposure during pregnancy. However, based on available human data, oxycodone does not appear to be associated with an increased risk of congenital anomalies. In addition, animal reproduction and developmental toxicology studies have revealed no evidence of harm to a developing fetus. Therefore, OxyContin is labeled as a pregnancy category B due to lack of adequate and well controlled studies in pregnant women and negative animal studies.

It is important to note that while OxyContin is labeled as pregnancy category B, we cannot conclude that it is safer than all other opioids when used during pregnancy. Some opioids are labeled as pregnancy category C simply because they lack both human and animal data. However, current human data on oxycodone exposure during pregnancy do not suggest an increased risk of congenital anomalies and animal data findings do not support a category change.

In addition, there are limited data on the effects of oxycodone exposure during breastfeeding. Based on available data, oxycodone is secreted into human milk. Infants exposed to oxycodone during pregnancy and breastfeeding may experience neonatal abstinence syndrome and should be monitored closely. Infants should also be monitored for excess sedation and respiratory depression.

Published data are important to include in product labeling to facilitate well informed risk/benefit decision making by patients and their healthcare practitioners when medicine is needed during pregnancy and lactation. Available data on drug use during pregnancy and lactation is limited to post-marketing experience since pregnant and lactating women are usually excluded from pre-marketing clinical trials. Label revisions suggested by MHT are intended to enable well informed and judicious use of oxycodone during pregnancy and lactation and are not intended to support approval of this application.

RECOMMENDATIONS

1. OxyContin should remain pregnancy category B. The MHT recommended revisions to the sponsors proposed labeling are provided on pages 19-22 of this review.

BACKGROUND

The Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) is reviewing a New Drug Application for reformulated OxyContin (oxycodone hydrochloride) Controlled-Release Tablets (NDA 22-272). Oxycodone is a pure μ opioid receptor agonist and is indicated for the management of moderate to severe pain when a continuous, around-the clock analgesic is needed for an extended period of time. The new OxyContin formulation was developed by Purdue Pharma, L.P. to provide improved resistance to physical and chemical alterations (crushing and chemical extraction) of OxyContin that are considered common forms of non-medical use and abuse of the current formulation.

There is limited human data on the effects of oxycodone in pregnancy and animal reproduction studies revealed no evidence of teratogenicity. Therefore, the current formulation of OxyContin is labeled as pregnancy category B. However, as part of NDA 22-272, the sponsor submitted final study reports from Segment I and Segment III reproductive toxicology studies. Data from the Segment III study revealed an unusual finding of visceral malformations involving the heart and lungs in rat offspring exposed to oxycodone during gestation. The sponsor attributed these findings to maternal toxicity and spontaneous events.

Based on the animal findings described above, DAARP consulted the MHT to determine if there are human data on the fetal effects of oxycodone exposure during pregnancy. In addition, DAARP would like MHT to provide any relevant new clinical data for the Labor and Delivery and Nursing Mothers subsections of labeling.

REVIEW OF DATA

This review responds to specific consult questions from DAARP and discusses relevant data included in the pharmacology/toxicology review for NDA 22-272. In addition, this review

provides revisions to the sponsor's proposed Pregnancy, Labor and Delivery, and Nursing Mothers subsections of labeling.

Animal Data

In support of this application, the sponsor submitted final study reports from Segment I and Segment III reproductive and developmental toxicology studies. Data from the Segment III study revealed an unusual finding of visceral malformations involving the heart and lungs in two male high dose pups from different rat litters treated with oxycodone. The heart defects were described as, "major vessels: aorta descends to the right side of the heart and intraventricular septal defect, cranial ¼." The lung malformations were described as, "accessory lung lobe absent and lung lobes fused on the right side." The incidence of these malformations were above historical controls. The sponsor attributed these findings to maternal toxicity and spontaneous events. A similar heart and lung malformation was observed in one F2 generation female pup from the low dose group. The sponsor concluded that these findings were not dose dependent and not related to treatment. Following review of these data, the DAARP Pharm/Tox review team concurred with the sponsor's conclusions that the Segment I and III studies conducted by the sponsor did not reveal an increased risk of teratogenicity or developmental abnormalities.

Reviewer comment:
Please see the pharmacology/toxicology review by Dr. Elizabeth Bolan for a detailed analysis of the reproductive and developmental toxicity studies submitted in support of this application.

Response to Consult Questions

1. **Review of nonclinical data with oxycodone suggests that there are no clear signals for embryo-lethal or teratogenic effects supporting the current classification as Pregnancy Category B. All other opioids are designated Pregnancy Category C due to either lack of any data and/or evidence of embryolethal and/or teratogenic effects. Are there any data in the clinical realm that would suggest that oxycodone is safer to use during pregnancy than other opioids?**

   Response: Many opioids are labeled as pregnancy category C because they lack adequate and well controlled studies in pregnant women, and animal reproduction studies have not been conducted or animal reproduction studies revealed adverse fetal effects. Examples of category C drugs that lack human data and have positive animal data include methadone, codeine, morphine, hydrocodone, and hydromorphone.

   There are limited human data on the fetal effects of oxycodone exposure during pregnancy. However, based on available human data, oxycodone does not appear to be associated with an increased risk of congenital malformations. As stated in product labels, infants exposed to opioids in utero may experience neonatal abstinence syndrome (NAS) or drug withdrawal depending on the timing of maternal opiate use and amount of drug used during pregnancy. Clinical features of NAS include neurologic excitability, gastrointestinal dysfunction, increased sweating, fever, nasal stuffiness, mottling, and temperature instability.[1]

[1] American Academy of Pediatrics, Committee on Drugs. Neonatal Drug Withdrawal. Pediatrics. June 1998: 101 (6); 1079-1088.

To determine if new clinical data exists on the fetal effects of oxycodone exposure during pregnancy, a PubMed search of the literature was performed using the following search terms:

- Oxycodone and pregnancy
- Oxycodone and fetus
- Oxycodone and neonate

In addition, the following sources were used to gather information on oxycodone exposure during pregnancy:

- TERIS-The Teratogen Information System
- Reprotox
- Shepard's Catalog of Teratogenic Agents

A summary of the most relevant human data regarding oxycodone exposure during pregnancy is described below:

a. Hadi I, da Silva O, Natale R, Boyd D, Morley-Forster PK. Opioids in the parturient with chronic nonmalignant pain: a retrospective review. J Opioid Manag. 2006: 2(1):31- 34.

Hadi and colleagues conducted a retrospective cohort study of the St. Joseph's Health Care perinatal and neonatal databases in Ontario, Canada to determine neonatal outcomes of women taking prescribed opioids during pregnancy from January 1, 1999 to September 20, 2002.

Fifteen pregnancies were identified. However, two cases were excluded due to documented co-addiction disorder with cocaine. Maternal data collected included:

- age, height, weight, parity,
- obstetric and medical antenatal risk factors,
- smoking/alcohol history,
- pain syndrome diagnosis,
- medication doses,
- labor analgesia, and
- type of delivery.

Neonatal data collected included:

- gestational age,
- birth weight,
- length,
- head circumference,
- Apgar score at one and five minutes,
- umbilical venous/arterial gases,
- neonatal abstinence syndrome (NAS) score,
- urine /meconium drug screen,

- nalaxone administration,
- mechanical ventilation,
- and duration of ventilatory support.

