CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20-553/S-002

Trade Name: OXYCONTIN 80 mg

Generic Name:(oxycodone hydrochloride controlled release tablets)

Sponsor: Purdue Pharma LP

Approval Date: December 9, 1996

Indication: Provides for 80 mg green colored tablets as a line extension to the approved 10, 20 and 40 mg tablets.

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APPLICATION: NDA 20-553/S-002

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Medical Review(s)	X			
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Clinical Pharmacology Biopharmaceutics Review(s)	X			
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Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20-553/S-002

APPROVAL LETTER

NDA 20-553/S-002

DEC 9 1996

Purdue Pharma LP
100 Connecticut Ave.
Norwalk, Connecticut 06850-3590

Attention: Lee Ann Storey, RN, MPH
Assistant Director
Drug Regulatory Affairs and Compliance

Dear Ms. Storey:

Please refer to your June 24, 1996, supplemental new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for OxyContin (Oxycodone hydrochloride controlled release tablets), 80 mg.

We acknowledge receipt of your amendment dated October 24, 1996.

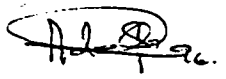
The supplemental application provides for 80 mg green colored tablets as a line extension to the approved 10, 20, and 40 mg tablets.

We have completed the review of this supplemental application, and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Ms.Bonnie McNeal, CSO, telephone 301-443-4250.

Sincerely yours,



Albinus M. D'Sa, Ph.D.
Chemist, Team Leader, DNDC II,
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-553
HFD-170 Div. Files
HFD-820/John Gibbs (only for NDAs and CMC supplements)
HFD-80
HFD-170/B.McNeal
HFD-170/P.Maturu, SDoddapaneni
HFD-170/A.D'Sa, DConner
Drafted by: P.Maturu
R/D Initials: CPMoody
F/T by

APPROVED

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-553/S-002

MEDICAL REVIEW(S)

JUL 20 1996

MEDICAL OFFICER REVIEW OF AN NDA SUPPLEMENT
DIVISION OF ANESTHETIC, CRITICAL CARE & ADDICTION DRUG PRODUCTS

NDA #: 20-553/S-002
NAME: OxyContin Controlled-Release Tablets 80 mg
APPLICANT: Purdue Pharma L.P.
TYPE: Clinical Data for NDA Supplement for 80 mg Tablet
SUBMISSION DATE: 6/24/96 Received: CDER 6/25/96 Reviewer 7/16/96
REVIEWER: Monte L. Scheinbaum PhD, MD
CSO: Bonnie McNeal

SUMMARY

Oxycodone is a well known, morphine-like opioid analgesic. A controlled-release form of oxycodone hydrochloride (OxyContin Controlled-Release Tablets, 10, 20 and 40 mg) was approved on 12/21/95. This submission seeks approval of an 80 mg strength oral controlled-release tablet for the treatment of pain in opioid tolerant patients for dosing on a q12h basis. A total of 29 adult patients received the 80 mg tablets in the course of open-label study OC92-1101 carried out from mid-1995 to March 1996. Patients were 25 to 71 years old (mean 53 years), 38% female. 66% white, 24% black and 10% hispanic. Doses ranged from 80 mg q12h daily to 960 mg (twelve tablets) in the morning and 400 mg (fivetablets) in the evening. Duration of therapy ranged from one dose to eight months treatment. No obvious changes in efficacy relative to use of the lower strengths were noted when patients were converted to 80 mg tablets or combinations of these with lower strengths or when upward or downward titrations were carried out. There were 3/29 (10%) who dropped for lack of efficacy owing to disease progression. There were three (10%) who dropped for adverse events, one with respiratory depression (a serious event), one with dizziness, confusion and ataxia, and one with severe constipation. One patient died of lung cancer, unrelated to the study drug. These findings are not unexpected. There appears to be no obvious clinical problems with the new dosage strength. Assuming it passes muster from a pharmacokinetic viewpoint, it will provide increased convenience of dosing for appropriate patients.

