CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-272

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-272**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**March 30, 2009**
PRODUCT:	**OxyContin reformulation**
INTENDED CLINICAL POPULATION:	**For management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time**
SPONSOR:	**Purdue Pharma L.P.**
DOCUMENTS REVIEWED:	**All nonclinical information in the above submission**
REVIEW DIVISION:	**Division of Anesthesia, Analgesia, and Rheumatology Products (HFD 170)**
PHARM/TOX REVIEWER:	**Elizabeth A. Bolan, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
DIVISION DIRECTOR:	**Bob Rappaport, M.D.**
PROJECT MANAGER:	**Lisa Basham**
Date of review submission to DARRTs:	**September 3, 2009**

EXECUTIVE SUMMARY

I. Recommendations

A. **Recommendation on approvability**

This NDA can be approved from a pharmacology/toxicology perspective.

B. Recommendation for nonclinical studies

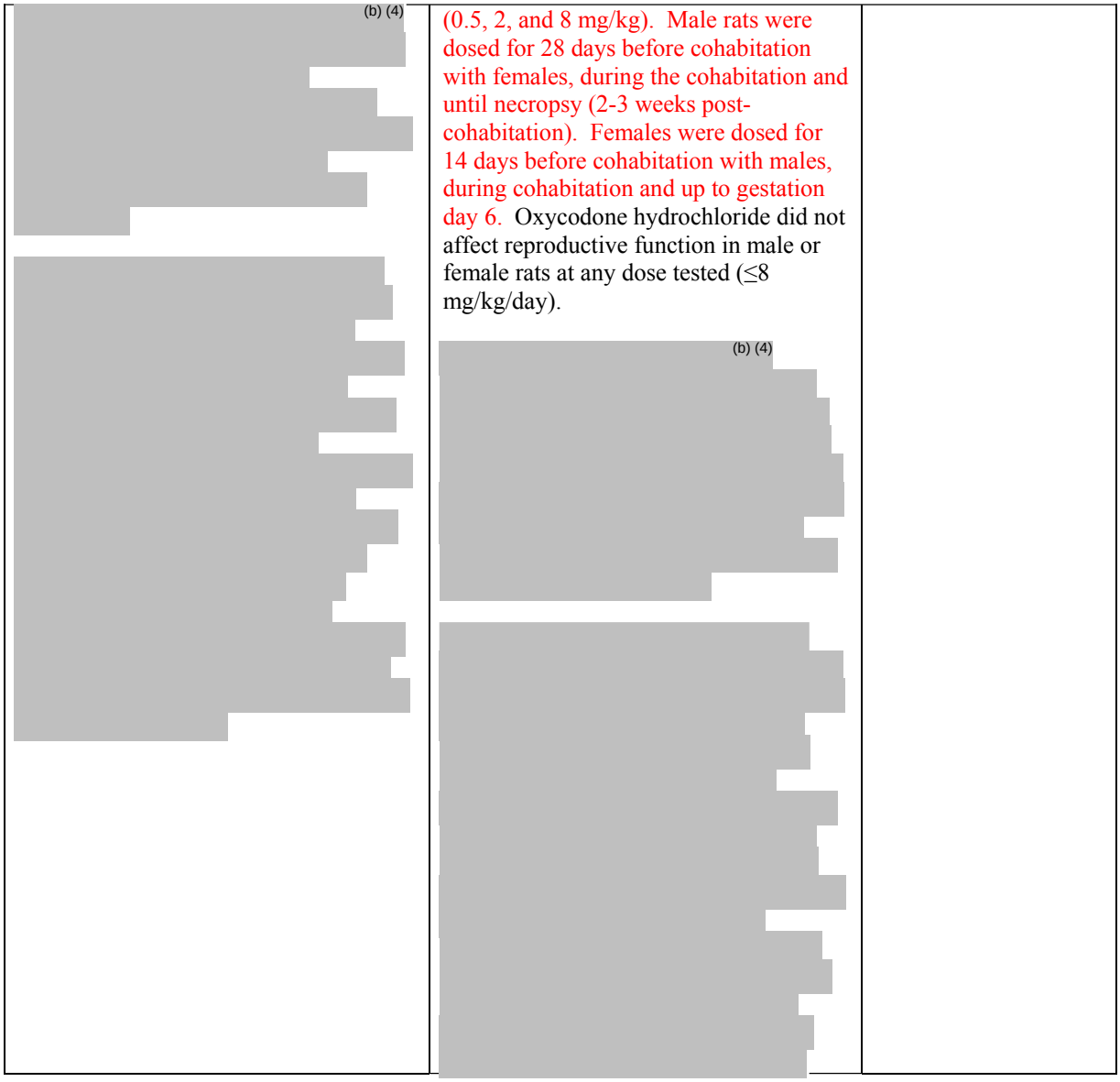
None

C. Recommendations on labeling

The following recommendations are being proposed for the nonclinical sections of the label. Note that this second cycle review of the labeling takes into consideration the new data submitted by the Applicant in the second cycle. For the final version of the label, please refer to the Action Letter. Note: The recommended changes from the proposed labeling are in red or strikeout font.

Applicant's proposed labeling	*Reviewer's proposed labeling*	*Rationale*
8 USE IN SPECIFIC POPULATIONS **8.1 Pregnancy** Teratogenic Effects - Category B: The effect of oxycodone in human reproduction has not been adequately studied. (b) (4) Non-Teratogenic Effects Oxycodone hydrochloride was administered orally to female rats during gestation and lactation in a pre- and postnatal toxicity study. There were no drug-related effects on reproductive performance in these females or any long-term developmental or reproductive effects in pups born to these rats. Decreased weight gain was found during lactation and the early post-weaning phase in pups nursed by mothers given the highest dose used (6 mg/kg/day, equivalent to approximately 2-times an adult human dose of 160 mg/day, on a mg/kg basis). However,	**8 USE IN SPECIFIC POPULATIONS** **8.1 Pregnancy** Teratogenic Effects - Category B The effect of oxycodone in human reproduction has not been adequately studied. (b) (4) Studies with oral doses of oxycodone hydrochloride in rats up to 8 mg/kg/day and rabbits up to 125 mg/kg/day, equivalent to 0.5 and 15 times an adult human dose of 160 mg/day, respectively on a mg/m^2 basis, did not reveal evidence of harm to the fetus due to oxycodone. Non-Teratogenic Effects Oxycodone hydrochloride was administered orally to female rats during gestation and lactation in a pre- and postnatal toxicity study. There were no drug-related effects on reproductive performance in these females or any long-term developmental or reproductive effects in pups born to these rats. Decreased weight gain was found during lactation and the early post-weaning	This section has been reworded for clarity and the exposure ratios were changed to the more appropriate comparison of mg/m^2. Dose ratios are expressed on a body surface area basis.

body weight of these pups recovered.	phase in pups nursed by mothers given the highest dose used (6 mg/kg/day, equivalent to approximately 0.4-times an adult human dose of 160 mg/day, on a mg/m^2 basis). However, body weight of these pups recovered.	
13 NONCLINICAL TOXICOLOGY **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenesis: No animal studies to evaluate the carcinogenic potential of oxycodone have been conducted. Mutagenesis: (b) (4) Oxycodone was not mutagenic in the following assays; Ames Salmonella and *E. coli* test with and without metabolic activation at doses of up to 5000 µg/plate, chromosomal aberration test in human lymphocytes (in the absence of metabolic activation) at doses of up to 1500 µg/mL, and with activation after 48 hours of exposure at doses of up to 5000 µg/mL, and in the in vivo bone marrow micronucleus assay in mice (at plasma levels of up to 48 µg/mL). Mutagenic results occurred in the presence of metabolic activation in one human chromosomal aberration test at greater than or equal to 1250 µg/mL at 24 but not 48 hours of exposure. (b) (4) Impairment of fertility: In a study of reproductive performance, (b) (4) (b) (4)	**13 NONCLINICAL TOXICOLOGY** **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenesis: No animal studies to evaluate the carcinogenic potential of oxycodone have been conducted. Mutagenesis: (b) (4) Oxycodone was genotoxic in the mouse lymphoma assay at concentrations of 50 µg/mL or greater with metabolic activation and at 400 µg/mL or greater without metabolic activation. Clastogenicity was observed with oxycodone in the presence of metabolic activation in one chromosomal aberration assay in human lymphocytes at concentrations greater than or equal to 1250 µg/mL at 24 but not 48 hours of exposure. In a second chromosomal aberration assay with human lymphocytes, no structural clastogenicity was observed either with or without metabolic activation. However, in the absence of metabolic activation, oxycodone increased numerical chromosomal aberrations (polyploidy). Oxycodone was not genotoxic in the following assays: Ames *S. typhimurium* and *E. coli* test with and without metabolic activation at concentrations up to 5000 µg/plate, chromosomal aberration test in human lymphocytes (in the absence of metabolic activation) at concentrations up to 1500 µg/mL, and with activation after 48 hours of exposure at concentrations up to 5000 µg/mL, and in the *in vivo* bone marrow micronucleus assay in mice (at plasma levels up to 48 µg/mL). Impairment of fertility: In a study of reproductive performance, rats were administered a once daily gavage dose of the vehicle or oxycodone hydrochloride	The suggestion of a (b) (4) has been removed. The order of the data presentation has been changed from the previous version of the label. The positive genotoxic findings with oxycodone are now presented before the negative findings Results from newly submitted Chromosomal Aberration study are described here. The finding of polyploidy was included. The word (b) (4) was replaced by more accurate word "concentration."



II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

In this cycle, the Applicant submitted one genetic toxicology study to support a proposed labeling change. An *in vitro* chromosomal aberration assay in human peripheral blood lymphocytes was conducted with oxycodone. The study showed that oxycodone did not produce clastogenicity. However, increased levels of polyploid cells were observed in cultures treated with oxycodone. The findings from this study will be described in the product label.

The specification set by the Applicant for residual solvent levels of (b) (4) in the (b) (4) excipient exceeded ICH Q3C guideline thresholds. The Applicant provided toxicologic justification of the proposed levels of this solvent. The Applicant's justification has been found adequate and the proposed specification of (b) (4) for the residual solvent level of (b) (4) in the (b) (4) is acceptable.

B. Nonclinical safety issues relevant to clinical use

No new nonclinical safety issues were identified.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

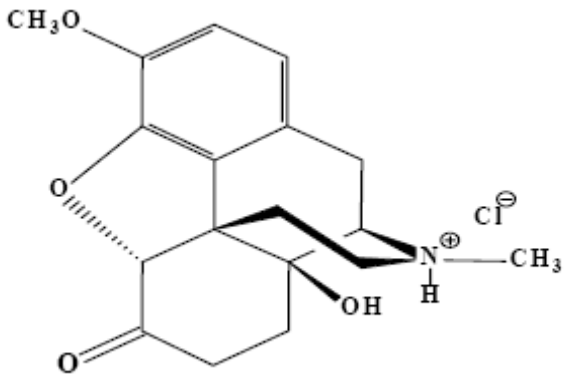
NDA number: 22-272
Review number: 2
Sequence number/date/type of submission: 000/March 30, 2009/second cycle NDA submission
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Purdue Pharma, L.P. Stamford, CT 06901
Manufacturer for drug substance: (b) (4)

Reviewer name: Elizabeth A. Bolan, Ph.D.
Division name: Division of Anesthesia, Analgesia, and Rheumatology Products

HFD #: 170
Review completion date: May 22, 2009

Drug:

Trade name: OxyContin
Generic name: oxycodone hydrochloride
Code name: N/A
Chemical name: 4, 5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.
CAS registry number: 124-90-3
Molecular formula/molecular weight: $C_{18}H_{21}NO_4 \bullet HCl$; MW 351.83 g/mol
Structure:



Background Pharmacology/Toxicology had recommended approval for NDA 22-272 in the first review cycle. The NDA was not approved due to CSS and Clinical issues. In the second cycle, the Applicant submitted one genetic toxicology study (Study # 778436) to support a proposed labeling change. Also in the second cycle, Dr. Craig Bertha (ONDQA) submitted an information request to the Applicant requesting justification of levels of the residual solvent (b) (4) in the (b) (4) excipient. The Applicant provided toxicologic justification of the levels of this solvent (Amendment 0031). This second cycle review contains the review of the new genetic toxicology study, the assessment of the adequacy of the Applicant's justification regarding the (b) (4) specification and updated edits to the product label.

Studies reviewed within this submission:

- Study # 778436: Oxycodone Hydrochloride Injection 50 mg/mL Containing (b) (4) and Oxycodone Hydrochloride Injection 50 mg/mL Reference Formulation (OH-Form) Chromosomal Aberrations Assay with Human Peripheral Lymphocytes Cultures *in vitro*

- Amendment 0031: Applicant's response to ONDQA information request regarding toxicologic justification of residual solvent levels of (b) (4)

Refer to the pharmacology/toxicology review of the original OxyContin NDA (Purdue Pharma; NDA 20-553) by BeLinda Hayes, Ph.D. dated August 21, 1995 and the pharmacology/toxicology review of the first cycle of NDA 22-272 by Elizabeth Bolan, Ph.D dated May 1, 2008.

Studies not reviewed within this submission: none

Study title: **Oxycodone Hydrochloride Injection 50 mg/mL Containing (b) (4) and Oxycodone Hydrochloride Injection 50 mg/mL Reference Formulation (OH-Form) Chromosomal Aberrations Assay with Human Peripheral Lymphocytes Cultures *in vitro***

Key findings: It is concluded that oxycodone and (b) (4) are not clastogenic in an *in vitro* chromosome aberration assay with human peripheral blood lymphocytes under conditions of the assays conducted. However, increased levels of polyploid cells were observed in cultures treated with oxycodone at concentrations of 2500 and 3750 mcg/mL and (b) (4) at concentrations of 1250, 2500 and 3750 mcg/mL.

Study no.: 778436
Volume #, and page #: Module 4.2.3.3.1.1
Conducting laboratory and location: (b) (4)
Date of study initiation: January 24, 2007
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Oxycodone hydrochloride, Batch # RM3015; purity: >94.3%; (b) (4) Batch # PN2969; purity: not specified; (b) (4) content: 0.68%

The objective of this study as stated in the study report was to determine whether or not the presence of the (b) (4) a potential oxycodone (OXY) impurity, would alter the potential of oxycodone alone to induce chromosomal aberrations in human peripheral lymphocyte cultures. Oxycodone and oxycodone with a given concentration of the (b) (4) were tested individually in this *in vitro* chromosomal aberration assay.