Women enrolled in the study were taking one or more of the following opioids: morphine, fentanyl patch, meperidine, codeine, and oxycodone. All drugs were taken throughout pregnancy.

Reviewer comment: The authors were unable to determine exact doses of the opioids prescribed.

Thirteen pregnancies were followed and resulted in 13 live births. Three neonates were exposed to oxycodone and acetaminophen in utero and four were exposed to oxycodone and other narcotics. No congenital malformations were reported. The mean gestational age was 37 $\pm$ 1 weeks; mean birth weight was 2,739 $\pm$ 1,035 g, mean head circumference was 32.8 $\pm$ 3.0 cm, and mean length was 46 $\pm$ 5.7 cm. Four of 13 neonates had one minute Apgar scores equal or less than 5 and two required active resuscitation and NICU admission. Five neonates had a NAS score equal to or more than eight and required NICU admission and treatment with morphine. Table 1 describes the maternal and neonatal characteristics of study participants.

The authors concluded that all neonatal growth markers measured were within normal limits. However, neonates born to opioid dependent women should be observed for signs and symptoms of NAS.

b. Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation 7th edition, Philadelphia, PA: Lippincott Williams & Wilkins, 2005: 1226-1227.

Briggs and colleagues described an unpublished Michigan Medicaid surveillance study conducted between 1985 and 1992 that included 229,101 completed pregnancies. Of these pregnancies, 281 newborns were exposed to oxycodone during the first trimester. A total of 13 (4.6%) major birth defects were observed (12 expected), including three cardiovascular defects (three expected) and one hypospadias (one expected). No congenital anomalies were observed in four other defect categories (oral clefts, spina bifida, polydactyly, and limb reduction defects). The authors concluded that oxycodone exposure during pregnancy is not associated with an increased risk of congenital malformations. No additional information was reported.

c. Rao R, Nirmala SD. Perinatal/Neonatal Case Presentation. Journal of Perinatology. 2002; 22:324-325.

Rao and Desai submitted a case report of a 39 week gestation male infant (birth weight 2864 g) born to a 24 year old, gravida three, woman by spontaneous vaginal delivery. The mother had two previous preterm deliveries and a history of barbiturate abuse during her second pregnancy. She smoked one pack of cigarettes per day for 10 years and had been injecting OxyContin (120 to 500 mg/d) intravenously for the past two years.

Detoxification with methadone was attempted in the second trimester of the present pregnancy, but the mother was noncompliant due to withdrawal symptoms. Pregnancy was further complicated by recurrent urinary tract infections and preterm labor at 36 weeks gestation. The patient developed seizures in her last trimester of pregnancy and was treated with phenytoin.

During her pregnancy, the patient also took methadone obtained illicitly three weeks before delivery. Maternal drug screen at delivery was positive for oxycodone, oxymorphone, norpropoxyphene, and phenothiazine derivatives.

At birth, the baby was noted to have a shrill cry, Apgar scores of seven and 10 at one and five minutes, and required oxygen therapy for transient respiratory distress.

Upon further observation, the baby was noted to be jittery and irritable. On physical examination no dysmorphic features were noted. During the first day, the baby exhibited hypertonia, tachypnea, tachycardia, and an exaggerated startle response. The baby's initial urine and meconium drug screens were negative. However, a subsequent urine analysis was positive for oxymorphone (567 ng/ml) but negative for methadone derivatives.

Over the next few days, the infant was not feeding well and developed emesis, watery diarrhea, short sleep cycles, mottling, and excoriations on the face and buttocks. The Neonatal Abstinence Scoring system was used for monitoring the infant. The mean score ranged from 10 to 21 during the first week but decreased thereafter.

The baby was treated with paregoric for 12 days followed by chloral hydrate for four days. The baby continued to improve and was discharged to foster care on day 16 of life.

Despite polydrug abuse by the mother, the authors concluded that the infant's withdrawal symptoms were due to OxyContin exposure during gestation. The authors based this conclusion on urine analysis results that were positive for oxymorphone and negative for methadone derivatives.

Reviewer comment: The Mother in this case report had a history of polysubstance abuse throughout pregnancy. While the infant experienced typical opiate withdrawal syndrome symptoms no congenital anomalies were otherwise noted.

d. Schick B, Hom M, Tolosa J, Librizzi R, Donnenfeld A. Preliminary analysis of first trimester exposure to oxycodone and hydrocodone (Abstract). Reprod Toxicol. 1996: 10(2):162.

Schick and colleagues prospectively obtained pregnancy outcome information from 118 women exposed to hydrocodone or oxycodone during the first trimester of pregnancy. Seventy-eight women reported oxycodone use and 40 used hydrocodone. The indications for medication use included surgery (53 cases) and general pain/upper respiratory infection (65 cases). Data was grouped according to medication used and indication. Pregnancy outcomes in exposed subjects were compared to 120 "non-teratogen" exposed controls including 59 women reporting first trimester surgery, and 82 women exposed to codeine for either general pain or upper respiratory infection.

Reviewer comment: In the control group, women were treated for pain with codeine and other non-specified pain relievers. It is unclear how the authors defined "non-teratogen" exposed.

Statistical analysis was performed using Fisher's exact test or chi-square. A non-significant increased risk of malformations was observed among oxycodone users (six cases) compared to controls [OR = 2.61 (0.6-11.5) p = 0.13]. However, no pattern of malformation or miscarriage was observed among oxycodone or hydrocodone exposed cases. No additional information was reported.

e. Bracken MB, Holford TR. Exposure to prescribed drugs in pregnancy and association with congenital malformations. Obstetrics and Gynecology. 1981: 58 (3); 336-344.

Bracken and Holford conducted a retrospective study to examine the association between drug use during pregnancy and risk of congenital malformations. The following cases were included in the study:

- All deliveries of infants with congenital malformations at five Connecticut hospitals between November 18, 1974 and November 17, 1976 (n=1110),
- Newborns and stillborns with congenital malformations delivered at the five Connecticut hospitals six months before control cases were sampled (n=188),
- Newborns with congenital malformations delivered at other facilities between May 18, 1974 and November 17, 1976, that were referred to the five Connecticut hospitals before one year of age, and infants less than one year of age identified at two pediatric clinics (n=129).

Medical records of all cases were examined by an internist or pediatrician. Attending physicians were contacted when necessary to obtain additional information. A total of 1427 case interviews were completed (76% of all cases identified).

Control cases were obtained by sampling all healthy live births at the five Connecticut hospitals between November 18, 1974 and November 17, 1976. The first control case was randomly chosen and all subsequent control cases were systematically chosen from a delivery room log book. A total of 3001 control cases were interviewed (94.5% of all control cases identified).

Reviewer comment: No information was provided regarding the system used to identify control cases.

Women were eligible for study enrollment if they could be interviewed within 12 months of delivery, spoke English, still lived in Connecticut, and had not placed their baby for adoption. Trained interviewers used a standardized questionnaire to obtain demographic information, contraception history, smoking status/history, and exposure to other possible risk factors for malformations. Only 13.6% of all case subjects were interviewed in the hospital, all others were interviewed at home. In contrast, almost all case controls were interviewed in the hospital, immediately postpartum.