Monte L. Scheinbaum, PhD, MD

Date:7/19/96

Celia Winchell, MD

Date:
7/20/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-553/S-002

CHEMISTRY REVIEW(S)

20-553

DEC 5 1996

Div File

Chemistry Review	1. Division HFD-170	2. NDA Number 20-553
3. Name and Address of Applicant Purdue Pharma LP, 100 Connecticut Ave, Norwalk, CT 06850-3590, Dr. James Conover, tel 203-854-7280.		4. Supplement Number Date SCF-002 6.24.96
5. Name of Drug OxyContin 80 mg tablets (for use in opioid tolerant patients only)	6. Nonproprietary Name Oxycodone HCl CR tablets	
7. Supplement Provides for: 80 mg green colored round convex tablets, a line extension to the approved 10, 20 and 40 mg CR tablets, dated 12.12.95.		8. Amendment(s) 10.24.96 final package insert
9. Pharmacological Category	10. How Dispensed	11. Related Documents DMF
12. Dosage Form CR tablets.	13. Potency(ies) 10, 20, 40 and 80 mg	
14. Chemical Name and Structure see USAN		

15. Comments

Green colored 80 mg OxyContin tablets contain FDA approved yellow iron oxide with FDC blue no 2 dyes. Just like other approves strength tablets, 80 mg tablets are supplied as 100s and 500s in plastic bottles, and in unit dose packages of 25s per card. Added US Pat 5,508,042, for composition in the patent certification section, 505 (j)(2)(vii), and in package insert.

In the development of the composition, the first observation was a slow release rate when 40 mg tablet granulation was compressed as 80 mg tablets. In order to obtain same release rate, Eudragit RS 30D retardant level was reduced from 28 to 20 mg per tablet and a biostudy was conducted with drug product lot 6E, processed at tablets batch size, from

Processing steps, quality control standards, and expiry date were identical to the approved NDA 20-553. Executed batch records and COA were supplied 3 full size batches, 6E, 5E and 0J. 3 year expiration date request was supported with stability data for these 3 batches stored either for 12 months at 30 C/60% RH or 6 months at 40 C/75% RH. Stability test results were within the proposed acceptance standards for appearance (round biconvex green film coated tablets), oxycodone HCl (90-110%), related substances (LT 1% for highest single impurity and LT 2% for total impurities), dissolution %/ hr, %/ hr, above %/ hr). Stability test samples were packaged in opaque HDPE bottles as 100s (60 cc) and 500s (250 cc), and in unit dose PVC blisters as 25s per card. There were no specification failures.

I believe that there may not be a need for EER (supposedly acceptable till 11.17.96) and MV (green coloring agents, yellow iron oxide and FDC Blue no 2) may not interfere. 6 enclosures: For biolot 6E, COA for OxyContin 80 mg, COA for oxycodone lot, master formula/production record, process equipment/flow chart and 1 year stability data; bottle label and EER.

16. Conclusions and Recommendations

Recommends approval of the supplement upon concurrence by PK. PK concurrence review attached 12/5/96

17. Name	Signature	Date
P.Maturu, PhD	P. Maturu	12.5.96
A.D'Sa, PhD, Chemistry Team Leader	A.D'Sa	12/5/96

cc: NDA 20-553/SCF-002/6.24.96
HFD-170/Division File,PMaturu,AD'Sa, BMcNeal
Doc ID: N205532.967
APPROVED

Div File

Chemistry Review	1. Division HFD-170	2. NDA Number 20-553
3. Name and Address of Applicant Purdue Pharma LP, 100 Connecticut Ave, Norwalk, CT 06850-3590, Dr. James Conover, tel 203-854-7280.		4. Supplement Number Date SCF-002 6.24.96
5. Name of Drug OxyContin 80 mg tablets (for use in opioid tolerant patients only)	6. Nonproprietary Name Oxycodone HCl CR tablets	
7. Supplement Provides for: 80 mg green colored round convex tablets, a line extension to the approved 10, 20 and 40 mg CR tablets, dated 12.12.95.		8. Amendment(s)
9. Pharmacological Category	10. How Dispensed	11. Related Documents DMF
12. Dosage Form CR tablets.	13. Potency(ies) 10, 20, 40 and 80 mg	
14. Chemical Name and Structure see USAN		

15. Comments

US Pat 5,508,042 for composition was cited in the patent certification section, 505 (j)(2)(vii), and in package insert. In the development of the composition, the first observation was a slow release rate when 40 mg tablet granulation was compressed as 80 mg tablets. In order to obtain same release rate, Eudragit RS 30D retardant level was reduced from 28 to 20 mg per tablet and a biostudy was conducted with drug product lot 6E, processed at tablets batch size, from .