The Applicant (Purdue Pharma LP) submitted this study in support of a statement added to the proposed label of reformulated OxyContin (NDA 22-272). The addition to the label explains that although some positive results were seen with a prior *in vitro* chromosomal aberration assay, this study demonstrates that structural aberrations were not seen with OXY treatment. Refer to the suggested labeling section under Conclusions for the proposed wording from the Applicant and the edits recommended by the reviewer.

Methods
Strains/species/cell line: Human peripheral blood lymphocytes

Doses used in definitive studies: See Table 1 (Assay 2)

Basis of dose selection: In the first assay, for each test article the Applicant used nine concentrations between 20 and 5000 mcg/mL in the presence or absence of S9 activation with harvest after 29 hours. In the second assay, the concentration range was narrowed and cells were incubated in the presence or absence of S9 activation with harvest after 29

hours or in the absence of S9 activation with harvest after 53 hours. In the presence or absence of S9 activation with a 29 hour harvest, the vehicle or test article was incubated with the cells for 5 hours. In the absence on S9 with the 53 hour harvest, the cells were incubated with the vehicle or test article for 25 hours. Water for injection was used as the vehicle as well as the diluent. In both assays, the highest concentrations selected for chromosomal aberration analysis were limited by cytotoxicity and reductions in mitotic activity. The assay parameters and concentrations at which cytotoxicity was observed are described in Table 1.

Table 1. Assay parameters

Assay	*test article*	*S9*	*treatment with test article, h*	*time to harvest, h*	*concentration, mcg/mL*	*cytotoxicity*
1	OXY	+	5	29	20, 39, 78, 156, 313, 625, 1250, 2500, 5000	5000
		-	5	29		>5000
	(b) (4)	+	5	29		≥2500
		-	5	29		5000
2, part I	OXY	+	5	29	625, 1250, 2500, 3750, 5000	>5000
		-	25	29		≥3750
	(b) (4)	+	5	29		≥3750
2, part II		-	25	29		≥3750
	OXY	-	25	53	156, 313, 625, 1250, 2500, 3750, 5000	5000
	(b) (4)	-	25	53		≥3750

The Applicant states that the procedures and assay design comply with the recommendations of the OECD guideline 473, European Commissions Annex V BIO, ICH guidelines, and Test Method B10.

Negative controls: The negative control was water for injection.

Positive controls: Mitomycin C (MMC) was used as the positive control at 0.1-0.8 mcg/mL in the presence of S9 activation and cyclophosphamide (CPH) was used at 10-20 mcg/mL in the absence of S9 activation.

Incubation and sampling times: See Table 1.

Three concentrations of test article not exhibiting cytotoxicity were selected for assessment of chromosomal aberrations. From two to four slides per culture, a total of 100 metaphase cells per were examined. The number of chromosomes in each metaphase cell and all abnormalities, using the nomenclature of Gebhart et al., was recorded (Gebhart E, 1970).

Assessment of polyploidy was also conducted. For this assessment, approximately 300 metaphase cells were examined and deemed to be either diploid, polyploid,

endoreduplicated. Polyploidy was only assessed in the absence of S9 at the 53 h harvest time point.

Cytotoxicity:
Mitotic indices were calculated by dividing the number of metaphase cells by the total number of metaphase plus interphase cells (approximately 1000 interphase cells were counted where possible). These were then compared with the mitotic indices of the vehicle control cultures. The Applicant considered a concentration to be cytotoxic if the mitotic indices were $\leq$50% of the mean vehicle control values. The Applicant also states that if mitotic indices are $\geq$50% the concentration can still be considered toxic if there are consistent changes to cellular morphology.

Structural and Numerical Chromosomal Aberrations:
For the analysis of chromosomal aberrations, five parameters were calculated and judged as negative, suspicious or positive. The parameters are listed below:

1. Lesions per cell
2. Percentage of aberrant cells including cells with gaps only
3. Percentage of aberrant cells excluding cells with gaps only
4. Percentage of aneuploid cells
5. Percentage of polyploid cells (normal and endoreduplicated) from additional assessment of polyploidy

The Applicant's criteria for a negative, positive or inconclusive determination of clastogenicity are reproduced verbatim below:

> The results for test item and positive control treated cultures are evaluated by comparison with the concurrent vehicle control cultures and with historical negative control data. A negative response was recorded if responses from the test item treated cultures are within the 95% confidence limits for the historical negative control data.
> The response at a single dose was classified as significant if the percent of aberrant cells is consistently greater than the 99% confidence limits for the historical negative control data or greater than double the frequency of an elevated vehicle or untreated control culture if appropriate.
>
> A test was positive if the response in at least one acceptable dose level is significant by the criterion described above.
>
> A test item was positive if Test 1 was positive, as described above or if one of the tests was positive and the other test gave indications of activity. These indications may be suspicious levels of aberrant cells (between 95% and 99% confidence limits).
>
> Experiments that met in part the criteria for a positive response, or marginally met all the criteria, were classed as inconclusive.

Results

Study validity: This study is valid. It utilizes appropriate replicates and cell counting/viability methodology. The vehicles and positive controls for the S9-activated and non-activated groups are within the range of the historical data set. The positive controls are higher than vehicle controls for all groups. No historical controls for the positive controls were provided.

Study outcome: It is concluded that OXY and (b) (4) are not clastogenic *in vitro* with human peripheral blood lymphocytes under conditions of the assays conducted. However, increased levels of polyploid cells were found in cultures treated with OXY at concentrations of 2500 and 3750 mcg/mL and (b) (4) at concentrations of 1250, 2500 and 3750 mcg/mL.

OXY Results

In the presence of S9, cultures treated with OXY and harvested at 29 h showed mean mitotic indices below 50% at 5000 mcg/mL in Assay 1 (40%; Table 2) but not Assay 2 (58%; Table 3). In the absence of S9, cultures treated with OXY and harvested at 29 h showed a mean mitotic index of 82% at 5000 mcg/mL in Assay 1 (Table 2) and 45% at 3750 mcg/mL in Assay 2 (Table 3). In the absence of S9, cultures treated with OXY and harvested at 53 h showed a mean mitotic index of 0% at 5000 mcg/mL with no metaphase cells present for evaluation and consistent changes to cellular morphology. At 3750 mcg/mL the mean mitotic index was 67% (Table 4). Structural and numerical aberrations (aneuploidy) were evaluated in cultures with at least three of the cultures having concentrations showing ≥50% reduction in the mean mitotic index. No precipitate or significant effects on osmolality or pH were observed at any dose. In cultures treated with OXY, no structural aberrations or changes in aneuploidy greater than control values were observed for any condition (Tables 2, 3, and 4). In the absence of S9 with a 53 h harvest the number of cells with polyploidy was further evaluated (Table 4). In OXY-treated cultures concentration-dependent increases in polyploidy were observed. The vehicle and untreated control showed 0.2% and 0% polyploid cells, respectively. Cultures treated with concentrations of OXY (1250, 2500, and 3750 mcg/mL) showed 0.5%, 1.8%, and 3.9% polyploid cells (not including endoreduplicated cells), respectively (Table 4). The positive controls were not evaluated for changes in ploidy. The historical negative control mean for polyploid cells including endoreduplicated cells was 0.20 +/- 0.28. The concentrations of 2500 and 3750 were judged as positive for polyploidy because the number of polyploidy cells fell outside the >99% confidence level. Historical negative control data are presented in Table 8. Statistical analyses were not conducted.

(b) (4) Results

In the presence of S9, cultures treated with (b) (4) showed mean mitotic indices below 50% at 2500 mcg/mL in Assay 1 (40%; Table 5). In Assay 2, although the mean mitotic indices for 3750 and 5000 mcg/mL were >50% (60% and 91%, respectively; data not shown) changes to cellular morphology consistent with toxicity as well as insufficient numbers of metaphase cells were present. The highest concentration assessed for

chromosomal aberrations was 2500 mcg/mL which showed a mean mitotic index of 88% (Table 6). In the absence of S9, cultures treated with (b) (4) showed a mean mitotic index of 40% at 5000 mcg/mL in Assay 1 (Table 6) and 46% at 3750 mcg/mL in Assay 2 (Table 7). In the absence of S9, cultures treated with (b) (4) and harvested at 53 h showed a mean mitotic index of 48% at 3750 mcg/mL. All (b) (4)-treated conditions with the exception of cultures in the absence of S9 at 29 and 53 h to harvest were evaluated for structural and numerical aberrations (aneuploidy) at three concentrations showing ≥50% reduction in the mean mitotic index. The two conditions in the absence of S9 (Tables 6 and 7) had only two concentrations each where the mean mitotic index was ≥50%, although the third concentration was very close to 50% in both cases. No precipitate or significant effects on osmolality or pH were observed at any dose. In cultures treated with (b) (4), no structural aberrations or changes in aneuploidy greater than vehicle controls were observed for any condition (Tables 5, 6, and 7). In the absence of S9 with a 53 h harvest the number of cells with polyploidy was further evaluated (Table 7). In (b) (4)-treated cultures concentration-dependent increases in polyploidy were observed. The vehicle and untreated control showed (b) (4) and 0% polyploid cells (not including endoreduplicated cells), respectively. Cultures treated with concentrations of (b) (4) (1250, 2500, and 3750 mcg/mL) showed (b) (4) and (b) (4) polyploid cells, respectively (Table 7). The positive controls were not evaluated for changes in ploidy. The historical negative control mean for polyploid cells plus endoreduplicated cells was 0.20 +/- 0.28. The concentrations of 2500 and 3750 were judged as positive by the Applicant for polyploidy because the number of polyploidy cells fell outside the >99% confidence level. The concentration of 1250 mcg/mL was considered "suspicious" by the Applicant because it fell within the ≥95-99% confidence level. Historical negative control data are presented in Table 8. Statistical analyses were not conducted.

Reviewer's comment:
If a cutoff of >95% confidence levels is used as the criterion for a positive response (instead of >99% as used by the Applicant), all three concentrations tested with (b) (4) *would be considered positive for inducing polyploidy.* ***This reviewer considers*** (b) (4) ***treated cultures at 1250, 2500 and 3750 mcg/mL to be positive for inducing polyploidy.***

Conclusions
No increases above control values were seen for structural aberrations or aneuploidy in any condition with either OXY or (b) (4) It is concluded that OXY and (b) (4) are not clastogenic *in vitro* with human peripheral blood lymphocytes under conditions of the assays conducted. However, increased levels of polyploid cells were found in cultures treated with OXY at concentrations of 2500 and 3750 mcg/mL and (b) (4) at concentrations of 1250, 2500, and 3750 mcg/mL.

The proposed wording for the label by the Applicant and the reviewer is detailed in the suggested labeling section under Conclusions. This study is being used by the Applicant to support the addition of the following statement (underlined) to the reformulated OxyContin label:

(b) (4)

Oxycodone was cytotoxic at several concentrations tested which were lower than 5000 mcg/mL and therefore those concentrations are not appropriate for evaluation of structural aberrations (Tables 2, 3, and 4). The concentration will be removed from the draft labeling (see suggested labeling under Conclusions). Although no structural aberrations were observed in cultures treated with OXY, concentration-dependent increases in numerical aberrations (specifically polyploidy) were seen. The additional wording is proposed to be added to the label:

(b) (4)

Refer to suggested labeling section under Conclusions for edits to the Applicant's proposed label.

Table 2. Oxycodone: Mean chromosomal and numerical aberrations and mitotic indices, 29 hour harvest (Assay 1)

Concentration, mcg/mL	S9	Mean Aberrant Cell Frequency, % (excluding gaps)	Mean Mitotic Index, %	Aneuploid Cells, %
Vehicle	+	0	100	0.5
625	+	0	89	0
1250	+	0	84	1
2500	+	0	63	0.5
5000	+	0.5	40	0.5
CPH, 10	+	2	NC	1
CPH, 20	+	10	NC	1
untreated	+	0	100	0
Vehicle	-	0	100	2.5
625	-	0	92	1
1250	-	0	96	1.5
2500	-	0	84	4
5000	-	0	82	2
MMC, 0.7	-	7	NC	7
MMC, 0.8	-	5	NC	5
untreated	-	0	97	1

NC: not calculated

Table 3. Oxycodone: Mean chromosomal and numerical aberrations and mitotic indices, 29 hour harvest (Assay 2, part I)				
Concentration, mcg/mL	***S9***	***Mean Aberrant Cell Frequency, % (excluding gaps)***	***Mean Mitotic Index, %***	***Aneuploid Cells, %***
Vehicle	+	0	100	0.5
1250	+	0	80	0.5
3750	+	0	80	0
5000	+	0.5	58	0.5
CPH, 10	+	5	NC	0
CPH, 20	+	8	NC	0
untreated	+	0	104	0.5
Vehicle	-	0	100	0
625	-	0	99	0
1250	-	0	93	0
2500	-	0	62	0
3750	-	0	45	0
MMC, 0.15	-	4	NC	0
MMC, 0.5	-	8	NC	0
untreated	-	0	107	0

NC: not calculated

Table 4. Oxycodone: Mean chromosomal and numerical aberrations and mitotic indices in the absence of metabolic activation, 53 hour harvest (Assay 2, part II)				
Concentration, mcg/mL	***Mean Aberrant Cell Frequency, % (excluding gaps)***	***Mean Mitotic Index, %***	***Aneuploid Cells, %***	***Polyploid Cells, % (negative or positive)***
Vehicle	0	100	0	0.2 (neg)
1250	0.5	90	1	0.5 (neg)
2500	0	92	0.5	1.8 (pos)
3750	0.5	67	0	3.9 (pos)
MMC, 0.1	7	NC	0	NC
MMC, 0.15	14	NC	0	NC
untreated	0.5	96	0.5	0 (neg)

NC: not calculated

Table 5. (b) (4): Mean chromosomal and numerical aberrations and mitotic indices, 29 hour harvest (Assay 1)				
Concentration, mcg/mL	***S9***	***Mean Aberrant Cell Frequency, % (excluding gaps)***	***Mean Mitotic Index, %***	***Aneuploid Cells, %***
Vehicle	+	0	100	0.5
313	+	0.5	90	0.5
625	+	1	72	0.5
1250	+	0.5	78	1.5
2500	+	0	40	0.5
CPH, 10	+	2	NC	1
CPH, 20	+	10	NC	1
untreated	+	0	97	0
Vehicle	-	0	100	2.5
625	-	0	88	1
1250	-	0.5	82	0.5
2500	-	0	55	3
5000	-	0	40	2.5
MMC, 0.7	-	7	NC	7
MMC, 0.8	-	5	NC	5
untreated	-	0	104	1