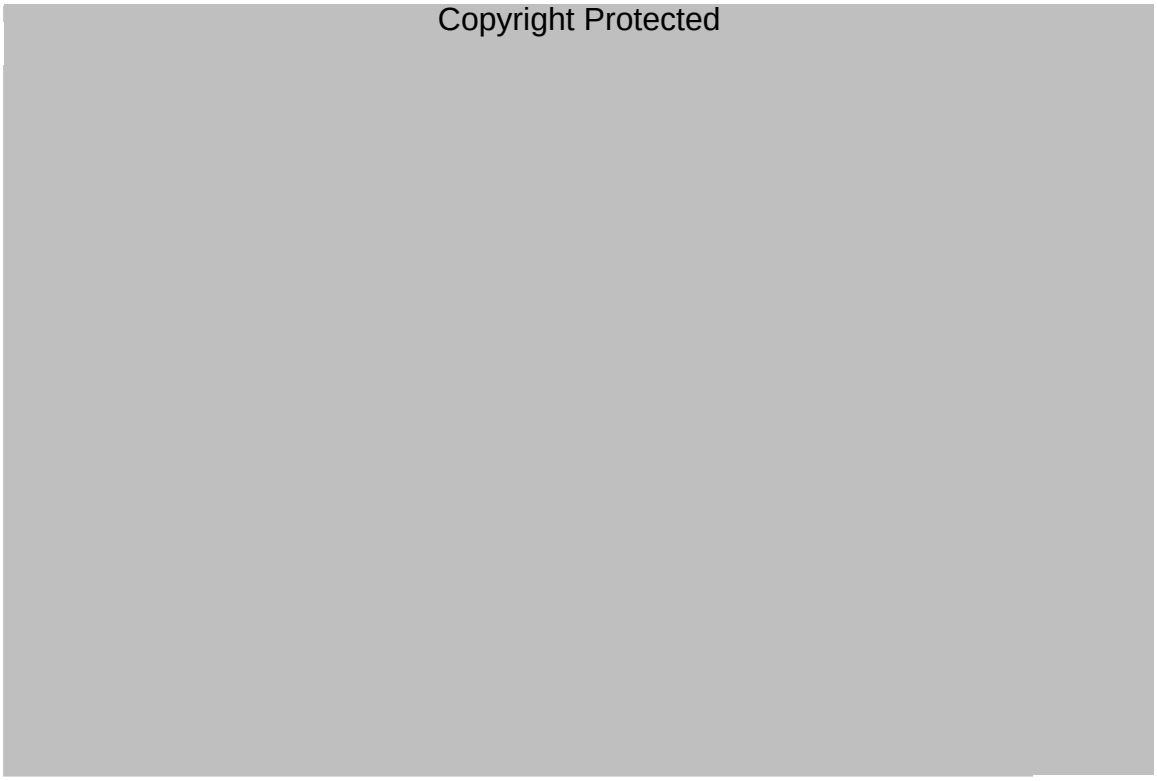
Reviewer comment: The authors did not provide an exact % of case controls interviewed in the hospital.

Compared to controls, case subjects were more likely to be over age 30 years, have married or gone beyond high school, and have "a head of household" in skilled manual occupation ($p<0.05$).

Twenty-four percent of mothers delivering were not interviewed but were included in the data calculations since diagnostic data on the presence or absence of congenital malformations was available.

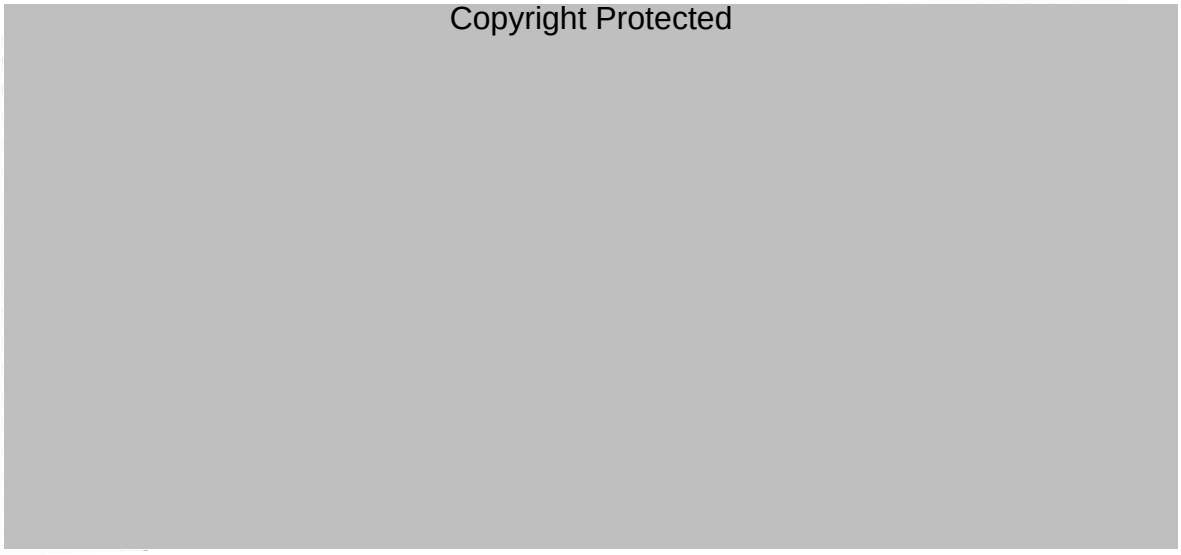
Of all women included in the study, 44.5% used one or more prescribed drugs during at least one month of pregnancy. Among mothers using a prescribed drug during pregnancy, 43.4% used two or more drugs, and 14.2% used three or more. When combining all diagnoses and all drug exposures, the authors found that exposure to a prescribed drug during pregnancy was associated with a 30% increased risk of delivering a malformed infant [$p < 0.001$].

Narcotic analgesics were used by 0.4% of mothers during the first trimester. In addition, the authors found that first trimester exposure to narcotic analgesics during pregnancy was associated with a odds ratio of 3.6 ($p<0.05$) for congenital malformations as shown in Table 2 below. Odds ratios for congenital malformations were not statistically increased following exposure to narcotics in the second and third trimesters.



Mothers who used narcotic analgesics and had a congenitally malformed infant were more likely to be separated or divorced, to smoke more than one pack of cigarettes/day during pregnancy, and to be older than mothers of healthy newborns who were not exposed to these drugs. Therefore, the authors adjusted for and recalculated the odds ratios evaluating the possible exposure to narcotic analgesics and tranquilizers with congenital malformations. The authors stated that, "none of the findings reported in Table 2 were essentially changed by this adjustment". Some women enrolled in the study used narcotic analgesics and tranquilizers at the same time during pregnancy. To look for malformations due to simultaneous exposure to both drugs, the authors recomputed the association of each drug with congenital malformations, and found no substantial difference.

The authors found that codeine was the most commonly used narcotic among case subjects when compared to controls. Only five first-trimester oxycodone exposed cases were included in the study (see Table 3 below).



The authors concluded that drug exposure during pregnancy is associated with an increased risk of congenital malformations. However, since many women enrolled in the study also smoked throughout pregnancy, the possibility of environmental substances and smoking contributing to this effect could not be ruled out.