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16. Conclusions and Recommendations

Recommends approval of the supplement upon concurrence by PK.

17. Name	Signature	Date
P.Maturu, PhD	P. Maturu	8.8.96
A.D'Sa, PhD, Chemistry Team Leader	AD'Sa	8/14/96

cc:

NDA 20-553/SCF-002/6.24.96
HFD-170/Division File
HFD-170/PMaturu,AD'Sa, BMcNeal
Doc ID: N205532.967
APPROVED

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-553/S-002

PHARMACOLOGY REVIEW(S)

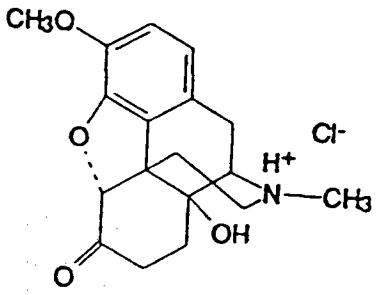
CENTER FOR DRUG EVALUATION AND RESEARCH DEC 18 1996

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCTS

REVIEW & EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

NDA 20-553 (SCF-002)

REVIEWER:	BeLinda A. Hayes, Ph.D.	
CSO:	Bonnie McNeal	
TYPE OF SUBMISSION:	Supplement	
INFORMATION TO SPONSOR:	Yes (x) No ( )	
DATES:	Submission:	June 24, 1996
	Received by CDER:	June 25, 1996
	Received by HFD-170:	June 25, 1996
	Received by Reviewer:	July 9, 1996
	Review Completed:	December 13, 1996
SPONSOR:	Purdue Pharma L.P. Norwalk, Connecticut	
PRODUCT:	OxyContin™	
DRUG:	Oxycodone Hydrochloride	
CHEMICAL NAME:	Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-17-methyl-hydrochloride, (5α).; 4,5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride	
CAS REGISTRY №:	CAS 124-90-3	
DRUG CLASS:	Opioid Narcotic	
STRUCTURE:		



MOLECULAR WEIGHT:	351.83
CLINICAL FORMULATION:	Tablets (controlled-release)
ROUTE OF ADMINISTRATION:	Oral
INDICATION:	Management of Pain
RELATED INDs/NDAs:	IND

BACKGROUND.

OxyContin® (a Controlled-released formulation of oxycodone hydrochloride), 4,5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinane-6-one hydrochloride, a semisynthetic derivative of thebaine was approved for the management of pain associated with a variety of pain syndromes on December 28, 1995. OxyContin® is currently available in three strengths, 10, 20, and 40 mg and is administered every 12 hours to manage pain.

On June 24, 1996, Purdue Pharma L.P. filed this supplement to its NDA Number 20-553 providing data to support the clinical use of an 80 mg strength OxyContin® Controlled-Release Tablet. This strength is intended for use in the management of pain in opioid tolerant patients stricken with a variety of pain syndromes. As with the other strengths available, dosing will be on a q12h bases. In addition to this information, the sponsor has supplied results from the Ames Assay, Mouse Lymphoma Mutation Assay, Human Lymphocytes Chromosomal Aberration Study, and Mouse Micronucleus Assay to revise the current mutagenicity/carcinogenicity section of the package insert.

SUMMARY OF MUTAGENICITY STUDIES

The ability of oxycodone hydrochloride to cause gene mutation or chromosomal damages was evaluated in four genotoxicty assays. The assays performed were the Bacterial Reverse Gene Mutation Assay (Ames Test), Mouse Lymphoma Cell Gene Mutation Test, Human Lymphocytes Metaphase Analyses and Mouse Micronucleus Test.

Oxycodone was assayed for mutagenicity in *Salmonella Typhimurium* strains TA98, TA100, TA1535 and TA1537, and in *E.Coli* strain WP2*uvrA* with and without the addition of S9 mix (Aroclor-induced rat liver S9). In the dose range-finding study, oxycodone HCl was tested in the concentration range of μg/plate. No cytotoxicity was observed at any concentrations tested either in the presence or absence of the metabolic activator. In the mutagenicity assay, oxycodone was tested in the concentration range from μg/plate. There were no oxycodone-related increase in revertant colonies in any of the tester strains with or without metabolic activation.