NC: not calculated

Table 6. (b) (4): Mean chromosomal and numerical aberrations and mitotic indices, 29 hour harvest (Assay 2, part I)				
Concentration, mcg/mL	***S9***	***Mean Aberrant Cell Frequency, % (excluding gaps)***	***Mean Mitotic Index, %***	***Aneuploid Cells, %***
Vehicle	+	0	100	0.5
625	+	0	88	0.5
1250	+	0.5	91	0
2500	+	0	88	0
CPH, 10	+	5	NC	0
CPH, 20	+	8	NC	0
untreated	+	0	104	0.5
Vehicle	-	0	100	0
1250	-	0	101	0
2500	-	0	60	0
3750	-	0.5	46	0

MMC, 0.15	-	4	NC	0
MMC, 0.5	-	8	NC	0
untreated	-	0	107	0

NC: not calculated

Table 7. (b) (4): Mean chromosomal and numerical aberrations and mitotic indices in the absence of metabolic activation, 53 hour harvest (Assay 2, part II)

Concentration, mcg/mL	***Mean Aberrant Cell Frequency, % (excluding gaps)***	***Mean Mitotic Index, %***	***Aneuploid Cells, %***	***Polyploid Cells, % (negative or positive)***
Vehicle	0	100	0	0.2 (neg)
1250	0	79	0	0.8 (pos)
2500	0	84	0	1.5 (pos)
3750	0	48	0	3.7 (pos)
MMC, 0.1	7	NC	0	NC
MMC, 0.15	14	NC	0	NC
untreated	0.5	96	0.5	0 (neg)

NC: not calculated

Table 8. Historical Negative Control Data (reproduced from NDA submission)

	Number of Records	Parameter	Confidence Levels for Negative Results			Mean and SDs for each parameter	
			0-95%	>95-≤99%	>99%	Mean	SD
Structural Aberrations	606	Lesions/cell	0.00-0.04	>0.04-≤0.06	>0.06	0.01	0.01
	668	Aberrant cell frequency including gaps (%)	0-3	>3-≤5	>5	1.1	1.2
		Aberrant cell frequency excluding gaps (%)	0-2	>2-≤4	>4	0.6	0.9
Numerical Aberrations1	620	AE (%)	0-2	>2-≤3	>3	0.3	0.8
	166	PP + ER (%)	0.00-0.66	>0.66-≤0.99	>0.99	0.20	0.28
Judgement of test item or positive control culture aberration values			Negative (-)	Suspicious (+-)	Positive (+)	NA	
QUALITY ASSURANCE	Last date data added to database: 07 May 2003 Auditor: (b) (4) Date audited: 16 May 2003						

1 = Aneuploidy (AE) measured in 100 cells assessed for structural aberrations
Polyploidy (PP + ER) measured in approximately 300 cells assessed for polyploidy only.

95% confidence limits : 95% of values from negative controls fall on or within the values given.

99% confidence limits : 99% of values from negative controls fall on or within the values given.

Evaluation of Amendment 0031: Applicant's response to FDA Comment/Request Question #2 (May 1, 2009)

Dr. Craig Bertha (ONDQA reviewer) noted in his Chemistry Review dated April 28, 2009 that since the review of the original application, the Applicant has added limits for (b) (4) in the excipient (b) (4) The Applicant has set the specification for (b) (4) at the level for a Class 3 solvent as designated by ICH Q3 guidelines. This specification is (b) (4) ppm. As Dr. Bertha notes in his review, (b) (4) is not included as a Class 3 solvent in ICH Q3C. Both the USP <467> general chapter and ICH Q3C include specific requirements for (b) (4), which is an isomer of (b) (4) is considered a class 3 solvent by both the USP and the ICH. (b) (4) are structurally similar and may have similar toxicologic profiles. Dr. Bertha submitted an information request to the Applicant requesting justification of the (b) (4) ppm limit for (b) (4). The Applicant provided a summary of the nonclinical toxicology literature of (b) (4) in support of their justification of the proposed specification for (b) (4). The question submitted to the Applicant as well as my evaluation of the adequacy of the Applicant's justification are below.

The following information request was submitted to the Applicant:

> Provide the data or other supporting information in justification of the limit of not more than (b) (4) ppm that is applied to residual (b) (4) in the (b) (4) excipient, which makes up the bulk of each formulated strength of the drug product. Neither ICH Q3C nor USP<467> include limits for this isomer of (b) (4) only for (b) (4). A limit of NMT (b) (4) ppm would equate to potential quantities of (b) (4) ranging from (b) (4) mg per tablet, depending on the strength**.**

Pharmacology/Toxicology Evaluation of the Applicant's response:

(b) (4) is considered a Class 3 solvent according to ICH Q3C. (b) (4) are closely related short chain saturated aliphatic hydrocarbons. The Applicant has provided literature references suggesting that (b) (4) have similar chemical and biological profiles. A structure-activity relationship exists for light aliphatic hydrocarbons with branched chain derivatives being less toxic than the corresponding straight chain alkane (b) (4) As a branched alkane, (b) (4) follows this rule and shows less anesthetic activity at a given concentration than (b) (4) In an acute study in mice, (b) (4) showed less lethality and a higher LD_{50} than (b) (4). No chronic toxicology studies with (b) (4) were found in the literature. The pharmacologic actions of (b) (4) are qualitatively similar. The toxicologic data in the literature, albeit limited, suggest that the toxicologic actions of (b) (4) are also qualitatively similar and (b) (4) appears to have a similar or even lesser toxicologic profile than (b) (4) (b) (4) is a Class 3 solvent according to ICH Q3B with a specification set at (b) (4) ppm. It is concluded that the specification of (b) (4) ppm for (b) (4) proposed by the Applicant is acceptable.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: In this cycle, the Applicant submitted one genetic toxicology study to support a proposed labeling change. An in vitro chromosomal aberration assay in human peripheral blood lymphocytes was conducted with oxycodone. The study showed that OXY is not clastogenic *in vitro* with human peripheral blood lymphocytes under conditions of the assays conducted. However, increased levels of polyploid cells were found in cultures treated with OXY at concentrations of 2500 and 3750 mcg/mL. The relevance of drug-induced increases in polyploidy to human carcinogenesis is unknown. The findings from this study will be described in the product label.

The specification set by the Applicant for residual solvent levels of (b) (4) in the (b) (4) excipient exceeded ICH Q3C guideline thresholds. The Applicant provided toxicologic justification of the proposed levels of this solvent. The Applicant's justification has been found adequate and the proposed specification of (b) (4) ppm for the residual solvent level of (b) (4) in the (b) (4) is acceptable.

Unresolved toxicology issues (if any): none

Recommendations: From a nonclinical pharmacology/toxicology perspective, based on the review of the data, this NDA may be approved.

Suggested labeling: The following recommendations are being proposed for the nonclinical sections of the label. Note that this second cycle review of the labeling takes into consideration the new data submitted by the Applicant in the second cycle. For the final version of the label, please refer to the Action Letter. Note: The recommended changes from the proposed labeling are in red or strikeout font.

Applicant's proposed labeling	*Reviewer's proposed labeling*	*Rationale*
8 USE IN SPECIFIC POPULATIONS **8.1 Pregnancy** Teratogenic Effects - Category B: The effect of oxycodone in human reproduction has not been adequately studied. (b) (4) Non-Teratogenic Effects	**8 USE IN SPECIFIC POPULATIONS** **8.1 Pregnancy** Teratogenic Effects - Category B The effect of oxycodone in human reproduction has not been adequately studied. (b) (4) Studies with oral doses of oxycodone hydrochloride in rats up to 8 mg/kg/day and rabbits up to 125 mg/kg/day, equivalent to 0.5 and 15 times an adult human dose of 160	This section has been reworded for clarity and the exposure ratios were changed to the more appropriate comparison of mg/m^2. Dose ratios are expressed on a body surface area basis.

Oxycodone hydrochloride was administered orally to female rats during gestation and lactation in a pre- and postnatal toxicity study. There were no drug-related effects on reproductive performance in these females or any long-term developmental or reproductive effects in pups born to these rats. Decreased weight gain was found during lactation and the early post-weaning phase in pups nursed by mothers given the highest dose used (6 mg/kg/day, equivalent to approximately 2-times an adult human dose of 160 mg/day, on a mg/kg basis). However, body weight of these pups recovered.	mg/day, respectively on a mg/m^2 basis, did not reveal evidence of harm to the fetus due to oxycodone. Non-Teratogenic Effects Oxycodone hydrochloride was administered orally to female rats during gestation and lactation in a pre- and postnatal toxicity study. There were no drug-related effects on reproductive performance in these females or any long-term developmental or reproductive effects in pups born to these rats. Decreased weight gain was found during lactation and the early post-weaning phase in pups nursed by mothers given the highest dose used (6 mg/kg/day, equivalent to approximately 0.4-times an adult human dose of 160 mg/day, on a mg/m^2 basis). However, body weight of these pups recovered.	
13 NONCLINICAL TOXICOLOGY **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenesis: No animal studies to evaluate the carcinogenic potential of oxycodone have been conducted. Mutagenesis: (b) (4) Oxycodone was not mutagenic in the following assays; Ames Salmonella and *E. coli* test with and without metabolic activation at doses of up to 5000 µg/plate, chromosomal aberration test in human lymphocytes (in the absence of metabolic activation) at doses of up to 1500 µg/mL, and with activation after 48 hours of exposure at doses of up to 5000 µg/mL, and in the in vivo bone marrow micronucleus assay in mice (at plasma levels of up to 48 µg/mL). Mutagenic results occurred in the presence of metabolic activation in one human chromosomal aberration test at greater than or equal to 1250 µg/mL at 24 but not 48 hours of exposure. (b) (4)	**13 NONCLINICAL TOXICOLOGY** **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenesis: No animal studies to evaluate the carcinogenic potential of oxycodone have been conducted. Mutagenesis: (b) (4) Oxycodone was genotoxic in the mouse lymphoma assay at concentrations of 50 µg/mL or greater with metabolic activation and at 400 µg/mL or greater without metabolic activation. Clastogenicity was observed with oxycodone in the presence of metabolic activation in one chromosomal aberration assay in human lymphocytes at concentrations greater than or equal to 1250 µg/mL at 24 but not 48 hours of exposure. In a second chromosomal aberration assay with human lymphocytes, no structural clastogenicity was observed either with or without metabolic activation. However, in the absence of metabolic activation, oxycodone increased numerical chromosomal aberrations (polyploidy). Oxycodone was not genotoxic in the following assays: Ames *S. typhimurium*	The suggestion of a (b) (4) has been removed. The order of the data presentation has been changed from the previous version of the label. The positive genotoxic findings with oxycodone are now presented before the negative findings Results from newly submitted Chromosomal Aberration study are described here. The finding of polyploidy was included.

(b) (4)). Mutagenicity was also observed in the mouse lymphoma assay at doses of 50 µg/mL or greater with metabolic activation and at 400 µg/mL or greater without metabolic activation. Impairment of fertility: In a study of reproductive performance, (b) (4) (b) (4)	and *E. coli* test with and without metabolic activation at concentrations up to 5000 µg/plate, chromosomal aberration test in human lymphocytes (in the absence of metabolic activation) at concentrations up to 1500 µg/mL, and with activation after 48 hours of exposure at concentrations up to 5000 µg/mL, and in the *in vivo* bone marrow micronucleus assay in mice (at plasma levels up to 48 µg/mL). Impairment of fertility: In a study of reproductive performance, rats were administered a once daily gavage dose of the vehicle or oxycodone hydrochloride (0.5, 2, and 8 mg/kg). Male rats were dosed for 28 days before cohabitation with females, during the cohabitation and until necropsy (2-3 weeks post-cohabitation). Females were dosed for 14 days before cohabitation with males, during cohabitation and up to gestation day 6. Oxycodone hydrochloride did not affect reproductive function in male or female rats at any dose tested (≤8 mg/kg/day). (b) (4)	The word (b) (4) was replaced by more accurate word "concentration."

APPENDIX/ATTACHMENTS

Reference List

(b) (4)

Gebhart E (1970) The Treatment of Human Chromosomes in vitro, in *Chemical Mutagenesis in Mammals and Man* (Vogel F and Rohrborn G eds) Springer-Verlag, Berlin.

(b) (4)

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

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

/s/

ELIZABETH BOLAN
09/03/2009

RICHARD D MELLON
09/03/2009

I concur with Dr. Bolan's recommendation that NDA 22-272 may be approved from a nonclinical pharmacology toxicology perspective and with her proposed labeling changes.

FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Rheumatology Products
10903 New Hampshire Avenue, Silver Spring, MD 20993

SUPERVISOR'S SECONDARY REVIEW
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA number:	**22-272**
Drug Substance:	**OxyContin (Reformulation)**
PDUFA Goal Date:	29-May-2008
Sponsor:	**Purdue Pharma**
Reviewer name:	R. Daniel Mellon, Ph.D., Pharmacology Toxicology Supervisor
Division name:	Division of Anesthesia, Analgesia, and Rheumatology Products
HFD #:	170
Review completion date:	1-May-2008
Recommendation:	**Approval**

I have read Dr. Elizabeth Bolan's review of the nonclinical pharmacology and toxicology sections of NDA 22-272 and agree with her conclusion that the NDA may be approved. I also concur with her recommendations for the nonclinical portions of the labeling.

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

/s/

R. Daniel Mellon
5/1/2008 04:35:12 PM
PHARMACOLOGIST

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-272**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**November 28, 2007**
PRODUCT:	**OxyContin reformulation**
INTENDED CLINICAL POPULATION:	**For management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time**
SPONSOR:	**Purdue Pharma L.P.**
DOCUMENTS REVIEWED:	**All nonclinical information in the above submission**
REVIEW DIVISION:	**Division of Anesthesia, Analgesia, and Rheumatology Products (HFD 170)**
PHARM/TOX REVIEWER:	**Elizabeth A. Bolan, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
DIVISION DIRECTOR:	**Bob Rappaport, M.D.**
PROJECT MANAGER:	**Lisa Basham**

Date of review submission to Division File System (DFS): May 1, 2008

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

This NDA can be approved from a pharmacology/toxicology perspective.

B. Recommendation for nonclinical studies

None

C. Recommendations on labeling

The following recommendations are being proposed for the nonclinical sections of the label. For the final version of the label, please refer to the Action Letter. Note: The recommended changes from the proposed labeling are in red or strikeout font.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects - Category B:
The effect of oxycodone in human reproduction has not been adequately studied. Studies in rats and rabbits with oral doses up to 8 and 125 mg/kg/day of oxycodone hydrochloride, equivalent to 0.5 and 15 times an adult human dose of 160 mg/day, respectively on a mg/m^2 basis, did not reveal evidence of harm to the fetus due to oxycodone.