Reviewer comment: This study included 1427 exposed cases; however only five cases included first trimester exposure to oxycodone. While the authors did find an increase in congenital malformations in infants exposed to narcotic analgesics during pregnancy, there is not sufficient data to determine if oxycodone is associated with an increased risk of congenital malformations.

f. Heinonen OP, Slone D, Shapiro S. Birth Defects and Drugs in Pregnancy. Publishing Sciences Group, Inc., Littleton, MA, 1977.

The Collaborative Perinatal Project (CPP) was a prospective study of neurologic disorders and other conditions in children. Pregnant women were enrolled from 1959-1965 when they presented for prenatal care at 12 university hospital clinics located throughout the U.S.

The CPP monitored 50,282 mother-child pairs, eight of which had first trimester exposure to oxycodone. No increase in the incidence of major or minor malformations was found.

2. Are there any new clinical data for oxycodone or opioids in general that should be included in the Labor and Delivery, Nursing Mothers, or Pregnancy sections of the current oxycodone label?

Response:

a. Labor and Delivery

Oxycodone is an oral opioid that is not used during labor and delivery. During labor, regional anesthesia/analgesia or systemic analgesia may be offered for pain control or relief. When opioids are given systemically during labor, clinicians administer intermittent doses by intravenous or intramuscular routes. Common opioids administered during labor and delivery include meperidine, nalbuphine, and fentanyl.[2]

Intravenous or intramuscular administration of opioids during labor and delivery is associated with increased risks of maternal sedation, respiratory depression, and nausea. In addition, opioids freely cross the placenta and may produce respiratory depression in the newborn.

Current Labeling

The current OxyContin Labor and Delivery labeling is provided below. The MHT suggested revisions to the Labor and Delivery subsection of the OxyContin label are provided on pages 20-21 of this review.

8.2 Labor and Delivery

Opioids cross the placenta and may produce respiratory depression and psychophysiologic effects in neonates. OxyContin® is not recommended for use in women immediately prior to and during labor, when use of shorter acting analgesics or other analgesic techniques are more appropriate. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor.

Neonates whose mothers received opioid analgesics during labor should be observed closely for signs of respiratory depression. A specific opioid antagonist, such as naloxone or nalmefene, should be available for reversal of opioid induced respiratory depression in the neonate.

Neonates whose mothers have been taking opioids chronically may also exhibit withdrawal signs, either at birth and/or in the nursery, because they have developed physical dependence. This is not, however, synonymous with addiction [see DRUG ABUSE AND DEPENDENCE (9.3)]. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal

[2] Hawkins JL, Goetzl L, Chestnut DH. (2007). Obstetric Analgesia. Gabbe SG, Niebyl JR & Simpson JL. (Eds), *Obstetrics: Normal and Problem Pregnancies.* 5th Edition (pp 400-403). Churchill Livingstone, Philadelphia, PA.

syndrome in adults, may be life threatening and should be treated according to protocols developed by neonatology experts.

b. Nursing Mothers

As described in the current OxyContin labeling, small amounts of oxycodone are present in human milk. Reported milk levels range from > 5 to 226 µg/ml[3].

The American Academy of Pediatrics (AAP) Committee on Drugs does not provide a recommendation on oxycodone and breastfeeding; however, codeine and morphine are listed as *maternal medications usually compatible with breastfeeding*.[4]

Newborns exposed to oxycodone during pregnancy and breastfeeding may experience neonatal drug withdrawal depending on the timing of maternal drug use, maternal dose and duration of use, and infant metabolism and excretion. However, the most likely unwanted side effects of oxycodone exposure in breastfed infants are sedation and respiratory depression.

To determine the effects of oxycodone in nursing infants, a PubMed search of the literature was performed using the following search terms:

- Oxycodone and breastfeeding
- Oxycodone and lactation
- Oxycodone and neonate
- Oxycodone and human milk

In addition, the following sources were used to gather information on oxycodone exposure during breastfeeding:

- TERIS-The Teratogen Information System
- Reprotox
- Shepard's Catalog of Teratogenic Agents
- The National Library of Medicine's Drug and Lactation Database

A summary of the most relevant data regarding oxycodone exposure during lactation is described below:

- **Seaton S, Reeves M, McLean S. Oxycodone as a component of multimodal analgesia for lactating mothers after Caesarean section: Relationships between maternal plasma, breast milk and neonatal plasma levels. Aust N Z J Obstet Gynaecol. 2007 ;47:181-5.**

  The aim of this study was to investigate the relationship between maternal oxycodone use after cesarean section (CS) and the amount of oxycodone in

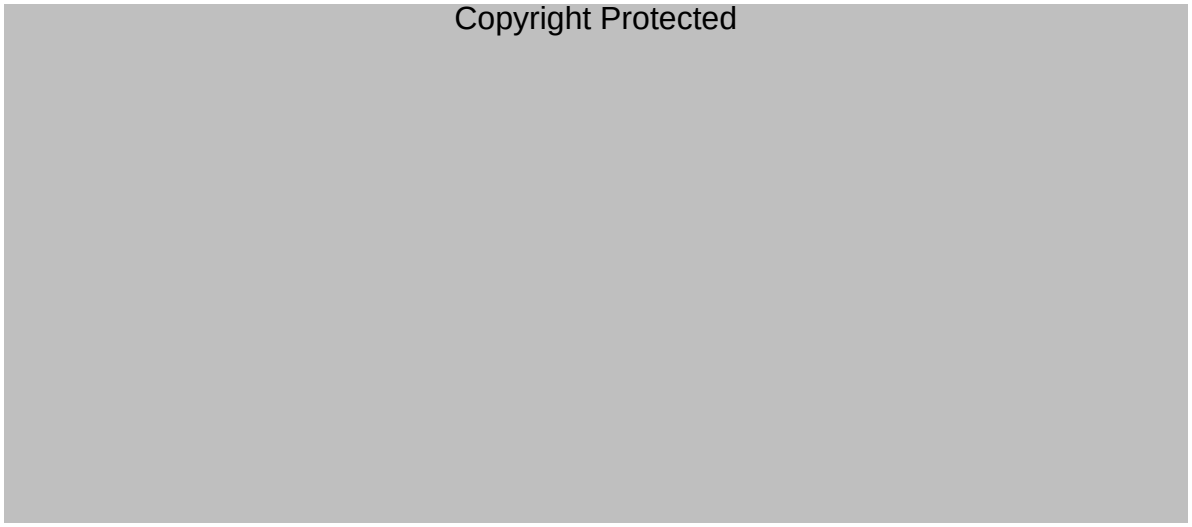
[3] Marx CM, Pucino F, Carlson JD et al. Oxycodone excretion in human milk in the puerperium. Drug Intell Clin Pharm. 1986;20:474. Abstract.

[4] The American Academy of Pediatrics, Committee on Drugs, The transfer of drugs and other chemicals into human milk. Pediatrics. 2001; 108(3):776-789.

breast milk and neonatal plasma. Fifty Australian mothers taking oxycodone post-cesarean section were enrolled in the study. All women received rectal oxycodone 30mg after CS and 10mg oral oxycodone as needed (no more than every two hours). Blood and breast milk samples were analyzed for oxycodone at 24 hour intervals post cesarean section. All neonates were observed for sedation and breast attachment. Forty-one neonates had blood samples collected at 48 hours post breastfeeding. Maternal and breast milk levels are shown in Table 4 below.