Oxycodone was analyzed for cytotoxicity and mutagenicity in culture L5178Y mouse lymphoma cells. Results from the mouse lymphoma mutagenicity assay suggested that oxycodone may possess mutagenic potential in cultured L5178Y mouse lymphoma cells. In the absence of metabolic activation, oxycodone (220 - 500 μg/ml) induced resistant mutants at 400 and 500 μg/ml. However, these doses were also cytotoxic; they produced a 80% and 86% reduction in the number of viable colonies. In the presence of the S9 metabolic activator, it appears that oxycodone is converted to a more active mutagen. Oxycodone μg/ml) induced a dose-related increase in the number of resistant mutants. Relative to vehicle control, the observed mutant frequency at the 4 highest doses of oxycodone was statistically significant. Analysis of the size distribution of the oxycodone-induced mutants in the presence of metabolic activation revealed that bimodal distribution, that is both small-colony and large-colony mutants were evident Small-colony mutants were more prevalent. These results suggest that the mutagenic activity of oxycodone may be the result of both point mutation and clastogenic events. Clastogenic events predominated since more small-colony mutants were observed than large-colony mutants.

Oxycodone's clastogenic potential was evaluated in the mouse micronucleus test at three dose levels (♀: 150.0, 300.0, and 600.0 mg/kg, p.o.; ♂: 87.5, 175.0, and 350.0 mg/kg, p.o.). Analysis was conducted at 24, 48 and 72 hours after treatment. No bone marrow toxicity was observed following oxycodone treatment. Also, no statistical significant increase over control values of the frequency of polychromatic erythrocyte-containing micronuclei was observed at any dose level or sampling time in either male or female mice.

The effects of oxycodone on chromosomal aberration were evaluated in cultured human lymphocytes with and without metabolic activation. The results demonstrated that oxycodone is a clastogen in human lymphocytes in the presence of the metabolic activator S9. Following a 24 hour harvest period, a weakly significant ($p<0.05$) increase in chromosome aberrations (gaps) were found at μg/ml. At a concentration of μg/ml, a more clearly statistically significant ($p<0.01$) increase in chromosome aberrations were observed. After a 48 hour harvest time, human lymphocytes treated with oxycodone at concentrations up to μg/ml, in the presence or absence of the metabolic activator S9 did not reveal a significant increase in cells with chromosome aberration.

These data showed that oxycodone is not a mutagen in bacteria cells in culture. However oxycodone did have mutagenicity activity in cultured L5178Y mouse lymphoma cells. Oxycodone was not clastogen to mouse bone marrow. However, oxycodone did have clastogen activity in cultured human lymphocytes in the presence of an exogenous metabolic activator. The available data suggest that oxycodone possesses genotoxic activity. The activity was observed at high concentrations (of μg/ml) that are probably not attainable clinically.

EVALUATION OF THE MUTAGENICITY STUDIES

Ames Test With Oxycodone Hydrochloride (Salmonella Typhimurium-Escherichia Coli/Mammalian Microsome Reverse Mutation Assay With Confirmatory Testing) (Report №: DSE-149-GLP).

The mutagenicity study was conducted at during November 8, 1995 to December 18, 1995. The study was conducted in compliance with the Good Laboratory Practice Regulation. A Quality Assurance Statement was included.

Salmonella typhimurium tester strains TA98, TA100, TA1535, and TA1537 were used in the assay. The mutagenicity test was performed according to the plate-incorporation procedures of Ames *et al.* (1975): The *Escherichia Coli* tester strain used was WP2*uvrA*; plate-incorporation procedures described by Green and Murrel (1976) was used for mutagenicity testing.

Oxycodone HCl was tested over a broad range of concentrations in two separate experiments. The first study was a dose range-finding study (Experiment 1) to assess the cytotoxicity of oxycodone and to select the appropriate doses to be evaluated in the mutagenicity assay (Experiment 2). In the first study, ten doses of oxycodone HCl was tested in the concentration range of)µg/plate. The results of the dose range-finding study were used to select the five doses to be evaluated in the mutagenicity assay. In the mutagenicity assay oxycodone was tested at 100, 333, 1000, 3330, and 5,000 µg/plate in the presence and absence of S9 metabolic activation.