Non-Teratogenic Effects
Oxycodone hydrochloride was administered orally to female rats during gestation and lactation in a pre- and postnatal toxicity study. There were no drug-related effects on reproductive performance in these females or any long-term developmental or reproductive effects in pups born to these rats. Decreased weight gain was found during lactation and the early post-weaning phase in pups nursed by mothers given the highest dose used (6 mg/kg/day, equivalent to approximately 0.4 times an adult human dose of 160 mg/day, on a mg/m^2 basis). However, body weight of these pups recovered.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis:
No animal studies to evaluate the carcinogenic potential of oxycodone have been conducted.

Mutagenesis:
(b) (4) - Oxycodone was not mutagenic in the following assays; Ames (b) (4) *S. typhimurium* and *E. coli* test with and without metabolic activation at (b) (4) concentrations of up to 5000 µg/mL, chromosomal aberration test in human lymphocytes (in the absence of metabolic activation) at (b) (4)-concentrations of up to 1500 µg/mL, and with activation after 48 hours of exposure at (b) (4) concentrations of up to 5000 µg/mL, and in the in vivo bone marrow micronucleus assay in mice (at plasma levels of up to 48 µg/mL). Mutagenic results occurred in the presence of metabolic activation in the human chromosomal aberration test at greater than or equal to 1250 µg/mL at 24 but not 48 hours of exposure and in the mouse lymphoma assay at (b) (4) concentrations of 50 µg/mL or greater with metabolic activation and at 400 µg/mL or greater without metabolic activation.

Impairment of fertility:
In a study of reproductive performance, rats were administered a once daily gavage dose of the vehicle or oxycodone (0.5, 2, and 8 mg/kg). Male rats were dosed for 28 days before cohabitation with females, during the cohabitation and until necropsy (2-3 weeks post-cohabitation). Females were dosed for 14 days before cohabitation with males, during cohabitation and up to gestation day 6. Oxycodone hydrochloride did not affect reproductive function in male or female rats at any dose tested (≤8 mg/kg/day).

Teratogenic Effects:
The effect of oxycodone in human reproduction has not been adequately studied. Studies in rats and rabbits with oral doses up to 8 and 125 mg/kg/day of oxycodone hydrochloride, equivalent to 0.5 and 15 times an adult human dose of 160 mg/day, respectively on a mg/m^2 basis, did not reveal evidence of harm to the fetus due to oxycodone.

Non-Teratogenic Effects:
Oxycodone hydrochloride was administered orally to female rats during gestation and lactation in a pre- and postnatal toxicity study. There were no drug-related effects on reproductive performance in these females or any long-term developmental or reproductive effects in pups born to these rats. Decreased weight gain was found during lactation and the early post-weaning phase in pups nursed by mothers given the highest dose used (6 mg/kg/day, equivalent to approximately 0.4 times an adult human dose of 160 mg/day, on a mg/m^2 basis). However, body weight of these pups recovered.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

This NDA describes a reformulation of OxyContin which contains commonly used excipients that do not require toxicologic evaluation. No new nonclinical studies were required by the Division; however, the Sponsor submitted Segment I and Segment III reproductive toxicology studies in order to update the label.

Although the F_0 rats in both studies exhibited signs of overt toxicity at the highest dose tested, the exposure margins are less than one on a mg/m^2 basis when compared to a daily dose of 160 mg/day in the human. Based on the nonclinical studies conducted to date with oxycodone there is no reason to change the Pregnancy Category from B to C.

Fertility and Early Embryonic Development (Segment I):
The Segment I study demonstrated that oxycodone did not affect reproductive function in male and female rats at levels that produced parental toxicity. The NOEL for male and female fertility and early embryonic development in this study is 8 mg/kg, the highest dose tested. This dose yields an exposure margin of 0.5 on a mg/m^2 basis when compared to a daily dose of 160 mg/day in the human.

Perinatal and Postnatal Development (Segment III):
The Segment III study demonstrated that oxycodone did not affect peri- and postnatal development in rats at doses that produced maternal toxicity with the exception of recoverable decreases in F_1 body weights observed at the highest dose (6 mg/kg). No other treatment-related toxicological findings were observed in the F_1 pups and no toxicologic findings were seen in the F_2 pups. Comparison of the highest dose tested in rats (6 mg/kg) yields an exposure margin of 0.4 on a mg/m^2 basis when compared to a daily dose of 160 mg/day in the human.

Three pups (two male F_1 high dose and one female F_2 low dose) showed major malformations involving the heart and lungs. The weight of evidence suggests that these observations are not treatment-related for the following reasons:

- No major malformations were observed in the Segment II teratogenicity studies in either the rat or the rabbit.
- There is no evidence from the clinic that the incidence of major malformations is increased in the offspring of pregnant women taking oxycodone (see Maternal Health Consult).
- There is no evidence that opioids are multigenerational teratogens therefore the appearance of the F_2 pup with major malformations suggests a background incidence of malformations in this rat population.
- The dams of the affected high dose F_1 pups exhibited overt maternal toxicity.

B. Nonclinical safety issues relevant to clinical use
No new nonclinical safety issues were identified.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

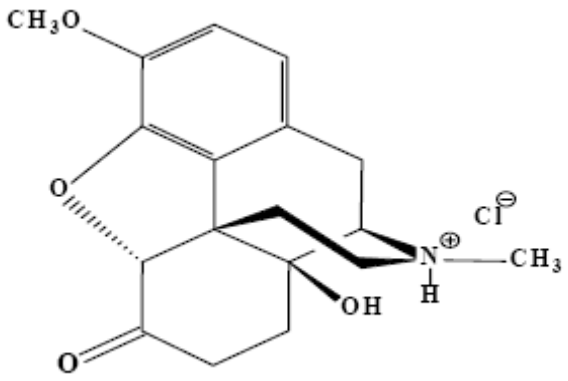
NDA number: 22-272
Review number: 1
Sequence number/date/type of submission: 000/November 28, 2007/original NDA submission
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Purdue Pharma, L.P. Stamford, CT 06901
Manufacturer for drug substance: (b) (4)

Reviewer name: Elizabeth A. Bolan, Ph.D.
Division name: Division of Anesthesia, Analgesia, and Rheumatology Products

HFD #: 170
Review completion date: April 7, 2008

Drug:

Trade name: OxyContin
Generic name: oxycodone hydrochloride
Code name: N/A
Chemical name: 4, 5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.
CAS registry number: 124-90-3
Molecular formula/molecular weight: $C_{18}H_{21}NO_4 \bullet HCl$; MW 351.83 g/mol
Structure:



Relevant INDs/NDAs/DMFs:

IND/NDA/DMF	*drug/compound*	*sponsor*	*division*	*status*
NDA 20-553	OxyContin	Purdue Pharma	DAARP	Approved 1995
IND 29,038	oxycodone HCl	Purdue Pharma	DAARP	Active
[redacted] (b) (4)			NA	reviewed: 6/29/2007

Drug class: semi-synthetic opioid

Intended clinical population: For management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

Clinical formulation: The clinical formulation of this product is a tablet containing 10, 15, 20, 30, and 40 mg of oxycodone with characteristics intended by the Sponsor to reduce the potential for abuse/misuse. The tablets are composed of oxycodone HCl, polyethylene oxide, magnesium stearate and (b) (4) The inactive ingredients are used below levels found in previously FDA-approved products.

Route of administration: oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

For this 505(b)(1) NDA, Purdue Pharma is cross-referencing the nonclinical data originally submitted for NDA 20-553, which is also owned by the Sponsor and was submitted as a 505(b)(1) NDA application.

Studies reviewed within this submission:

- Study # OXY-N-003: Oxycodone Hydrochloride: an Oral Fertility and Embryonic Development Study in Rats

- Study # OXY-N-004: Oxycodone HCl: an Oral Pre- and Postnatal Development Study in Rats

- Refer to the pharmacology/toxicology review of the original OxyContin NDA (Purdue Pharma; NDA 20-553) by BeLinda Hayes, Ph.D. dated August 21, 1995. Portions of Dr. Hayes' review have been reproduced verbatim in this review for background purposes.

Studies <u>not</u> reviewed within this submission: none

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

The following summary of oxycodone pharmacology was excerpted verbatim from the original OxyContin (Purdue Pharma, NDA 20-553) review by BeLinda Hayes, Ph.D. dated August 21, 1995.

> Oxycodone hydrochloride, a semisynthetic derivative of thebaine, is an opioid agonist that is pharmacologically similar to morphine. Preclinical studies have shown that oxycodone is an agonist with potent analgesic activity in a variety of preclinical antinociceptive assays. Oxycodone also has the typical opioid-like CNS depressant activity.
>
> The analgesic activity of oxycodone has been evaluated in rats (Carter, 1991; Poyhia and Kalso, 1992; Leow and Smith, 1994) and mice (Weinstein and Gaylord, 1979; Swedberg, 1994). The analgesic activity of oxycodone was compared to that of morphine and codeine in the rat 55° hot plate assay using hind paw lick and hind paw lick or jump as the endpoint (Carter, 1991). Oxycodone's analgesic activity was qualitatively similar to morphine and codeine regardless of the endpoint measured. Oxycodone (p.o.) was more potent than codeine (p.o.) but less potent than morphine (i.p., s.c.).
>
> The antinociceptive activity of oxycodone hydrochloride was compared to that of morphine hydrochloride in the rat tail flick and hot plate nociceptive tests following intraperitoneal, intrathecal and subcutaneous administrations (Poyhia and Kalso, 1992). Poyhia and Kalso (1992) reported that the strength of oxycodone's analgesic activity is route-dependent. Oxycodone was more potent than morphine in both thermal nociceptive tests following systemic administration; oxycodone was 2 and 4 times more potent than morphine following subcutaneous and intraperitoneal administration, respectively. However, weak antinociceptive effects were observed following intrathecally administered oxycodone; it was approximately 14 times less potent than morphine. Plummer et al. and Poyhia et al. have also reported similar findings in rats using the hot plate and tail flick assays (Plummer, et al., 1990; Poyhia, et al., 1992).
>
> Poyhia and Kalso (1992) also compared the onset and duration of oxycodone's analgesic activity to that of morphine following intraperitoneal, intrathecal and subcutaneous administrations. In the rat tail flick and hot plate nociceptive assays, the antinociceptive effects of oxycodone (2.5-5.0 mg/kg) had a significantly ($p \leq 0.05$) faster onset (mean = 15 min) in comparison to morphine (5-10 mg/kg) which had a mean onset of 30 minutes following both subcutaneous and intraperitoneal administrations. In contrast to the onset of antinociceptive effects observed with the lower doses, the highest dose of oxycodone (10 mg/kg)

and morphine (20 mg/kg) had similar onset of analgesic activity following both routes of administration. The duration of action was similar for both drugs following subcutaneous administration; whereas, intraperitoneal oxycodone had a significantly ($p \leq 0.05$) longer duration of action in comparison to intraperitoneal morphine. Intrathecal oxycodone had a shorter onset and duration of action in comparison to morphine. Plummer et al. (1990) postulated that the weak antinociceptive effects, fast onset and short duration of action, observed following intrathecal administration are due to its low polarity in comparison to the high polarity of morphine.

The antinociceptive activity of oxycodone was compared to morphine and its metabolite noroxycodone in Sprague Dawley rats following intracerebroventricular (ICV) administration (Leow and Smith, 1994). Oxycodone and its metabolite noroxycodone were effective analgesics following ICV administration. Relative to morphine, oxycodone and noroxycodone were 2.3 and 5.9 times less potent than morphine, respectively. Oxycodone's analgesic activity had a more rapid onset than morphine or noroxycodone. Oxycodone's maximum antinociception occurred at 9.3 minutes ($p \leq 0.05$) post-injection; whereas morphine's and noroxycodone's antinociceptive effects occurred at 31.8 and 34.6 minutes post-dosing, respectively. Consistent with morphine-induced analgesia, the analgesic effects of oxycodone and noroxycodone are mediated by opioid receptors. Naloxone pre-administration (55 nmol, ICV, 15 min pre) abolished the antinociceptive effects of oxycodone (227 nmol) and reduced the antinociceptive effects of both noroxycodone (332 nmol) and morphine (93 nmol).

The analgesic activity of oxycodone and its metabolite noroxycodone has also been evaluated in mice (Weinstein and Gaylord, 1979). Using a modification of the mouse phenylquinone test, noroxycodone was less potent than oxycodone following oral or subcutaneous administration. It was 35 and 138 times less potent than oxycodone following oral and subcutaneous administration, respectively.

Using the mouse grid-shock analgesia test, Swedberg (1994) compared the analgesic activity of oxycodone to that of morphine and several other mu agonists (i.e. methadone, fentanyl, codeine, etorphine and meperidine). Consistent with results obtained in rats following subcutaneous administration, oxycodone was more potent than morphine. The ED_{50}s (95% C.L.) for oxycodone and morphine were 1.87 (1.26-2.77) mg/kg and 2.36 (1.50-3.71) mg/kg, respectively. Analysis of the data showed that the results in mice correlated well ($R = .989$) with their clinical doses.

Oxycodone produces opioid-type CNS depression (i.e. loss of righting, placing and corneal reflexes and catalepsy) in rats. The CNS depressant effects of oxycodone were compared to those of morphine following subcutaneous, intraperitoneal and intrathecal administration (Poyhia and Kalso, 1992).

Consistent with its analgesic properties, its CNS depressant effects are route-dependent. Oxycodone (2.5-10.0 mg/kg) was more potent than morphine in eliciting CNS depressant effects following both subcutaneous and intraperitoneal administrations. Subcutaneously and intraperitoneally administered oxycodone caused a dose-dependent loss in all reflexes measured and induced catalepsy; whereas subcutaneously administered morphine (10 and 20 mg/kg) only affected the righting and corneal reflexes and induced catalepsy. Only the righting reflex was loss and morphine-induced catalepsy were observed following the intraperitoneal administration of 20 mg/kg morphine. Neither oxycodone (12.5 and 100 µg) nor morphine (6.25 and 50 µg) elicited any CNS depressant activity following intrathecal administration.