Oxycodone was detected in the milk of all mothers taking oxycodone. Milk levels > 100 ng/ml were found in mothers that had taken $\geq$ 60mg of oxycodone in a 24 hour period. Of the 41 neonates that had blood samples taken, only one had detectable levels of oxycodone (7.4 ng/ml and on retest 6.6 ng/ml). Less than 4% of neonates had an average sedation score (over 48 hours) of three and no infant had a score greater than three (1=fully alert, 5=difficult to arouse). The authors were not able to correlate sedation scores with maternal dose or breast milk levels.

During the initial 24 hour period the authors saw a correlation between breast milk and plasma levels, however in subsequent 24 to 72 hour periods the authors observed oxycodone accumulation in the breast milk of five mothers (see Table 5 below).



The authors concluded that:

- Oxycodone is concentrated in human milk up to 72 hours postpartum.
- Breastfed infants may receive > 10% of a therapeutic infant dose.
- Maternal oxycodone use up to 72 hours postpartum poses only minimal risk to a breastfeeding infant.

- *Reviewer comment: During the first three days postpartum mothers are producing colostrum and not mature milk. Therefore, infants in this study were likely only exposed to small amounts of colostrum during the first three days postpartum. While the concentration of oxycodone in colostrum may be greater than the concentration in mature breast milk, due to the small volume of colostrum produced, total infant daily dose is usually smaller than when breastfeeding is well established.*

- **Levine B, Moore KA, Aronica-Pollak P et al.** Oxycodone **intoxication in an infant: accidental or intentional exposure? J Forensic Science. 2004;49:1358-60.**

  A 10-month-old, 7.7 kg, African American male infant went into cardiac arrest at a local toy store. The infant was transported to the hospital by paramedics and later pronounced dead. The infant's mother and grandmother reported periods of lethargy, somnolence, and dyspnea prior to the cardiac arrest. The infant had a recent history of fever that was treated with acetaminophen. The mother had a significant medical history of anxiety, autoimmune disease, cluster headaches, depression, chronic intractable pain syndrome, migraine, muscular dystrophy, and lumbar radiculoneuropathy/muscle spasm.

  At that time, the mother was prescribed oxycodone (30 mg po qid), Fioricet (codeine, acetaminophen, butalbital, and caffeine) [1 tablet po qid], and Soma (carisoprodol) [350 mg po qid]. She also had prescriptions from previous

doctors for alprazolam, hydrocodone, amitriptyline, mirtazapine, venlafaxine, and neurontin. Both the mother and her husband were informed that she should not breastfeed while taking these medications. Earlier in the year, the husband called child protective services to report his wife was "abusing her medications while the children are in her care" with specific concerns about her breastfeeding.

Upon investigation of the infant's death, the mother stated she had been breastfeeding the infant three times a day for several weeks and had taken a total of 180 mg of oxycodone and 700 mg of carisoprodol the day before to the infant's death. On the day of the infant's death, she reported taking only one hydrocodone/acetaminophen tablet. The infant's postmortem blood and liver oxycodone concentrations were 0.6 mg/L and 1.6 mg/kg, respectively. The medical examiner ruled the cause of death to be oxycodone intoxication and the manner of death a homicide.

- **Marx CM, Pucino F, Carlson JD et al. Oxycodone excretion in human milk in the puerperium. Drug Intell Clin Pharm. 1986; 20: 474. Abstract.**

Marx and colleagues studied six healthy post-cesarean section nursing mothers receiving Tylox (oxycodone and acetaminophen), one to two capsules every four to seven hours for pain. Plasma and milk samples were collected prior to dosing and at 0.25, 0.5, 1, 1.5, 2, and 3 hours after the initial dose. Samples were also collected prior to and 2 hours after each successive dose, and at 4, 8, and 12 hours after the final dose. Maternal oxycodone plasma levels ranged from 14-35 ng/ml. Breast milk levels ranged from <5 to 226 ng/ml. Maximum oxycodone breast milk levels occurred between 1.5 and 2 hours after the initial dose and variably after multiple doses. Oxycodone remained in milk for 4, 12, and 36 hours after the fourth, ninth, and eleventh doses respectively. The mean milk: plasma ratio was 3.4:1. The authors estimated that maximum exposure to oxycodone in breast milk would not exceed 8% of the recommended weight corrected adult dose.

Current Labeling

The current OxyContin Nursing Mothers labeling is provided below. The MHT suggested revisions to the Nursing Mothers subsection of the OxyContin label are provided on page 21 of this review.

8.3 Nursing Mothers

(b) (4)

c. Pregnancy

A summary of the most relevant human data on oxycodone exposure during pregnancy is provided on pages 5-12 of this review.

The current OxyContin pregnancy labeling is provided below. The MHT suggested revisions to the Pregnancy subsection of the OxyContin label are provided on pages 19-20 of this review.

3. Major malformations involving the heart or lungs have been observed in one study in a few offspring of rats treated with oxycodone during gestation. It is not clear whether these malformations are spontaneous background occurrences or if they are treatment-related. Are there any clinical data that would shed light on whether these findings in the rat are biologically relevant?

Response:

In response to consult question one on page 5-11 of this review, a literature search was conducted to determine if any new clinical data exists on the effects of oxycodone exposure during pregnancy. Based on available human data, oxycodone does not appear to be associated with an increased risk of congenital anomalies.

DISCUSSION/CONCLUSIONS

There are limited human data on the fetal effects of oxycodone exposure during pregnancy. However, based on available human data, oxycodone does not appear to be associated with an increased risk of congenital anomalies. In addition, animal reproduction and developmental toxicology studies have revealed no evidence of harm to a developing fetus. Therefore,

OxyContin is labeled as a pregnancy category B due to lack of adequate and well controlled studies in pregnant women and negative animal studies.

It is important to note that while OxyContin is labeled as pregnancy category B, we cannot conclude that it is safer than all other opioids when used during pregnancy. Some opioids are labeled as pregnancy category C simply because they lack both human and animal data. However, current human data on oxycodone exposure during pregnancy do not suggest an increased risk of congenital anomalies, and animal data findings do not support a category change.