Appropriate negative and positive control experiments for each strain were ran simultaneously. The diagnostic mutagens were 2-aminoanthracene (2.5 µg/plate) for TA98, TA100, TA1535, TA1537 and WP2*uvrA* with S9 activation; 2-nitrofluorene (1.0 µg/plate) for TA98 without the S9 metabolic activator; sodium azide (2.0 µg/plate) for TA100 and TA1534 without the S9 activator; ICR-191 (2.0 µg/plate) for TA1539 without the S9 activator and 4-nitroquinole-N-oxide (1.0 µg/plate) for WP2*uvrA* without S9 activation.

Results. The toxicity limit of oxycodone was not achieved in the dose range-finding study. No cytotoxicity was observed in either the presence or absence of S9 activator. None of the oxycodone's concentrations (66.7, 100, 333, 667,1000, 3330, and 5000 µ/plate) affected the normal background lawn or decrease the number of revertants per plate.

In the mutagenicity assay, both the negative and positive controls induced mutation frequencies as expected. Oxycodone HCl did not induce mutation frequencies in any of the *Salmonella typhimurium* strains (TA98, TA100, TA1535 or TA1537) or the WP2*uvrA Escherichia coli* tester strain tested with or without S9.

L5178Y TK+/- Mouse Lymphoma Forward Mutation Assay With Oxycodone Hydrochloride (With Confirmatory Assay) (Report №: DSE-150-GLP).

This mutagenicity study was conducted at during November 8, 1995 to December 21, 1995. The study was conducted in compliance with GLP regulations. A signed Quality Assurance Statement was submitted.

L5178Y mouse lymphoma cells, obtained from were used for both the cytotoxicity and mutagenicity experiments. Cells were maintained in a growth medium consisting of RPMI 1640 medium supplemented with Pluronic®F68, L-glutamine, sodium pyruvate, antibiotics, and heat-inactivated horse serum (10% by volume).

In the cytotoxicity study, cultured L5178Y mouse lymphoma cells were treated with oxycodone hydrochloride (9.77, 19.75, 39.1, 78.1, 156.0, 313.0, 625.0, 1250.0, 2500.0 and 5000.0 μg/ml) in the presence and absence of the S9 metabolic activator, or the negative (untreated) control or the vehicle control (10% water) for 4 hours. Following treatment, cells for the cytotoxicity analyses were washed twice and resuspended in fresh growth medium and allowed to recover during a 24 hour incubation period at 37°C. The cells were than counted to measure the reduction in cell growth relative to the concurrent vehicle control cultures. The data was expressed as percentage survival calculated against the vehicle control.

Two mutagenicity assays were performed. Procedures used for the mutagenicity study were performed in accordance to procedures described by Clive and Spector (1975), Clive *et al.* (1979), Amacher *et al.* (1980), and Clive *et al.* (1987). In the first mutagenicity study, duplicate cultures of L5178Y mouse lymphoma cells (6 x 10^6 cells/tube) in the logarithmic growth phase were treated with 100, 150, 200, 300, 400, and 500 μg/ml of oxycodone HCl in the absence of metabolic activation, and with 50, 75, 100, 150, 200 and 250 μg/ml of oxycodone HCl in the presence of the S9 metabolic activator. In the second mutagenicity assay, duplicate cultures of L5178Y mouse lymphoma cells (6 x 10^6 cells/tube) in the logarithmic growth phase were treated with 12.5, 25.0, 50.0, 75.0, 100.0, and 200.0 μg/ml of oxycodone HCl in the absence and presence of the metabolic activator S9. For both mutagenicity assays, the positive controls were: methylmethanesulfonate (MMS, 5, 10, and 15 ng/ml) in the absence of the S9 metabolic activator, and 20-methylcholanthrene (MCA; 2.0 and 4.0 μg/ml) in the presence of the metabolic activator. The cultured mouse lymphoma cells were exposed to the treatment medium for 4 hours. Following treatment, cells were centrifuged, washed twice, resuspended in 20.0 ml of growth medium and incubated for 48 hours at 37°C to recover. The cells were then counted, diluted to 1 x 10^6 cells/ml in growth medium and incubated at 37°C. After 10 to 14 days in the incubator, the number of resistant (mutant) colonies, and viable colonies were determined. The mutant frequencies expressed as the ratio of resistant colonies to total viable cells number, adjusted by the absolute selection colony efficiency. Cytotoxicity was expressed as the relative suspension growth of the cells over the two day expression period multiplied by the relative colony efficiency at the time of selection.