The binding profile of oxycodone has been evaluated in rat brain (Pert and Snyder, 1973; Chen, et al., 1991). Using ^{3}H-naloxone or ^{3}H-DAMGO as the ligand for the mu opioid receptor, both groups of investigators demonstrated that oxycodone binds to the mu opioid receptors with weak affinity. These results were surprising considering that oxycodone was a potent analgesic agent in rats and has an analgesic potency approximately 0.7 fold that of morphine in humans (Ross and Hill, 1993). These findings suggest that oxycodone's analgesic efficacy may be due to the formation of an active metabolite or metabolites. Beaver (1978), Kalso (1990) and Inturrisi (1990) have suggested that part of the analgesic effects of oxycodone can be attributed to active metabolites (Beaver, et al., 1978; Inturrisi, et al., 1990; Kalso, et al., 1990). In a clinical study comparing the pharmacokinetic profile of oxycodone after intramuscular and oral administrations, Poyhia (1992) reported that noroxycodone and oxymorphone are two major metabolites of oxycodone (Poyhia, et al., 1992).

2.6.2.2 Primary pharmacodynamics

No new studies were submitted by the Sponsor.

Mechanism of action: Oxycodone is a semisynthetic thebaine-derived opioid which has been shown to have agonist activity predominantly mediated by the mu opioid receptor, but agonist activity via the delta and kappa opioid receptor subtypes has also been demonstrated (Ordonez, et al., 2007).

Drug activity related to proposed indication: The opioid agonist activity described above is responsible for the analgesic actions observed in humans.

2.6.2.3 Secondary pharmacodynamics

No new studies were submitted by the Sponsor.

2.6.2.4 Safety pharmacology

No new studies were submitted by the Sponsor.

2.6.2.5 Pharmacodynamic drug interactions
No new studies were submitted by the Sponsor.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

No new studies were submitted by the Sponsor for any of the following pharmacokinetic parameters.

2.6.4.1 Brief summary

2.6.4.2 Methods of Analysis

2.6.4.3 Absorption

2.6.4.4 Distribution

2.6.4.5 Metabolism

2.6.4.6 Excretion

2.6.4.7 Pharmacokinetic drug interactions

2.6.4.8 Other Pharmacokinetic Studies

2.6.4.9 Discussion and Conclusions

2.6.4.10 Tables and figures to include comparative TK summary

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: No new studies were submitted by the Sponsor.

Genetic toxicology: No new studies were submitted by the Sponsor.

Carcinogenicity: No new studies were submitted by the Sponsor.

Reproductive toxicology: The Sponsor submitted Segment I and Segment III reproductive and developmental toxicology studies. Segment II studies were previously

reviewed during the original approval and the results appear in the current version of the label.

The Segment I study demonstrated that oxycodone did not affect reproductive function in male and female rats at levels that produced parental toxicity. The NOEL for male and female fertility and early embryonic development in this study is 8 mg/kg, the highest dose tested.

The NOEL for developmental toxicity in the Segment III study was 2 mg/kg in the F_1 generation and 6 mg/kg in the F_2 generation. Decreased body weights in the F_1 generation were observed at the highest dose (6 mg/kg) in the Segment III study. No other toxicological findings were observed in the F_1 pups and no toxicologic findings were seen in the F_2 pups. Three pups (two male F_1 high dose and one female F_2 low dose) showed major malformations involving the heart and lungs but the weight of evidence suggests that these observations are not treatment-related. Although the F_0 rats in both studies exhibited signs of overt toxicity at the highest dose tested, the exposure margin is less than one when compared to a daily dose of 160 mg/day in the human.

Special toxicology: No new studies were submitted by the Sponsor.

2.6.6.2 Single-dose toxicity
No new studies were submitted by the Sponsor.

2.6.6.3 Repeat-dose toxicity
No new studies were submitted by the Sponsor.

2.6.6.4 Genetic toxicology
No new studies were submitted by the Sponsor.

2.6.6.5 Carcinogenicity
No new studies were submitted by the Sponsor.

2.6.6.6 Reproductive and developmental toxicology

Fertility and early embryonic development

Study title: Oxycodone Hydrochloride: an Oral Fertility and Embryonic Development Study in Rats

Key study findings:

- Decreased group mean body weights and gains or losses in body weight changes were observed for males and females at 8 mg/kg during the treatment period.
- Decreased food consumption for males and females was observed at 8 mg/kg during the treatment period.

- Clinical signs including increased or decreased activity, excessive licking, grooming and scratching, chewing of paws, limbs or cage, and hyperreactivity were observed for both males and females at ≥0.5 mg/kg. Abnormal gait and uncoordination were observed in males at 8 mg/kg.
- The NOAEL for parental overt toxic effects for both males and females in this study is 2 mg/kg.
- The NOEL for male and female fertility and early embryonic development in this study is 8 mg/kg, the highest dose tested.

Study no.: OXY-N-003
Volume #, and page #: EDR 4.2.3.5.1
Conducting laboratory and location: (b) (4)

Date of study initiation: September 13, 2005
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Oxycodone HCl USP, 200410050003, 98.76%

Methods

Doses: 0, 0.5, 2, 8 mg/kg/day; doses are in terms of oxycodone base
Species/strain: Sprague Dawley rat/Crl:CD(SD)
Number/sex/group: 22 rats/sex/group
Route, formulation, volume, and infusion rate: oral gavage, volume: 10 mL/kg
Satellite groups used for toxicokinetics: none

Study design: Each rat was administered a once daily gavage dose of the vehicle or test article. Male rats were dosed for 28 days before cohabitation with females, during the cohabitation and until necropsy (2-3 weeks post-cohabitation). Females were dosed for 14 days before cohabitation with males, during cohabitation and up to gestation day (GD) 6. Cohabitation was a maximum of 21 days. Caesarean sections were performed on GD 13.

Parameters and endpoints evaluated: Clinical signs, body weights, food consumption**,** mortality, gross pathology. Female specific data included determination of estrous cycle 29 days before cohabitation and during cohabitation until a positive identification of mating was made, number of corpora lutea, number of live and dead embryos and resorptions were recorded. Male specific data included evaluation of sperm motility, spermatozoa count and sperm morphology.

The following organs were weighed: brain, epididymides, ovaries, prostate, seminal vesicles and testes. The following organs were preserved for possible histopathologic examination: abnormal tissues, epididymides, mammary gland, ovaries, prostate, seminal vesicles and testes, uterus and vagina.

Results

The study is valid. The dosing of the dams in this study reached overtly toxic levels at the high dose (8 mg/kg) as evidenced by clinical signs of excessive chewing of fore and

hind limbs and paws accompanied by redness, scabbing and thinning fur in some animals as well as decreases in food consumption and body weights ≥10%.

Mortality: There was no mortality in the study. One 2 mg/kg group female was euthanized on study day 32 because the rat was pregnant but mating had not been detected. A necropsy of this rat was performed and no gross pathological observations were noted.

Clinical signs: Clinical observations were performed twice daily (one observation within two hours post dose). Treatment-related findings in all treatment groups for both males and females included periods of increased or decreased activity, excessive licking, grooming and scratching, chewing of paws, limbs or cage, and hyperreactivity (Tables 1 and 2). Effects secondary to the excessive grooming, licking and chewing were fur thin cover, skin scabs and/or redness of the affected area were observed in some animals. Abnormal gait and uncoordination were observed in males at 8 mg/kg. The sponsor states that all of the clinical signs were observed within two hours of dosing and were no longer apparent by the end of the day.

The Sponsor states that the NOAEL for toxicity for males and females is below 0.5 mg/kg based on the occurrence of clinical signs. This reviewer argues that the occurrence of clinical signs such as increased or decreased activity, chewing on the cage and excessive grooming are not necessarily "adverse" and do not demonstrate overt toxicity of oxycodone. The clinical signs which I considered to reach levels of overt toxicity were such as excessive chewing of limbs/paws when accompanied by scabbing, lesions or thin fur cover, abnormal gait and uncoordination as well as weight changes and decreases in food consumption greater than 10%.

Table 1. Clinical Observations: Males

Males		*Dose of oxycodone mg/kg/day*			
		0	***0.5***	***2***	***8***
n		*22*	*22*	*22*	*22*
Increased activity		2	**20**	**22**	**22**
Decreased activity		13	**20**	**21**	**21**
Chewing/ cage		2	**12**	**18**	**19**
Excessive grooming		5	**11**	**22**	**21**
Excessive licking		-	**4**	**12**	**11**
Excessive scratching		2	**8**	**20**	**10**
Hyperreactive		-	**6**	**12**	**22**
Abnormal gait		-	-	-	**6**
Uncoordinated		-	-	-	**4**
Left Forelimb	***Chewing***	1	3	**15**	**16**
	Skin lesion	-	-	-	-
	Skin scab	-	-	-	-
	Fur thin cover	3	1	4	4
Left Forepaw	***Chewing***	5	**12**	**22**	**22**
	Skin lesion	-	-	-	-
	Skin scab	3	4	4	4
	Fur thin cover	7	3	7	8
Right Forelimb	***Chewing***	-	**4**	**16**	**15**
	Skin lesion	-	-	-	-
	Skin scab	-	-	-	-
	Fur thin cover	4	-	3	5
Right Forepaw	***Chewing***	4	**11**	**22**	**22**
	Skin lesion	-	-	1	-
	Skin scab	6	3	3	5
	Fur thin cover	7	2	7	8
Tail	***Chewing***	-	2	**13**	**6**
	Skin scab	2	2	4	**6**

Table 2. Clinical Observations: Females

Females		Dose of oxycodone mg/kg/day							
		0		0.5		2		8	
		Pre - mating	Post-mating	Pre - mating	Post-mating	Pre - mating	Post-mating	Pre - mating	Post-mating
n		22	22	22	22	22	21	22	22
Increased activity		1	-	**21**	**10**	**22**	**18**	**21**	**11**
Decreased activity		2	-	**9**	3	**16**	-	**16**	**7**
Chewing/ cage		2	-	**15**	**7**	**18**	**6**	**10**	**6**
Excessive grooming		3	-	**20**	**11**	**18**	**17**	**12**	**6**
Excessive licking		-	-	**5**	-	3	-	-	1
Excessive scratching		2	2	**9**	**7**	**6**	3	1	1
Hyperreactive		-	-	-	-	**3**	-	**4**	-
Left Forelimb	Chewing	1	1	**5**	2	**8**	1	**11**	-
	Skin lesion	-	-	-	-	-	-	1	-
	Skin scab	-	-	-	-	1	-	1	1
	Fur thin cover	-	-	-	-	2	2	**6**	**6**
Left Forepaw	Chewing	2	-	**11**	**8**	**21**	**17**	**20**	**20**
	Skin lesion	-	-	-	-	1	-	2	-
	Skin scab	-	-	-	-	1	-	2	**4**
	Fur thin cover	1	3	1	1	2	2	**8**	**8**
Right Forelimb	Chewing	1	-	**4**	**3**	**7**	**4**	**7**	1
	Skin lesion	-	-	-	-	-	-	-	-
	Skin scab	-	-	-	-	-	-	-	1
	Fur thin cover	-	1	-	-	1	3	**5**	**6**
Right Forepaw	Chewing	5	1	**11**	**9**	**19**	**16**	**21**	**18**
	Skin lesion	-	-	-	-	1	-	1	-
	Skin scab	-	-	1	-	-	-	**2**	**3**
	Fur thin cover	-	3	1	2	**4**	3	**7**	**6**
Tail	Chewing	-	1	**7**	**7**	**8**	**4**	**9**	3
	Skin red	-	-	-	-	-	-	1	3

Body weight: Individual body weights were recorded twice weekly. Statistically significant decreases in group mean body weight were observed in males at the high dose from day 8 through the completion of the study (day 64; Figure 1, Table 3). These decreases ranged from 6.3-10.3%. Females showed statistically significant reductions in group mean body weight at the high dose from premating day 11 through GD 9 (Figure 2 and Table 4) with decreases ranging from 4.5-10%.

As compared to control, males at the high dose showed statistically significant increases in group mean body weight changes from dosing days 1-4 (3.1 g ± 6.2) and days 53-57

(6.1 g ± 4.5) and statistically significant decreases on days 4-8 (-2.5 g ± 16.1) and days 57-60 (-2.5 g ± 6.3). As compared to control, high dose females showed statistically significant increases in group mean body weight changes from dosing days -4 through -8 (2.9 g ± 5.2), GD 0-3 (12.6 g ± 5.3), GD 6-9 (19.5 g ± 9.4) and GD 9-13 (30.8 g ± 6.4) statistically significant decreases on days -11 through -4 (-1.9 g ± 7.1). The low and mid dose females showed increases (24.9 g ± 5.2 and 25.5 g ± 4.8, respectively) as compared to control (19.3 g ± 5.8) in body weight changes at the last time point. There were no other significant differences in the low and mid dose at other time points.