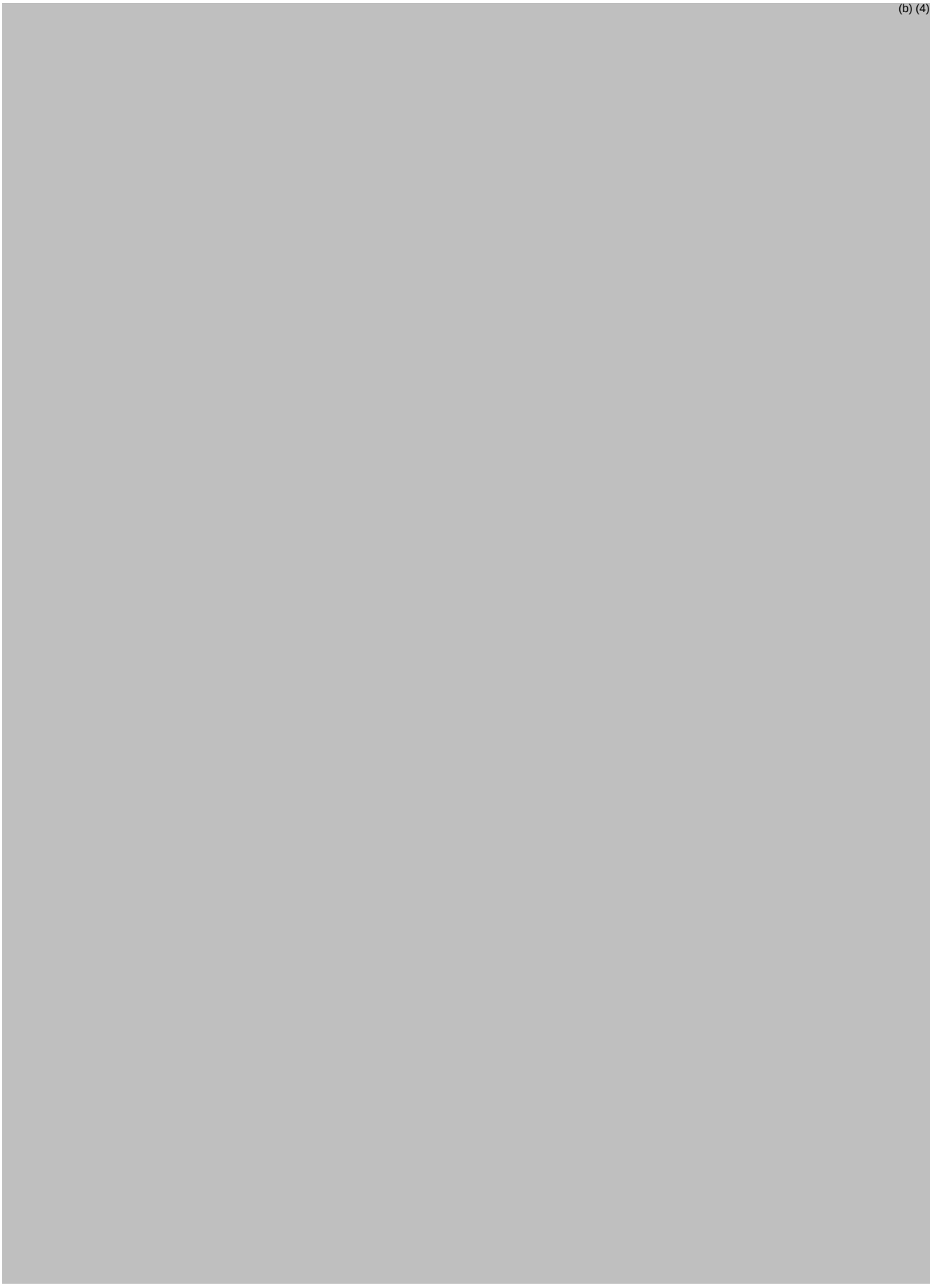
In addition, there are limited data on the effects of oxycodone exposure during breastfeeding. Based on available data, oxycodone is secreted into human milk. Infants exposed to oxycodone during pregnancy and breastfeeding may experience NAS and should be monitored closely. Infants should also be monitored for excess sedation and respiratory depression.

Published data are important to include in product labeling to facilitate well informed risk/benefit decision making when medicine is needed during pregnancy and lactation. Available data on drug use during pregnancy and lactation are limited to post-marketing experience since pregnant and lactating women are usually excluded from pre-marketing clinical trials. The MHT revisions to the sponsors proposed labeling are provided below. These revisions do not support approval of this application. The changes made add safety data to help clinicians make well informed decisions when oxycodone use is needed during pregnancy and lactation. As described in the FDA Guidance for Industry entitled, "E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs", the overall safety evaluation for approved drugs should address any new safety information related to positive or negative experiences during pregnancy and lactation.

RECOMMENDATIONS

The MHT recommended revisions to the sponsors proposed labeling are provided below. Recommended additions are underlined and deletions are struck-out.

(b) (4)



Neonates whose mothers have been taking opioids chronically may also exhibit withdrawal signs, either at birth and/or in the nursery, because they have developed physical dependence. This is not, however, synonymous with addiction [see DRUG ABUSE AND DEPENDENCE (9.3)]. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life threatening and should be treated according to protocols developed by neonatology experts.

Withdrawal symptoms can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

(b) (4)

[redacted]

17.1 Information for Patients/Caregivers

7. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.

17.2 FDA-Approved Patient Labeling

If you are pregnant or plan to become pregnant, talk with your doctor. OxyContin may not be right for you. **Tell your doctor if you are breast-feeding**. OxyContin will pass through the milk and may harm the baby.

_____
Richardae Araojo, Pharm.D.
Regulatory Reviewer, Maternal Health Team

_____
Karen Feibus, MD
Medical Team Leader, Maternal Health Team

_____
Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

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

/s/

Chardae Araojo
7/16/2008 01:59:51 PM
CSO

Karen Feibus
7/23/2008 10:51:29 AM
MEDICAL OFFICER

Lisa - Chardae finally entered as we got no more feedback from DARRP on regulatory issue

Lisa Mathis
8/4/2008 05:25:17 PM
MEDICAL OFFICER

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: May 22, 2008

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology Products
(HFD-170)

Through: Michael Klein, Ph.D., Acting Director
Controlled Substance Staff (HFD-009)

From: Silvia Calderon, Ph.D., Team Leader
Lori Love, M.D., Ph.D., Medical Officer
Controlled Substance Staff (HFD-009)

Subject: NDA 22-272 OxyContin (Oxycodone Hydrochloride Controlled Release, New Formulation) 10, 15, 20, 30 and 40 mg Tablets

Indication: Management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

Company: Purdue Pharma L.P. (Purdue)

Submission: NDA 22-272 is located in the EDR. In preparation for the upcoming Advisory Committee on May 2008, CSS has reviewed the following sections of the Original Application (11/30/2007): "*Tamper Evaluation Report*" (Module 3.2.P2 Pharmaceutical Development), and "*Report of the Effect of* (b) (4) *on Reformulated Oxycodone HCl q 12h In Vitro Dissolution (10, 15, 20, 30 and 40 mg Tablets)*" (Module 3.2.P2 Pharmaceutical Development)

This review provides recommendations to the Division of Anesthesia, Analgesia, and Rheumatology Products regarding the abuse deterrent properties of the new OxyContin formulation.

SUMMARY

Purdue has filed this New Drug Application (NDA 22-272) in support of their new reformulated OxyContin tablets. The reformulated product uses an (b) (4) with polyethylene oxide as a (b) (4) This new formulation is intended to be bioequivalent to the currently marketed OxyContin tablets, with the claim of being

comparatively less susceptible to physical manipulation of the dosage form, such as crushing and chewing, to alter the drug delivery performance. The new OxyContin tamper resistant (OTR) formulation will be available in 10, 15, 20 and 40 mg oral tablets, to be taken q12h. The Sponsor intends to develop reformulated 80 mg strength in the near future.