RESULTS.

Cytotoxicity Assay. Cytotoxic doses of oxycodone were achieved in this study. Oxycodone, in the absence of S9 metabolic activator, was non-cytotoxic or weakly cytotoxic in the concentration range of μg/ml. Oxycodone was cytotoxic at 625, 1250, 2500, and 5000 μg/ml in the presence and absence of metabolic activation; these concentrations killed % of the cells during the 4 hour incubation period. 625 μg/ml of oxycodone was more toxic in the presence of metabolic activation; there were no viable cells detected. These results were used to select the doses to be evaluated in the first mutagenicity study.

Mutagenicity Study 1 (Trial 1). As depicted in Table 1, oxycodone, in the absence of metabolic activation was toxic at concentrations of 100 μg/ml and higher. A weak to moderate cytotoxic response was observed at concentrations of μg/ml; relative to the vehicle control the percent relative growth was %. The μg/ml concentrations of oxycodone was very toxic; the observed percent relative growth was %, respectively. Mutagenicity activity was observed following treatment with μg/ml of oxycodone in the absence of metabolic activation. However, since theses concentrations were also very cytotoxic, these results are considered to be invalid.

In the presence of metabolic activation, the mutagenicity potential of oxycodone was evaluated at concentrations ranging from μg/ml. Weak to moderate cytotoxic activity was observed at concentrations ranging from μg/ml. Oxycodone was very cytotoxic in the concentration range of μg/ml. Mutagenicity activity was observed at all concentration of oxycodone. Because of the high degree of cytotoxicity observed at the concentrations evaluated in this mutagenicity study, a second mutagenicity study was performed with lower doses of oxycodone in order to better characterize the mutagenic potential of oxycodone.

Mutagenicity Assay 2 (Trial 2). Results from this mutagenicity assay are presented in Table 2. As anticipated, the positive controls MMS and MCA both induced a statistically significant increase in the mutant frequencies. Oxycodone had weak mutagenic activity in the absence of the S9 metabolic activator. A statistically significant increase in the mutant frequencies was observed in the mouse lymphoma cells treated with μg/ml of oxycodone.

Oxycodone appears to be metabolically converted to a more active mutagen. In the presence of the S9 metabolic activator, oxycodone induced a clear dose-related increase in the mutant frequency. A strong cytotoxic response was induced by μg/ml of oxycodone; the percent relative growth was %.

Thymidine kinase-deficient mutants characteristically seen in the mouse lymphoma assay is bimodal; that is, they consist of both mall-colony mutants and large-colony mutants. As expected, the positive control treatments induced the characteristics bimodal distribution. Analysis of the oxycodone-induced mutants in the presence of the S9 metabolic activator revealed that the increased mutant frequency was due to the presence of both small-colony and large-colony mutants. The small-colony mutants represented a greater percentage of the oxycodone-induced mutant colonies.

Table 1. Mutagenicity of Oxycodone In The L5178/TK$^{+/-}$ Mouse Lymphoma Assay (Trial 1).[a]

MUTATION ASSAY WITHOUT ACTIVATION - TRIAL 1

A. TEST ARTICLE: OXYCODONE HYDROCHLORIDE
B. GENETICS ASSAY NO: 17261
C. VEHICLE: WATER
D. SELECTIVE AGENT: 3 µg/ml TFT
E. TEST DATE: 11/14/95