Figure 1. Group Mean Body Weights: Males

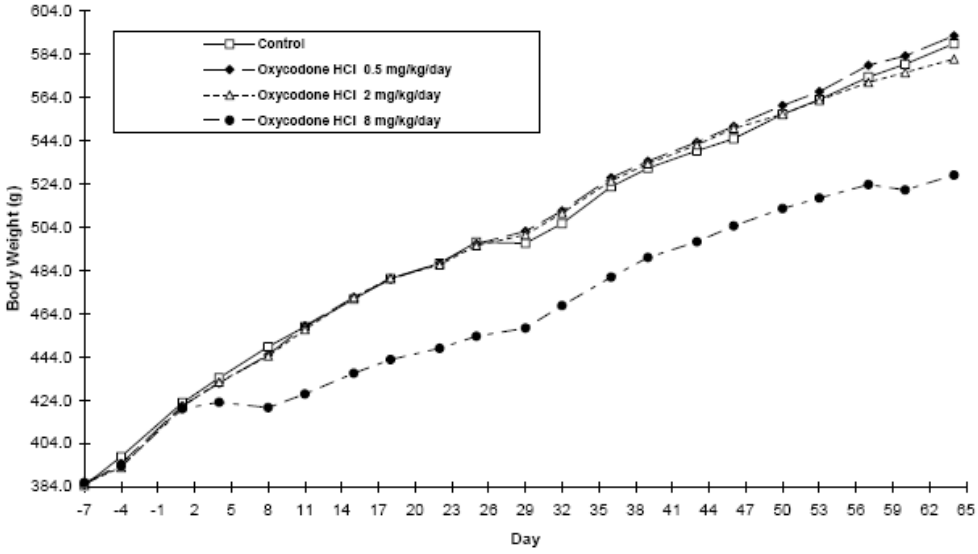


Figure 2. Group Mean Body Weights: Females

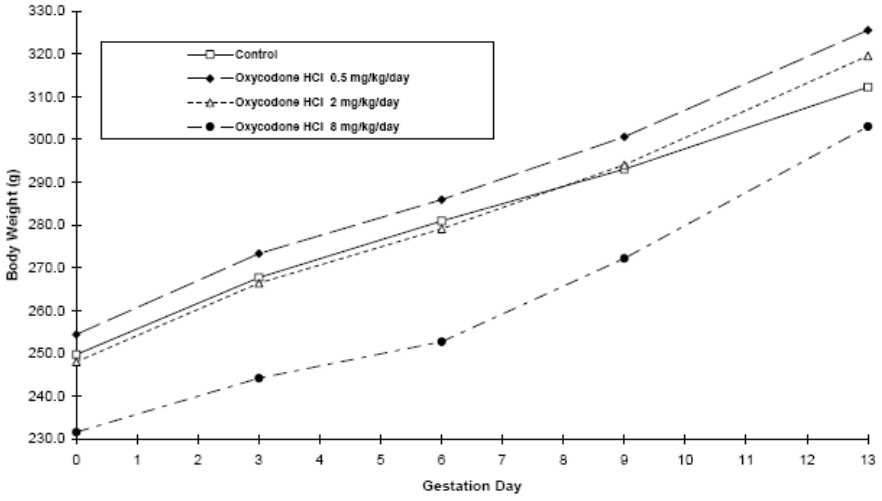


Table 3. Group Mean Body Weights: Males

Group mean body weights F_0 males: Percent change from control											
Dose	***Day***										
mg/kg	***-7***	***-4***	***1***	***4***	***8***	***11***	***15***	***18***	***22***	***25***	***29***
0.5	0.1	-0.8	-0.3	-0.6	-0.8	0.1	0.2	-.01	0	-.02	1.1
2	0.3	-1.2	-0.4	-0.4	-1.0	-0.3	0.2	0	-0.2	-0.3	0.7
6	0.4	-1.1	-0.7	-2.6	**-6.3C**	**-6.8C**	**-7.3C**	**-7.8C**	**-8.1C**	**-8.8C**	**-8.0C**

Group mean body weights F_0 males: Percent change from control, continued										
Dose	***Day***									
mg/kg	***32***	***36***	***39***	***43***	***46***	***50***	***53***	***57***	***60***	***64***
0.5	1.1	0.8	0.6	0.7	1.1	0.7	0.7	1.0	0.7	0.6
2	0.9	0.5	0.4	0.5	0.9	0	-0.1	-0.4	-0.7	-1.2
6	**-7.5C**	**-8.0C**	**-7.8C**	**-7.8C**	**-7.4C**	**-7.8C**	**-8.1C**	**-8.7C**	**-10.0C**	**-10.3C**

Raw data (group means) significantly different from control group:
A P≤ 0.05, **B** P≤ 0.01, **C** P≤ 0.001 (Dunnett)

Table 4. Group Mean Body Weights: Females

Group mean body weights F_0 females: Percent change from control										
Dose	***Premating Day***					***Pregnant Day***				
mg/kg	***-4***	***1***	***4***	***8***	***11***	***0***	***3***	***6***	***9***	***13***
0.5	0	0.7	0.1	1	1.6	1.9	2.1	1.8	2.6	4.3
2	-0.1	0.5	0.4	0.3	0.6	-0.7	-0.5	-0.6	0.3	2.3
6	-0.1	0.5	-2.0	-3.7	**-4.5A**	**-7.2C**	**-8.8C**	**-10.0C**	**-7.1B**	-2.9

Raw data (group means) significantly different from control group:
A P≤ 0.05, **B** P≤ 0.01, **C** P≤ 0.001 (Dunnett)

Food consumption: Individual food consumption was determined twice weekly except during the cohabitation period. Food consumption for pregnant females was determined

for GD 0-3, GD 3-6, GD 6-9, and GD 9-13. During the treatment period, reduced food consumption was observed in both males and females at the high dose only. High dose males showed statistically significant decreases in food consumption at ten of eleven time points from day 1 to the end of treatment (day 64) with decreases ranging from 8.8-15.6% (Table 5). Females showed statistically significant decreases in food consumption at the five time points between premating days 1-4 to GD 3-6 at the high dose with decreases ranging from 10-15.4% (Table 6). Dosing for females ended on GD 6. The high dose group did not show further reductions in weight after the dosing had ended. The mid dose group showed a statistically significant increase of 7.4% at the GD 9-13 time point only.

Table 5. Group Mean Food Consumption: Males

Group mean food consumption F_0 males: Percent change from control													
Dose	***Days***												
mg/kg	***-7 - -4***	***-4- 1***	***1- 4***	***4-8***	***8-11***	***11-15***	***15-17***	***18-22***	***22-25***	***50-53***	***53-57***	***57-60***	***60-64***
0.5	-3.1	0	-3.2	-3.3	0	0	-3.2	-3.3	0	-2.9	-2.9	-5.7	-3.1
2	0	3.3	-3.2	-3.3	0	3.3	0	0	0	-5.9	-5.9	-2.9	-6.3
6	0	3.3	**-9.7C**	**-13.3C**	**-16.7C**	**-10.0B**	**-9.7A**	-6.7	**-9.7A**	**-11.8B**	**-8.8B**	**-11.4C**	**-15.6C**

Raw data (group means) significantly different from control group:
A P≤ 0.05, **B** P≤ 0.01, **C** P≤ 0.001 (Dunnett)

Table 6. Group Mean Food Consumption: Females

Group mean food consumption F_0 females: Percent change from control								
Dose	***Premating Day***				***Gestation Day***			
mg/kg	***-4-1***	***1-4***	***4-8***	***8-11***	***0-3***	***3-6***	***6-9***	***9-13***
0.5	0	0	-5.0	5.0	0	0	7.7	3.7
2	0	-4.8	0	5.0	-3.8	-3.7	3.8	**7.4A**
6	0	**-14.3B**	**-10.0A**	**-10.0C**	**-15.4C**	**-14.8C**	0	7.4

Raw data (group means) significantly different from control group:
A P≤ 0.05, **B** P≤ 0.01, **C** P≤ 0.001 (Dunnett)

Toxicokinetics: Not performed.

Necropsy: There were no treatment-related effects on organ weights for males or females. No treatment-related gross pathology findings were observed for males or females.

Fertility parameters (mating/fertility index, corpora lutea, preimplantation loss, etc.):
Female reproductive assessments:
No treatment-related effects were observed on number of days in estrous, number of cycles seen or average cycle length during predosing or dosing. Mean day-to-mating, mating and fertility indices and conception rate also showed no treatment-related effects. No treatment-related effects were observed on the total number of corpora lutea, implantation sites, live and dead embryos, early resorptions and the pre and post implantation losses. Statistically significant decreases in the total number of implantation sites and number of live embryos were seen in the high dose group but the numbers were with in the historical control range. Selected fertility parameters are summarized in Table 7.

Table 7. Selected Fertility Parameters

mg/kg oxycodone	n	Total number of corpora lutea	Total number of implantation sites	Number of live embryos	Number of dead embryos
0	22	17.4 ± 3.4	15.5 ± 3.5	14.8 ± 3.2	0
0.5	22	18.1 ± 2.1	16.6 ± 1.5	15.6 ± 2.3	0
2	20	17.2 ± 2.6	14.5 ± 3.8	13.8 ± 3.8	0
8	21	16.7 ± 2.5	**14.2* ± 2.2**	**13.3** ± 2.2**	0

* P≤ 0.05; ** P≤ 0.01
Historical control range for total number of implantation sites and number of live embryos are 13.7-18.6 and 12.7-17.3, respectively.

Male reproductive assessments:
No treatment-related effects were observed on individual spermatozoa counts, morphology and percentages of motile sperm.

Embryofetal development

The Segment II studies in rat and rabbit were reviewed for the initial approval of OxyContin (NDA 20-553) in 1995. With the exception of examining the raw data for the occurrence of structural malformations, the studies have not been re-reviewed. Summaries of the rat and rabbit studies from the original review by BeLinda Hayes, Ph.D. have been reproduced verbatim below.

> The developmental and reproductive toxicity potential of oxycodone was evaluated in both rats and rabbits according to the standard protocol for a Segment II reproductive toxicity study. The Segment II reproductive study in rats was

conducted at (b) (4) during the period December 21, 1993 thru January 21, 1994. The Segment II reproductive toxicity study in rabbits was performed by (b) (4) during the period December 3, 1993 thru January 7, 1994. Both studies were conducted in compliance with the Good Laboratory Practice Regulations.

SEGMENT II STUDY IN RATS (STUDY # DSE-061)

This Segment II reproductive study was conducted in 125 time-mated female Sprague-Dawley rats (Crl:CD BR VAF/Plus). The rats were equally and randomly divided into five treatment groups (N =25/group). The treatment groups were: 1) vehicle control (distilled water, 10 ml/kg/day); 2) 0.5 mg oxycodone HCl/kg/day; 3) 2.0 mg oxycodone HCl/kg/day; 4) 4.0 mg oxycodone HCl/kg/day and 5) 8.0 mg oxycodone HCl/kg/day. These doses were selected based on results from the preliminary dose-range finding study ((b) (4) Study # DSE-060). The pregnant rats were treated orally with vehicle or oxycodone on days 6-15 of gestation. On day 20 of pregnancy, the rats were sacrificed and evaluated at necropsy. Measurements included bodyweight of live fetuses, number and distribution of implantation sites, number of resorptions, number of dead and live fetus, number of corpora lutea, type of abnormalities in major organs, skeletal variants and external malformations in fetuses. Observations during the dosing period included: overt signs of toxicity (daily, pre-and post-dosing), body weight measurement (gestation days 0, 6, 9, 12, 16, and 20) and food consumption (gestation days 0-6, 6-9, 9-12, 12-16, 16-20, 6-16 and 0-20).

RESULTS. There were no treatment-related mortalities. Oxycodone-induced overt signs of toxicity were observed in the 4.0 and 8.0 mg/kg groups. These overt signs included: decreased activity, excessive gnawing of the forelimbs, lacrimation, salivation, exophthalmus, increased hair loss on the forelimbs; these signs were less severe in the 4.0 mg/kg group. A dose-dependent suppression of body weight gain (from day 0-20) was observed. Relative to control, a -0.5%, 0.25%, 1.0%, and 3.77% suppression in maternal body weight was observed in the 0.5, 2.0, 4.0, and 8.0 mg/kg groups, respectively; the lower body weight gain observed in the high dose group was statistically significant. Food consumption was significantly lower on gestation days 6-9, 9-12, and 6-16 for rats in the 4.0 mg/kg treatment group, and on days 6-9, 9-12, 12-16, 6-16, and 0-20 for rats in the 8.0 mg/kg group.

Oxycodone at doses of 0.5, 2.0, 4.0, and 8.0 mg/kg was without teratogenic or embryocidal effects; no significant effects on the mean number of corpora lutea, implantation sites, live fetuses, pre- and post-implantation loss, late and early resorption, visceral or skeletal anomalies/malformations. No treatment related fetal death occurred; all fetuses were viable at time of cesarean section. No statistically significant effect was observed in mean fetal weight. The mean fetal weight was 3.6, 3.5, 3.6, 3.7, 3.6 grams for the 0.0, 0.5, 2.0, 4.0 and 8.0 mg/kg treatment group, respectively.

SEGMENT II STUDY IN RABBITS (STUDY # DSE-059)

New Zealand White SPF rabbits, artificially inseminated to induce pregnancy, were subjects for the reproductive study that evaluated the teratogenic and embryocidal potential of oxycodone following oral administration. The rabbits were assigned to five treatment groups (n= 20/group): 1) vehicle control, distilled water (3.0 mL/kg); 2) 1.0 mg oxycodone/kg/day; 3) 5.0 mg oxycodone/kg/day; 4) 25.0 mg oxycodone/kg/day; and 125.0 mg oxycodone/kg/day. These doses were selected based on results from the preliminary dose-range finding study (b) (4) Study # DSE-058). The rabbits were dosed once daily during day 6 to day 18 of presumed gestation. On day 29 of gestation, rabbits were sacrificed to examine fetuses for implantation, sex ratio, viability, resorption, visceral and skeletal malformations. Observations during the dosing period included: overt signs of toxicity (daily, pre-dosing and 1 hr. post-dosing), body weight measurement (gestation days 0, 6, 12, 19, and 24) and food consumption (gestation days 0-6, 6-12,12-19,19-24,24-29,6-19 and 0-29).

RESULTS. No treatment-related maternal deaths occurred. One doe in the 1.0 mg/kg group died from a mechanical injury (i.e. misintubation). One doe in the 1.0 mg/kg group and 1 doe in the 125.0 mg/kg group aborted. No oxycodone-induced clinical signs were observed in the 1.0 and 5.0 mg/kg groups. Does in the 25.0 and 125.0 mg/kg groups exhibited decreased activity and decreased defecation. These effects were dose dependent; 40% and 100% of the subjects in the 25.0 and 125.0 mg/kg groups displayed decreased activity, respectively. Decreased defecation was observed in 30% and 90% of the subjects in the 25.0 and 125.0 mg/kg groups, respectively.

No significant suppression in maternal body weight was observed during the entire gestational period (days 0-29) in the 1.0 and 5.0 mg/kg groups relative to the control. A non-significant reduction in body weight gain was observed in the 25.0 mg/kg group; relative to the control group, a 6.3% suppression in body weight gain during the entire gestational period was noted. However, a statistically significant ($p \leq 0.05$) decrease in body weight was measured during the gestational periods 6-9 and 6-19. Maternal body weight (from days 0-29) was significantly ($p \leq 0.01$) reduced in the 125.0 mg/kg treatment group. In comparison to the control, a 41% suppression in body weight was observed in this high dose group.

Consistent with the significant reduction in body weight gain, food consumed in the high dose group (125.0 mg/kg) was significantly reduced ($p \leq 0.01$) over the entire treatment and gestational periods. Paralleling the reduction in body weight and body weight gain, there was a reduction in food consumption by the rabbits in the 25.0 mg/kg group during gestational days 6 to 12 ($p \leq 0.01$), 12 thru 19 ($p \leq 0.05$) and 6 to 19 ($p \leq 0.05$).

Oxycodone-treatment had no significant adverse effects on pregnancy rate, mean number of corpora lutea, pre- and post-implantation losses, mean number of implantation sites, number of live and dead fetuses, fetal body weight or fetal sex ratio. Also, no significant gross external, visceral, or skeletal malformations were observed. However, two statistically significant developmental variants were observed. In the high dose group (125 mg/kg), 27 incidences of presacral vertebrae were observed. Increases in extra pairs of full ribs were observed in the 5.0, 25.0 and 125.0 mg/kg groups, in comparison to the control fetuses.