BACKGROUND

The OTR tablets are formulated using an (b) (4) with polyethylene oxide as a (b) (4). The rate of oxycodone release is controlled by (b) (4) The manufacturing process is a combination of (b) (4)

Data from the National Survey on Drug Use and Health (NSDUH) and the Drug Abuse Warning Network (DAWN) show that the abuse of OxyContin is a continuing problem. As indicated by the Sponsor, information on routes of administration involved in the nonmedical use or abuse of OxyContin tablets is limited. Nevertheless, a review conducted by the Sponsor of published literature and analysis of 2006 NSDUH data shows that the oral route is the most commonly used route for the misuse and abuse of OxyContin. However, more experienced abusers report injecting crushed tablets or snorting crushed tablets. Nevertheless, the percentage of OxyContin abusers who chose to use parenteral routes seems to be low when compared to the number of abusers who use the oral route.

REVIEW

The Controlled Substance Staff (CSS) in CDER has reviewed the data on the tamper resistant properties of the novel formulation.

While data from *in vitro* studies indicate that the currently proposed formulation may provide enhanced protection for the intended population against dose dumping when tablets are crushed or chewed, review of the "tamper-resistance" studies provided by the Sponsor, indicates that simple manipulation of the tablets such as (b) (4)

2 pp withheld in full immediately after this page as (b)(4) CCI/TS.

No information has been provided regarding the release properties of other strengths. This information is relevant because the highest dosage strengths contain lower amounts of polyethylene oxide, which is the excipient that confers to the new formulation [redacted] (all strengths have the same weight of 156 mg, [redacted]. Therefore, the Sponsor needs to demonstrate that the different compositions of the tablets do not alter the rate of release after [redacted] and that dose-dumping does not occur with the higher dosage strengths.

- Particle size distribution of crushed and [redacted] tablets

[redacted] tablets [redacted] and crushed OxyContin tablets [redacted] were analyzed by [redacted] to evaluate the particle size distribution of the material. The material was [redacted] This study shows that [redacted] of particles from [redacted] tablets are larger than [redacted] OxyContin tablets resulted in a much [redacted] distribution in which much of the material retained on the [redacted] was [redacted].

[redacted]

CONCLUSIONS

1- The new formulation lacks any feature that will reduce the harmful consequences associated with the abuse and overdose of OxyContin, and the reformulated product should not be viewed as an abuse resistant formulation since oral abuse of the intact formulation can still occur.

2- Based on the relative rate of release of the active pharmaceutical ingredient (API) from (b) (4) oxycodone tamper resistant (OTR) 10 mg tablets in (b) (4) the **10 mg OTR tablets** may provide enhanced protection for the intended population against dose dumping when tablets are accidentally crushed or chewed. The Sponsor did not provide full evidence that this is the case for all dosage strengths.

3- No information has been provided regarding the relative release of the active pharmaceutical ingredient from all strengths (15 mg, 20 mg and 40 mg tablets) of (b) (4) and crushed tablets. Therefore, it could not be concluded that these strengths provide an enhanced protection to the patients if tablets are accidentally crushed or chewed.

4- Simple manipulation, such as grinding of the tablets using (b) (4), of the newly reformulated OxyContin tablets results in approximately (b) (4) release of the labeled claim API in (b) (4), whereas (b) (4) of the label API is released from crushed OxyContin tablets. Though the newly reformulated product might be seen as an improved version of OxyContin, (b) (4)

5- (b) (4) was the most efficient solvent tested by the Sponsor for extracting the API from all strengths of (b) (4) tablets. (b) (4) afforded (b) (4) of the API, using (b) (4) CSS recognizes the toxicity of (b) (4) but also recognizes that (b) (4) can be (b) (4)

6- The fact that the reformulation of 80 mg OxyContin tablets will not coincide with that of the lower strengths is of concern because these tablets will release (b) (4) of the label claim API when chewed or ground.

RECOMMENDATIONS

In order to evaluate if all strengths of the current formulation will protect patients who inadvertently chew or crush the tablets from overdosing, CSS recommends the Sponsor to provide the following for all dosage strengths of the reformulated tablets:

1- Data about the amount of oxycodone released if a tablet of the reformulated product which has been crushed or previously softened in water or in other solvents is chewed.

2- Studies conducted to determine the relative rate of release of the active pharmaceutical ingredient from all strengths of crushed and (b) (4) oxycodone (b) (4) tablets before concluding that all dosage strengths retain the controlled release properties after crushing and (b) (4) and that dose dumping does not occur.

   a. It is recommended that for these studies as well as for extraction studies, the Sponsor should (b) (4)

3- Data on how altering the grinding conditions, (b) (4) might affect the final particle size distribution of the tablets for all strengths rendering a product suitable for insufflation.

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

/s/

Silvia Calderon
5/22/2008 04:13:53 PM
CHEMIST

Lori Love
5/22/2008 04:14:28 PM
MEDICAL OFFICER

Michael Klein
5/22/2008 04:18:44 PM
PHARMACOLOGIST
Acting Director - Controlled Substance Staff

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

MEMORANDUM

Pre-Decisional Agency Information

Date: January 25, 2008

To: Lisa Basham – Regulatory Project Manager
Division of Anesthetics, Analgesics, and Rheumatology Products (DAARP)

From: Michelle Safarik, PA-C – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: DDMAC labeling comments for OxyContin (oxycodone hydrochloride controlled-release) Tablets for oral administration, CII
NDA 22-272

DDMAC has reviewed the proposed product labeling (PI) for OxyContin (oxycodone hydrochloride controlled-release) Tablets for oral administration, CII (OxyContin) submitted for consult on January 23, 2008.

DDMAC acknowledges this is a new NDA for OxyContin (initial NDA 20-553) that provides data supporting a change in formulation of OxyContin for purposes of deterring abuse. We also acknowledge that this submission covers the 10, 15, 20, 30, and 40 mg strengths (b) (4)

DDMAC further acknowledges the following:

1) The sponsor is seeking the same indication and trade name approved for NDA 20-553;
2) The proposed PI has been reformatted in accordance with the Physician Labeling Rule (PLR) per 21 CFR 201.56-57;
3) The proposed RiskMAP for NDA 22-272 does not reflect the Agency's comments dated October 16, 2007, for the RiskMAP for NDA 20-553. Per communication with DAARP on October 30, 2007, the sponsor will amend the RiskMAP for NDA 22-272 accordingly after agreement has been reached on the RiskMAP for NDA 20-553. Therefore, DDMAC will not provide comments on the proposed RiskMAP for NDA 22-272 at this time.

DDMAC has reviewed the entire label and thus may be commenting on sections of the label that are already approved. We offer the following comments.

HIGHLIGHTS

Boxed Warning

1. "**OxyContin is indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time**." (emphasis original)

   For consistency with the Boxed Warning section of the proposed PI, we recommend adding that "OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride."

2. "**OxyContin 80 mg Tablets, or doses greater than 40 mg, ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY**." (emphasis original)

   For consistency with the Boxed Warning section of the proposed PI, we recommend adding the material fact that the 80 mg strength is for use in opioid-tolerant patients only because it "[m]ay cause fatal respiratory depression when administered to patients who are not **tolerant to the respiratory depressant effects** of opioids." (emphasis original)

Indications and Usage

1. (b) (4)

   For consistency with the Indications and Usage section of the proposed PI, we recommend adding the material fact that OxyContin is also not for use "[i]f the pain is mild, or not expected to persist for an extended period of time."