TEST CONDITION:	DAILY CELL COUNTS (CELLS/ML.10ES UNITS) 1	2	SUSPENSION GROWTH*	TOTAL MUTANT COLONIES	TOTAL VIABLE COLONIES	CLONING EFFICIENCY*	RELATIVE GROWTH (%)*	MUTANT FREQUENCY (10E-6 UNITS)*
NONACTIVATION CONTROLS*			AVG VEHICLE CONTROL			AVG VEHICLE CONTROL		
VEHICLE CONTROL	20.3	20.9	47.1	114	569	93.2	100.0	40.8
VEHICLE CONTROL	16.8	18.1	33.8	124	491	81.8	100.0	50.5
VEHICLE CONTROL	17.3	13.6	26.1 35.7	139	494	82.3 85.8	100.0	56 3
MMS 5 ml/ml	12.5	16.8	22.2	341	483	80.5	58.3	141.2*
MMS 10 ml/ml	13.8	12.6	19.3	485	275	45.8	26.9	352.7*
MMS 15 ml/ml	10.4	10.1	11.7	435	159	26.5	10.1	547.2*
TEST COMPOUND			RELATIVE TO VEHICLE CONTROL (%)			RELATIVE TO VEHICLE CONTROL (%)		
100 µg/ml	16.5	13.4	68.8	103	463	89.9	61.9	44.5
150 µg/ml	16.7	13.5	70.2	122	499	96.9	68.0	48.9
200 µg/ml	12.1	11.6	43.7	159	544	105.7	46.2	58.5
300 µg/ml	11.3	9.0	31.7	164	610	118.5	37.6	53.8
400 µg/ml	4.6	10.7	15.3	232	465	90.3	13.8	99.8*
500 µg/ml	3.2*	7.8	7.3	291	438	85.1	6.2	132.9*

*SUSPENSION GROWTH = (DAY 1 COUNT/3) * (DAY 2 COUNT)/(3 OR DAY 1 COUNT IF NOT SPLIT BACK)

*CLONING EFFICIENCY = TOTAL VIABLE COLONY COUNT/NUMBER OF CELLS SEEDED * 100

*RELATIVE GROWTH = (RELATIVE SUSPENSION GROWTH * RELATIVE CLONING EFFICIENCY) / 100

*MUTANT FREQUENCY = (TOTAL MUTANT COLONIES/TOTAL VIABLE COLONIES) X 2X10E-4. DECIMAL IS MOVED TO EXPRESS THE FREQUENCY IN UNITS OF 10E-6

*VEHICLE CONTROL = 10% WATER: POSITIVE CONTROL = MMS = METHYL METHANESULFONATE

*MUTAGENIC. EXCEEDS MINIMUM CRITERION OF 98.4 X 10E-6

* NOT SPLIT BACK

MUTATION ASSAY WITH ACTIVATION - TRIAL 1

A. TEST ARTICLE: OXYCODONE HYDROCHLORIDE
B. GENETICS ASSAY NO: 17261
C. VEHICLE: WATER
D. SELECTIVE AGENT: 3 µg/ml TFT
E. TEST DATE: 11/14/95

TEST CONDITION:	DAILY CELL COUNTS (CELLS/ML.10ES UNITS) 1	2	SUSPENSION GROWTH*	TOTAL MUTANT COLONIES	TOTAL VIABLE COLONIES	CLONING EFFICIENCY*	RELATIVE GROWTH (%)*	MUTANT FREQUENCY (10E-6 UNITS)*
S9 ACTIVATION INDUCED* BATCH NO: 0568			AVG VEHICLE CONTROL			AVG VEHICLE CONTROL		
VEHICLE CONTROL	19.6	18.2	39.6	114	499	83.2	100.0	45.7
VEHICLE CONTROL	17.9	17.2	34.2	164	534	89.0	100.0	61.4
VEHICLE CONTROL	18.3	18.4	37.4 37.1	142	529	88.2 86.8	100.0	53.7
MCA 2 µg/ml	12.8	16.0	22.8	766	484	67.3	42.6	379.2*
MCA 4 µg/ml	11.5	13.5	17.3	789	444	74.0	39.8	355.4*
TEST COMPOUND			RELATIVE TO VEHICLE CONTROL (%)			RELATIVE TO VEHICLE CONTROL (%)		
50.0 µg/ml	11.8	20.0	70.7	352	480	92.2	65.2	146.7*
75.0 µg/ml	11.1	13.4	44.5	584	535	102.7	45.7	218.3*
100 µg/ml	9.2	14.6	40.2	621	438	84.1	33.8	283.6*
150 µg/ml	4.0*	12.2	11.0	594	337	64.7	7.1	352.5*
200 µg/ml	3.8*	9.8	8.8	586	258	49.5	4.4	454.3*
250 µg/ml	2.1*	5.6	5.0	268	274	52.6	2.6	195.6*

*SUSPENSION GROWTH = (DAY 1 COUNT/3) * (DAY 2 COUNT)/(3 OR DAY 1 COUNT IF NOT SPLIT BACK)