Prenatal and postnatal development

Study title: Oxycodone HCl: an Oral Pre- and Postnatal Development Study in Rats

Key study findings:

- Decreased body weights were observed for the F_0 dams at the high dose from GD 12 through lactation day 21 with decreases ranging from 4.5-12.1%.
- Transient clinical signs observed at all doses for the F_0 dams during gestation and lactation included periods of increased or decreased activity, alternating periods of increased and decreased activity in the same observation session, excessive licking, grooming, scratching and chewing of paws. Hyperreactivity was observed at the mid and high dose during gestation and at the high dose during lactation. Effects secondary to the excessive grooming, licking and chewing were fur thin cover, skin scabs and/or redness of the affected area and were observed in some animals at the mid and high doses during both gestation and lactation.
- Excessive licking of pups by F_0 dams was noted at all doses.
- Gestation length for the F_0 dams at the mid and high doses was significantly longer than controls, but was inside historical control range.
- Three pups (two male F_1 high dose and one female F_2 low dose) showed major malformations involving the heart and lungs but the weight of evidence suggests that these observations are not treatment-related.
- Decreased body weights were observed for the F_1 pups (males and females) at the high dose from day 4 through day 21 with decreases ranging from 6.5-13.2%.
- The NOAEL in this study for overt toxicity in the F_0 dams is 0.5 mg/kg.
- The NOEL for developmental toxicity in this study in the F_1 generation is the mid dose, 2 mg/kg, due to reduced mean fetal body weight in the high dose treatment group.
- The NOEL for developmental toxicity in this study in the F_2 generation is >6 mg/kg, the highest dose tested.

Study no.: OXY-N-004
Volume #, and page #: EDR 4.2.3.5.3

Conducting laboratory and location: (b) (4)

Date of study initiation: August 22, 2005
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Oxycodone HCl USP, 200410050003, 98.76%

Methods

Doses: 0, 0.5, 2, 6 mg/kg/day; doses are in terms of oxycodone base
Species/strain: Sprague Dawley rat/Crl:CD(SD)
Number/sex/group: 25 females/group
Route, formulation, volume, and infusion rate: oral gavage, volume: 10 mL/kg
Satellite groups used for toxicokinetics: none
Study design: Females were treated from GD 6 through lactation day 21 or 23
Parameters and endpoints evaluated in the F_0 generation: Clinical observations, body weights, food consumption and various reproductive parameters (described in Results section). Viability of the F_1 generation, as well as clinical observations, body weights, physical and behavioral development and reproductive parameters (described in Results section) were evaluated. Viability, body weights and clinical observations of the F_2 generation were evaluated.

Results

The study is valid. The dosing of dams in this study reached toxic levels at the high dose (6 mg/kg) as evidenced by clinical signs of excessive chewing of fore limbs and paws accompanied by redness, scabbing and thinning fur in some animals as well as decreases in food consumption and body weights $\geq$10%.

F_0 in-life:
Mortality: There was no mortality among the F_0 females.

Clinical signs: Beginning from GD 20, females were observed at least three times each day for signs of parturition. Treatment-related clinical signs at all doses included periods of increased or decreased activity, alternating periods of increased and decreased activity in the same observation session, excessive licking, grooming, scratching and chewing of paws was observed at all doses. Hyperreactivity was observed at the mid and high dose during gestation and at the high dose during lactation. Effects secondary to the excessive grooming, licking and chewing were fur thin cover, skin scabs and/or redness of the affected area and were observed in some animals at the mid and high doses during both gestation and lactation. Excessive licking of pups was noted at all doses for lactating dams. Tables 1 and 2 summarize selected clinical observations noted during gestation and lactation. The sponsor states that all of the clinical signs were observed within two hours of dosing and were no longer apparent by the end of the day. Two dams in the high dose group and one in the mid dose group were observed to reject pups from the litter between days 4-6 post partum. Evidence of cannibalism/pup injuries inflicted by the dam was later observed for the same dam in the mid dose group where pup rejection was observed.

Table 1. Clinical Observations: F_0 females during gestation

Clinical signs: F_0 Females During gestation		*Oxycodone mg/kg/day*			
		0	*0.5*	*2*	*6*
n		*25*	*25*	*25*	*25*
Increased activity		1	**24**	**25**	**25**
Decreased activity		-	**9**	**9**	**20**
Alternating increased and decreased activity		-	**5**	**4**	**6**
Excessive grooming		-	**21**	**23**	**24**
Excessive licking		-	**8**	**16**	**23**
Excessive scratching		-	**19**	**18**	**4**
Hyperreactive		-	3	**8**	**12**
Left Forepaw	***Chewing***	-	**6**	**16**	**21**
	Skin red	-	-	1	**6**
	Skin scab	1	1	**4**	**6**
	Skin lesion w/ discharge	-	-	-	1
	Fur thin cover	5	3	**9**	**7**
Right Forepaw	***Chewing***	-	**6**	**18**	**21**
	Skin red	-	-	1	3
	Skin scab	4	-	6	**8**
	Skin lesion w/discharge	-	-	-	1
	Fur thin cover	6	2	**11**	7

Table 2. Clinical Observations: F_0 females during lactation

Clinical signs: F_0 females During lactation		*Oxycodone mg/kg/day*			
		0	*0.5*	*2*	*6*
n		*22*	*22*	*25*	*22*
Increased activity		1	**18**	**25**	**22**
Excessive grooming		-	**21**	**25**	**22**
Excessive licking		1	**5**	**4**	**10**
Hyperreactive		-	-	1	**4**
Excessive licking of pups		1	**19**	**15**	**6**
Rejection of pups from rest of the litter		-	-	**1**	**2**
Left Forepaw	***Chewing***	-	**4**	**11**	**18**
	Skin scab	3	1	**5**	**7**
	Fur thin cover	7	7	**13**	8
Right Forepaw	***Chewing***	-	**3**	**11**	**17**
	Skin scab	3	2	4	**7**
	Fur thin cover	9	7	**13**	9

Body weights: Individual maternal body weights were recorded on GD 0, 3, 6, 9, 12, 15, 18, and 20, and on lactation day 0, 4, 7, 10, 14, 17, and 21. Statistically significant decreases in group mean body weight were observed at the high dose at each of 11 consecutive time points during GD 12 through lactation day 21 with decreases ranging from 4.5-12.1%. The mid dose group showed statistically significant decreases at each of three consecutive time points during lactation day 0-7 with decreases ranging from 4.4-5.6%. Table 3 summarizes percent change from control of group mean body weights for F_0 females during gestation and lactation.

Table 3. Group Mean Body Weights: F_0 females during gestation and lactation

Group mean body weights F_0 females: Percent change from control															
Dose	***Gestation Day***								***Lactation Day***						
mg/kg	***0***	***3***	***6***	***9***	***12***	***15***	***18***	***20***	***0***	***4***	***7***	***10***	***14***	***17***	***21***
0.5	-0.5	-0.6	-0.7	-0.2	-0.3	-0.5	-0.2	-0.1	-0.6	0.2	0.0	0.3	0.1	-1.1	0.7
2	0.0	-0.3	-0.8	-1.5	-2.6	-2.0	-3.7	-3.9	**-4.5A**	**-5.6B**	**-4.4A**	-2.5	-3.8	-3.4	-1.3
6	0.9	0.9	0.0	-3.9	**-6.1B**	**-6.8B**	**-8.0C**	**-9.1C**	**-8.6C**	**-12.1C**	**-10.8C**	**-10.0C**	**-9.3C**	**-7.6C**	**-4.5A**

Raw data (group means) significantly different from control group:
A P≤ 0.05, **B** P≤ 0.01, **C** P≤ 0.001 (Dunnett)

Food consumption: Individual maternal food consumption was determined during GD 3-6, 6-9, 9-12, 12-15, 15-18, and 18-20. Reduced food consumption was observed in pregnant females at the mid and high dose. At the high dose, statistically significant decreases were observed during each of five consecutive determinations between GD 6-20 with decreases ranging from 13.3-19.2%. The mid dose group showed a statistically significant decrease of 9.4% at the GD 15-18 time point only. Table 4 summarizes percent change from control of group mean food consumption for F_0 females during gestation.

Table 4. Group Mean Food Consumption: F_0 females during gestation

Group mean food consumption F_0 females: Percent change from control						
Dose	***Gestation Day***					
mg/kg	***3-6***	***6-9***	***9-12***	***12-15***	***15-18***	***18-20***
0.5	4.0	0	0	3.3	0	3.8
2	4.0	-7.1	-7.1	-6.7	**-9.4A**	-7.7
6	4.0	**-17.9C**	**-17.9C**	**-13.3C**	**-15.6C**	**-19.2C**

Raw data (group means) significantly different from control group:
A P≤ 0.05, B P≤ 0.01, C P≤ 0.001 (Dunnett)

Toxicokinetics: Toxicokinetics were not performed.

Mating/Fertility: The pregnancy rate ranged from 88% for the high dose group to 100% for the mid dose group. The control and low dose group had a pregnancy rate of 96%. The gestation index was 100% for each group. One female from the control group, one from the low dose group and three from the high dose group failed to litter. Uterine examination confirmed that these females were not pregnant. Gestation length for the mid and high doses was longer than controls but was within the range of historical control values. The duration of parturition, the number of live and dead pups, the number of implant scars, the live birth index and sex ratio were not affected by the treatment. Table 5 summarizes selected maternal performance parameters.

No treatment-related differences between groups were observed for the viability, survival or lactation indices for the F_1 pups (Table 6). Two male high dose pups from different litters found dead on post natal day (PND) 0 showed major malformations in the heart and lungs. These findings are discussed in more detail in the Discussion and Conclusion section.

Table 5. Group Mean Maternal Performance: F_0 dams

Group mean maternal performance: F_0 dams					
Dose, mg/kg	***# Mated Females/ Pregnant Females***	***# rats with Live Litters***	***Pregnancy Rate, %***	***Gestation Index, %***	***Length of gestation, days***
0	25/24	24	96	100	21.3 ± 0.46
0.5	25/24	24	96	100	21.5 ± 0.51
2	25/25	25	100	100	21.8 ± 0.37**
6	25/22	22	88	100	21.8 ± 0.43*

*p≤ 0.01 (Wilcoxin)
**p≤ 0.001 (Wilcoxin)
Historical control values for length of gestation: 21.3-22.1 days

F_0 necropsy: There were no treatment related findings observed in the gross necropsy of the F_0 dams.

F_1 physical development: On day 0 post partum, the pups were evaluated for malformations, sexed, and the number of live and dead pups in each litter was recorded. Live pups were weighed individually and dead pups were placed in Bouin's fluid for later examination. Litters were culled to four pups of each sex on day 4 post partum. There were no treatment-related effects on litter size, viability, survival or lactation indices in the F_1 generation (Table 6). Two male high dose pups from different litters found dead on PND 0 showed major malformations in the heart and lungs. The significance of these findings are discussed in detail in the Discussion and Conclusion section.

Table 6. Group Mean Viability Data: F_1 pups

Group Mean Viability Data: F_1 pups					
Dose, mg/kg	***Malformed Pups/litters affected***	***Viability Index (PND 4)***	***Survival Index (PND 7)***	***Survival Index (PND 14)***	***Lactation Index (PND 21)***
0	0/0	99.2	100.0	100.0	100.0
0.5	0/0	99.3	100.0	100.0	100.0
2	0/0	99.7	99.5	99.5	99.0
6	2/2	95.8	100.0	100.0	100.0

There were no treatment-related clinical signs or body weight changes in the F_1 generation. Statistically significant decreases in group litter mean pup body weights were observed in males at the high dose from day 4 (pre-cull through the completion of the study on day 21. Decreases in males ranged from 7.8-13.2%. Females showed statistically significant reductions in group mean body weight at the high dose at the same time points as males with decreases ranging from 6.5-11.7%. The mid dose female group showed one statistically significant increase at day 0 of 6.2%. The low and mid dose groups were similar to control at all other time points. Day 28 throughout the reproductive phase there were no toxicologically significant group mean body weights or body weight changes for any dose in the F_1 generation. As adults (beginning day 28), the high dose group showed lower body weights as compared to controls throughout the entire reproductive phase of the study, although statistical significance was reached at only one time point for females (day 35) and two time points for males (days 28 and 35). There were no differences as adults between groups for body weight changes.

There were no treatment-related changes in the time required for pinna unfolding, tooth eruption, and eye opening. The mid dose males showed small but statistically significant decreases in pinna unfolding and tooth eruption but the differences were not seen in females or at the high dose and are not considered toxicologically significant.

F_1 behavioral evaluation:
No treatment-related changes were observed in the righting reflex, negative geotaxis, auricular startle, motor activity, or water maze performance.

There were no treatment-related effects on the days of attainment to vaginal opening and preputial separation as well as the pupillary closure and visual placing responses.

F_1 reproduction:
There were no treatment-related effects on estrous cycling, mean day to mating, mating and fertility indices, pregnancy rate and gestation index. The length of gestation, duration of parturition, the number of live and dead pups, the number of implant scars, the live birth index and sex ratio were also comparable between groups.

F_2 findings:
There were no treatment-related effects on viability, clinical signs or changes in body weight in the F_2 generation. One malformed female pup found dead on PND 0 was observed in the low dose group. Examination revealed findings in the heart (right sided aortic arch and descending aorta; interventricular septum absent and the ductus arteriosus merging into the aortic arch on the right side) and lungs (all lobes fused and right accessory lung lobe absent). The malformations observed in this F_2 female pup are very similar to major malformations observed in two male F_1 pups at the high dose. The Sponsor did not consider this finding related to treatment because it was not dose-related. For a detailed discussion please refer to the Discussion and Conclusions and Tables 7 and 8.

2.6.6.7 Local tolerance
No studies were conducted by the Sponsor.

2.6.6.8 Special toxicology studies
No studies were conducted by the Sponsor.

2.6.6.9 Discussion and Conclusions
The Sponsor submitted Segment I and III reproductive toxicology studies. No other studies were submitted. The Segment I study demonstrated that oxycodone did not affect reproductive function in male and female rats at levels that produced parental toxicity. The NOEL for male and female fertility and early embryonic development in this study is 8 mg/kg, the highest dose tested. The NOEL for developmental toxicity in the Segment III study was 2 mg/kg in the F_1 generation and 6 mg/kg in the F_2 generation. Decreased body weights in the F_1 generation were observed at the highest dose (6 mg/kg) in the Segment III study. No other toxicological findings were observed in the F_1 pups and no toxicologic findings were seen in the F_2 pups. In the Segment III study, three pups (two male F_1 high dose and one female F_2 low dose) showed major malformations involving the heart and lungs but the weight of evidence suggests that these observations are not treatment-related (discussed below).