Dosage and Administration and Dosage Forms and Strengths

1. We recommend specifying that the 80 mg strength is for use in opioid-tolerant patients only for consistency with the Dosage and Administration and Dosage Forms and Strengths sections of the proposed PI.

Warnings and Precautions

1. (b) (4)

   This statement minimizes the risks of OxyContin therapy. For consistency with the Warnings and Precautions section of the proposed PI, we recommend strengthening the above statement to reflect that OxyContin is contraindicated in patients who have or who are suspected to have paralytic ileus.

2. For consistency with the Warnings and Precautions section of the proposed PI (section 5.5), we recommend including the material facts that OxyContin may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures.

Drug Interactions

1. For consistency with the Drug Interactions section of the proposed PI (sections 7.3 and 7.4), we recommend including the material facts that OxyContin has drug interactions with CNS depressants and mixed agonist/antagonist opioid analgesics.

Use in Specific Populations

1. "Ordinarily, nursing should not be undertaken while a patient is receiving OxyContin."

   For consistency with the Use in Specific Populations section of the proposed PI, we recommend adding the material fact "[b]ecause of the possibility of sedation or respiratory depression in the infant."

Full Prescribing Information: Contents

1. For consistency with the proposed PI, we recommend revising "(b) (4) to "7.1 Neuromuscular Junction Blocking Agents" for consistency with the Drug Interactions section of the proposed PI.

PI

Indications and Usage

1. "OxyContin is **NOT** indicated for rectal administration." (emphasis original)

   Is it appropriate to include the following information from the Pharmacokinetics section of the current PI: "(b) (4)

Warnings and Precautions

1. "OxyContin should be used with caution in the following conditions, due to an increased risk for adverse experiences:. . .CNS depression. . . ."

We recommend including “coma” for consistency with the Precautions-General section of the current PI.

Adverse Reactions

1. Did the Agency or the sponsor decide to move the following adverse events from those that occurred in less than 1% of patients in clinical trials to disclaiming that “it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure”: amenorrhea, symptoms associated with anaphylactic or anaphylactoid reaction, increased hepatic enzymes, muscular hypertonia, hyponatremia, ileus, palpitations (in the context of withdrawal), seizures, syndrome of inappropriate antidiuretic hormone secretion, and urticaria. In addition, the adverse reaction of (b) (4) that appears in the current PI is not in the proposed PI.

Use in Specific Populations

Geriatric Use

1. “However, as with all opioids, the starting dose should be reduced in debilitated, non-opioid-tolerant patients.”

   For consistency with the Precautions-Geriatric Use section of the current PI, we recommend adding context that the starting dose should be reduced by 1/3 to ½.

Clinical Pharmacology

Pharmacokinetics

1. “Oxycodone is (b) (4) absorbed from OxyContin Tablets with an oral bioavailability of (b) (4)

   The word (b) (4) is promotional in tone. Therefore, we recommend deletion, particularly as context (b) (4) is provided.

2. “About (b) (4) of an oral dose of oxycodone reached the central compartment in comparison to a parenteral dose. This (b) (4) oral bioavailability is due to low pre-systemic metabolism.”

   The word (b) (4) is promotional in tone. Therefore, we recommend deletion, particularly as context (b) (4) is provided. In addition, is it appropriate to include the following from the Pharmacokinetics-Absorption section of the current PI: (b) (4)

[redacted]

3. [redacted]

   We recommend providing context that "The apparent elimination half-life of oxycodone following the administration of OxyContin was 4.5 hours compared to 3.2 hours for immediate-release oxycodone."

4. "The plasma concentrations of oxycodone are only [redacted] affected by age, being 15% greater in elderly as compared to young subjects (age 21-45)."

   The word [redacted] is promotional in tone. Therefore, we recommend deletion, particularly as context "[redacted] is provided.

Patient Counseling Information

1. [redacted] patients receiving OxyContin Tablets or their caregivers should be given the following information by the physician, nurse, pharmacist, or caregiver."

   The phrase [redacted] is promotional in tone and minimizes the risks of OxyContin therapy, as it implies that this information should not be consistently reinforced with patients.

FDA-Approved Patient Labeling

1. We recommend converting this section to a Medication Guide, and consulting DSRCS for comments on readability, consistency, and formatting.

What is OxyContin?

1. "OxyContin treats moderate to severe pain that is expected to last for an extended period of time."

   We recommend adding that the drug is for use in patients ≥18 years of age for consistency with the current and proposed PIs.

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

/s/

Michelle Safarik
1/25/2008 04:46:44 PM
DDMAC REVIEWER

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 022272 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: OxyContin Established/Proper Name: Oxycodone Hydrochloride Controlled-Release Dosage Form: Tablets Strengths: 10, 15, 20, 30, 40 mg		
Applicant: Purdue Pharma L{ Agent for Applicant (if applicable):		
Date of Application: November 29, 2007 Date of Receipt: November 29, 2007 Date clock started after UN:		
PDUFA Goal Date: May 29, 2008	Action Goal Date (if different):	
Filing Date: January 28, 2008	Date of Filing Meeting: January 8, 2008	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time		

Type of Original NDA: AND (if applicable)	☒ 505(b)(1) ☐ 505(b)(2)
Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 029083	

Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*	

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***		X		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	**X**			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:*		**X**		**Schedule II**
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?			X	
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			

Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***				

Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		X		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?				
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***				

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***			X	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
REMS consulted to OSE/DRISK?	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	X			CSS-consult sent

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** June 9, 2007 ***If yes, distribute minutes before filing meeting***				
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 8, 2008

BLA/NDA/Supp #: 022272

PROPRIETARY NAME: OxyContin

ESTABLISHED/PROPER NAME: Oxycodone Hydrochloride Controlled-Release

DOSAGE FORM/STRENGTH: 10, 15, 20, 30, 40-mg

APPLICANT: Purdue Pharma LP

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time

BACKGROUND: This is a reformulation of OxyContin (NDA 20-553) intended to deter abuse via its physical characteristics.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Lisa Basham	Y
	CPMS/TL:	Parinda Jani	
Cross-Discipline Team Leader (CDTL)	Sharon Hertz		Y
Clinical	Reviewer:	Jin Chen	Y
	TL:	Sharon Hertz	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Sayed Al Habet	Y
	TL:	Suresh Doddapaneni	Y
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Elizabeth Bolan	Y
	TL:	Dan Mellon	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Craig Bertha	Y
	TL:	Ali Al Hakim	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Jacqueline A. O'Shaughnessy	Y
	TL:	CT. Viswanathan	Y
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		

Other reviewers		
Other attendees		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☒ YES Date if known: 5/5/08 ☐ NO ☐ To be determined Reason:

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☐ Not Applicable ☐ YES ☒ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Comments:	

Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs/BLA supplements only) **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Bob rappaport **21st Century Review Milestones (see attached)** (optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☒ Priority Review
ACTIONS ITEMS	
☒	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Other

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

/s/

LISA E BASHAM
09/30/2009