In the Segment III study, necropsies were performed on all unscheduled deaths of pups. In the F_1 generation, several pups in all groups were found dead between PND 0 and PND 7, with the majority of pups found dead on PND 0. Two male high dose pups from different litters found dead on PND 0 showed the same major malformations in the heart

and lungs. It is not clear whether these pups were stillborn or died on PND 0. The heart defects were described in the pathologist's report as: Major vessels: aorta descends to the right side of the heart and interventricular septal defect, cranial ¼. The lung malformations were described as: Accessory lung lobe absent and lung lobes fused on the right side. Maternal toxicity was evident in the dams of both of these pups and the Sponsor attributes the findings to maternal toxicity. The F_1 litters were culled on PND 4 to 4 pups per sex. The culled pups were euthanized and discarded without further evaluation. No MMs were observed in the terminal necropsies of the adult F_1 generation or in any other unscheduled deaths. The nature of the MMs observed in the two pups found dead on PND 0 could result in lethality, therefore the malformations would not be observed in the adult necropsies. However, no differences were observed between groups in any endpoints suggesting embryo-fetal lethality in the Segment I, II or III studies.

Historical control (HC) data for the laboratory performing the Segment III studies was requested from the Sponsor. The Sponsor provided HC data from 1996-2005 from Segment II studies stating that the laboratory does not maintain a historical database for Segment I and Segment III studies. The reason is that the incidence of structural malformations in pups in these types of studies will likely be under represented due to cannibalism and other biological/study design related factors. The Sponsor states the following: "in speaking with the scientific staff at the (b) (4) we believe that the historical the Segment II studies, as provided, are the most accurate data to address the questions that arose during the pharmacology/toxicology review." I agree with the Sponsor's reasoning. According to the historical control data, the background incidence of the specific heart and lung malformations was very low (Tables 7 and 8). An accurate percentage of the incidence for the MMs observed in the Segment III study can not be calculated because only pups found dead were necropsied.

A similar heart malformation and the same lung malformations were observed in one female pup from the low dose of the F_2 generation. The Sponsor concluded that the MMs observed in this pup were not treatment-related because they were not dose dependent. The F_0 dams were treated GD 6 through lactation day 23. The F_2 pup was never treated with drug. There is no evidence in the literature for opioids as a class to be multi-generational teratogens. The observation of the heart and lung malformations in this F_2 pup supports the idea that the MMs observed in the two studies are spontaneous background occurrences.

The Segment II studies in rat and rabbit which appear in the current label of OxyContin were conducted in 1994 and not originally re-submitted with this NDA. We requested that the Sponsor submit the final study reports in order for us to evaluate the incidence of structural malformations observed in the study in the context of the recent Segment I and Segment III study findings. The Segment II studies would be the most appropriate studies in which to assess whether oxycodone increases the incidence of MMs. In the rat study, the dams were treated daily GD 6 through GD 15 with 0, 0.5, 2, 4 or 8 mg/kg of oxycodone HCl (equivalent to: 0.4, 1.8, 3.6 7.2 mg/kg oxycodone base). Signs of overt maternal toxicity were observed at the two highest doses. Two visceral malformations

were observed. One control pup showed a diaphragmatic hernia and one high dose pup was found to have a right sided aortic arch (Tables 7 and 8). In the original review by Dr. Hayes, these findings were not considered to be test article-related. This study was conducted by (b) (4) The historical control data submitted by the Sponsor for the Segment I and III studies was from (b) (4) Extrapolation of the historical control data to the Segment II data may not be appropriate. The Segment II rat data are included in tables 7 and 8 for comparison purposes only. Taking into consideration the lack of dose-response and treatment-related overt maternal toxicity, the findings of the heart and lung MMs will not be considered treatment-related in this review. This is in agreement with the conclusions from Dr. Hayes' review.

No evidence of visceral malformations or increased embryo-fetal lethality was observed in the Segment II rabbit study. The rabbit study was formally reviewed in Dr. Hayes' review of NDA 20-553.

No reports of human teratogenicity resulting from pregnant women taking oxycodone were reported in the literature or found in the various reproductive toxicology databases (TERIS, Shepard's Catalog of Teratogenic Agents, DART, LactMed). To confirm that there are no human data that would alter the Pregnancy Category for this drug, the Division consulted the Maternal Health Team (MHT). Taking into consideration the nonclinical evidence and the clinical evidence found thus far by this reviewer, the weight of evidence suggests that the occurrence of the visceral MMs noted in the Segment III study were most likely spontaneous and not treatment-related. From the nonclinical perspective, there are not adequate data to suggest that the Pregnancy Category should be changed. The reader is referred to the Maternal Health Team Review for a discussion of the existing clinical information regarding pregnancy and nursing mothers.

Table 7. Comparison of Segment II and III studies: Developmental structural malformations per litter in rats

Comparison of Segment II and III studies: Developmental structural malformations per litter in rats									
Visceral major malformation:		***Segment II High dose***		***Segment III F_1 generation High dose***		***Segment III F_2 generation High Dose***		***Historical Controls 1996-2005***	
		affected/ total	% affected	affected/ total	% affected	affected/ total	% affected	affected/ total	% affected, min-max
Heart	Interventricular septal defect	0/24	0	**2*/5**	NA	0/4	NA	1/1041	0.1, 0-5
	Interventricular septum absent	0/24	0	0/5	NA	**1**/4**	NA	no data	-
	Right ascending aortic arch	0	0	**2*/5**	NA	0/4	NA	no data	-
	Right sided aortic arch and descending aorta	1/24***	4.2	0/5	NA	**1**/4**	NA	1/1041#	0.1, 0-5
	ductus arteriosus merging into the aortic arch on the right side	0/24	0	0/5	NA	**1**/4**	NA	3/1041##	0.29, 0-5
Lungs	Lung lobes absent (accessory)	0/24	0	**2*/5**	NA	**1**/4**	NA	1/1041	0.1, 0-4.8
	Lung lobes fused	0/24	0	**2*/5**	NA	**1**/4**	NA	no data	-

NA= not applicable
*male pups 4510a and 4521a, both found dead PND 0, both HD: 10 pups total HD examined from 5 litters that died PND 0 through PND 7; no other abnormalities; no major malformations observed in the necropsies at end of study, 82 pups examined
**female pup 2544b, found dead PND 0, LD: 4 pups total LD examined from 2 litters that died PND 0 through PND 4; no other abnormalities; remaining pups showed no external defects therefore pups were not necropsied at end of study
***Right-sided aortic arch only was observed in HD pup
major malformation in historical controls described as Heart: Right descending aorta
major malformation in historical controls described as Heart: Transposition of major vessels

Table 8. Comparison of Segment II and III studies: Developmental structural malformations per pup in rats

Comparison of Segment II and III studies: Developmental structural malformations per pup in rats									
Visceral major malformation:		***Segment II High dose***		***Segment III F_1 generation High dose***		***Segment III F_2 generation High dose***		***Historical Controls 1996-2005***	
		affected/ total	% affected	affected/ total	% affected	affected/ total	% affected	affected/ total	% affected, min-max
Heart	Interventricular septal defect	0/173	0	**2*/10**	NA	0/5	NA	1/ 7796	0.01, 0-0.7
	Interventricular septum absent	0/173	0	0/10	NA	**1**/5**	NA	no data	-
	Right ascending aortic arch	0	0	**2*/10**	NA	0/5	NA	no data	-
	Right sided aortic arch and descending aorta	**1/173*****	**0.6**	0/10	NA	**1**/5**	NA	1/7796#	0.01, 0-0.7
	ductus arteriosus merging into the aortic arch on the right side	0/173	0	0/10	NA	**1**/5**	NA	3/7796##	0.04, 0-0.7
Lungs	Lung lobes absent (accessory)	0/173	0	**2*/10**	NA	**1**/5**	NA	1/7796	0.01, 0-0.7
	Lung lobes fused	0/173	0	**2*/10**	NA	**1**/5**	NA	no data	-

NA= not applicable
*male pups 4510a and 4521a, both found dead PND 0, both HD: 10 pups total HD examined from 5 litters that died PND 0 through PND 7; no other abnormalities; no major malformations observed in the necropsies at end of study, 82 pups examined
**female pup 2544b, found dead PND 0, LD: 4 pups total LD examined from 2 litters that died PND 0 through PND 4; no other abnormalities; remaining pups showed no external defects therefore pups were not necropsied at end of study
***Right-sided aortic arch only was observed in HD pup
major malformation in historical controls described as Heart: Right descending aorta
major malformation in historical controls described as Heart: Transposition of major vessels

2.6.6.10 Tables and Figures

2.6.7 TOXICOLOGY TABULATED SUMMARY

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: NDA 20-553 for OxyContin, submitted by Purdue Pharma, was approved December 12, 1995. The nonclinical pharmacology/toxicology section was reviewed by BeLinda Hayes, Ph.D. Review of the Segment II studies and the standard battery of genetic toxicology assays, as well as a review of the pharmacology literature of oxycodone was conducted by Dr. Hayes. The results of toxicology studies appear in the current version of the label.

The current NDA (22-272; Purdue Pharma) describes a reformulation of OxyContin with characteristics intended by the Sponsor to reduce the potential for abuse/misuse. On their own initiative, the Sponsor conducted and submitted Segment I and Segment III reproductive and developmental toxicology studies with this NDA. No other nonclinical studies were submitted.

The reproductive toxicology studies show that oxycodone is not a reproductive toxicant under the conditions tested. The Segment I study demonstrated that oxycodone did not affect reproductive function in male and female rats at levels that produced parental toxicity. The NOEL for male and female fertility and early embryonic development in this study is 8 mg/kg, the highest dose tested. The NOEL for developmental toxicity in the Segment III study was 2 mg/kg in the F_1 generation and 6 mg/kg in the F_2 generation. Decreased body weights in the F_1 generation were observed at the highest dose (6 mg/kg) in the Segment III study. No other findings of toxicologic significance were observed in the F_1 pups and none were seen in the F_2 pups. Although the F_0 rats in both studies exhibited signs of overt toxicity at the highest dose tested, the exposure margins are less than one when compared to a daily dose of 160 mg/day in the human.

Unresolved toxicology issues (if any): none

Recommendations: From a nonclinical pharmacology/toxicology perspective, based on the review of the data, this NDA may be approved.

Suggested labeling: The following recommendations are being proposed for the nonclinical sections of the label. For the final version of the label, please refer to the Action Letter. Note: The recommended changes from the proposed labeling are in red or strikeout font.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects - Category B:
The effect of oxycodone in human reproduction has not been adequately studied. Studies in rats and rabbits with oral doses up to 8 and 125 mg/kg/day of oxycodone hydrochloride, equivalent to 0.5 and 15 times an adult human dose of 160 mg/day,

respectively on a mg/m^2 basis, did not reveal evidence of harm to the fetus due to oxycodone.

Non-Teratogenic Effects
Oxycodone hydrochloride was administered orally to female rats during gestation and lactation in a pre- and postnatal toxicity study. There were no drug-related effects on reproductive performance in these females or any long-term developmental or reproductive effects in pups born to these rats. Decreased weight gain was found during lactation and the early post-weaning phase in pups nursed by mothers given the highest dose used (6 mg/kg/day, equivalent to approximately 0.4 times an adult human dose of 160 mg/day, on a mg/m^2 basis). However, body weight of these pups recovered.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis:
No animal studies to evaluate the carcinogenic potential of oxycodone have been conducted.

Mutagenesis:
(b) (4) - Oxycodone was not mutagenic in the following assays; Ames (b) (4) *S. typhimurium* and *E. coli* test with and without metabolic activation at ~~doses~~ concentrations of up to 5000 µg/mL, chromosomal aberration test in human lymphocytes (in the absence of metabolic activation) at (b) (4) concentrations of up to 1500 µg/mL, and with activation after 48 hours of exposure a (b) (4) concentrations of up to 5000 µg/mL, and in the in vivo bone marrow micronucleus assay in mice (at plasma levels of up to 48 µg/mL). Mutagenic results occurred in the presence of metabolic activation in the human chromosomal aberration test at greater than or equal to 1250 µg/mL at 24 but not 48 hours of exposure and in the mouse lymphoma assay at ~~doses~~ concentrations of 50 µg/mL or greater with metabolic activation and at 400 µg/mL or greater without metabolic activation.

Impairment of fertility:
In a study of reproductive performance, rats were administered a once daily gavage dose of the vehicle or oxycodone (0.5, 2, and 8 mg/kg). Male rats were dosed for 28 days before cohabitation with females, during the cohabitation and until necropsy (2-3 weeks post-cohabitation). Females were dosed for 14 days before cohabitation with males, during cohabitation and up to gestation day 6. Oxycodone hydrochloride did not affect reproductive function in male or female rats at any dose tested (≤8 mg/kg/day).

Teratogenic Effects:
The effect of oxycodone in human reproduction has not been adequately studied. Studies in rats and rabbits with oral doses up to 8 and 125 mg/kg/day of oxycodone

hydrochloride, equivalent to 0.5 and 15 times an adult human dose of 160 mg/day, respectively on a mg/m^2 basis, did not reveal evidence of harm to the fetus due to oxycodone.

Non-Teratogenic Effects:
Oxycodone hydrochloride was administered orally to female rats during gestation and lactation in a pre- and postnatal toxicity study. There were no drug-related effects on reproductive performance in these females or any long-term developmental or reproductive effects in pups born to these rats. Decreased weight gain was found during lactation and the early post-weaning phase in pups nursed by mothers given the highest dose used (6 mg/kg/day, equivalent to approximately 0.4 times an adult human dose of 160 mg/day, on a mg/m^2 basis). However, body weight of these pups recovered.

Signatures (optional):

Reviewer Signature _Elizabeth A. Bolan, PhD._____

Supervisor Signature_____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

Reference List

Beaver WT, Wallenstein SL, Rogers A and Houde RW (1978) Analgesic studies of codeine and oxycodone in patients with cancer. I. Comparisons of oral with intramuscular codeine and of oral with intramuscular oxycodone. *J Pharmacol Exp Ther* **207**:92-100.

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/s/

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5/1/2008 04:13:01 PM
PHARMACOLOGIST

R. Daniel Mellon
5/1/2008 04:26:03 PM
PHARMACOLOGIST
I concur.