*CLONING EFFICIENCY = TOTAL VIABLE COLONY COUNT/NUMBER OF CELLS SEEDED * 100

*RELATIVE GROWTH = (RELATIVE SUSPENSION GROWTH * RELATIVE CLONING EFFICIENCY) / 100

*MUTANT FREQUENCY = (TOTAL MUTANT COLONIES/TOTAL VIABLE COLONIES) X 2X10E-4. DECIMAL IS MOVED TO EXPRESS THE FREQUENCY IN UNITS OF 10E-6

*VEHICLE CONTROL = 10% WATER: POSITIVE CONTROL = MCA = METHYLCHOLANTHRENE

*MUTAGENIC. EXCEEDS MINIMUM CRITERION OF 107.2 X 10E-6

* NOT SPLIT BACK

a: These tables were copied from the sponsor submission.

Table 2. Mutagenicity of Oxycodone In The L5178/TK$^{+/-}$ Mouse Lymphoma Assay (Trial 2).[a]

MUTATION ASSAY WITHOUT ACTIVATION - TRIAL 2

A. TEST ARTICLE: OXYCODONE HYDROCHLORIDE
B. GENETICS ASSAY NO: 17261
C. VEHICLE: WATER
D. SELECTIVE AGENT: TFT 3.0 µg/ml
E. TEST DATE: 12/05/95

TEST CONDITION:	DAILY CELL COUNTS (CELLS/ML..10ES UNITS) 1	2	SUSPENSION GROWTH*	TOTAL MUTANT COLONIES	TOTAL VIABLE COLONIES	CLONING EFFICIENCY*	RELATIVE GROWTH (%)*	MUTANT FREQUENCY (10E-6 UNITS)*
NONACTIVATION CONTROLS*								
VEHICLE CONTROL	17.6	11.1	AVG VEHICLE CONTROL 21.7			AVG VEHICLE CONTROL		
VEHICLE CONTROL	13.2	14.9	21.9	93	429	71.5	100.0	43.4
VEHICLE CONTROL	17.0	13.8	26.1 23.2	97	549	91.5	100.0	35.3
				107	449	74.8 79.3	100.0	47.7
MMS 5 ml/ml	7.4	14.4	11.8					
MMS 10 ml/ml	8.0	8.2	7.3	394	240	40.0	25.7	328.3*
MMS 15 ml/ml	6.4	4.6	3.3	454	92	15.3	6.1	987.8*
				264	46	7.7	1.4	1147.8*
TEST COMPOUND			RELATIVE TO VEHICLE CONTROL (%)			RELATIVE TO VEHICLE CONTROL (%)		
200 µg/ml	10.4	9.9	49.3	112	529	111.2		
300 µg/ml	9.3	7.0	31.2	144	470	98.8	54.8	42.3
350 µg/ml	8.1	7.2	27.9	184	645	135.6	30.8	61.3
400 µg/ml	4.9	10.5	24.6	169	392	82.4	37.8	57.1
450 µg/ml	4.5	9.6	20.7	142	413	86.8	20.3	86.2*
500 µg/ml	2.7*	8.8	12.6	314	512	107.6	18.0 13.6	68.8 122.7*

*SUSPENSION GROWTH = (DAY 1 COUNT/3) + (DAY 2 COUNT)/(3 OR DAY 1 COUNT IF NOT SPLIT BACK)

*CLONING EFFICIENCY = TOTAL VIABLE COLONY COUNT/NUMBER OF CELLS SEEDED * 100

*RELATIVE GROWTH = (RELATIVE SUSPENSION GROWTH * RELATIVE CLONING EFFICIENCY) / 100

*MUTANT FREQUENCY = (TOTAL MUTANT COLONIES/TOTAL VIABLE COLONIES) X 2X10E-4. DECIMAL IS MOVED TO EXPRESS THE FREQUENCY IN UNITS OF 10E-6

*VEHICLE CONTROL = 10% WATER; POSITIVE CONTROL = MMS = METHYL METHANESULFONATE

*MUTAGENIC. EXCEEDS MINIMUM CRITERION OF 84.3 X 10E-6

* NOT SPLIT BACK

MUTATION ASSAY WITH ACTIVATION - TRIAL 2

A. TEST ARTICLE: OXYCODONE HYDROCHLORIDE
B. GENETICS ASSAY NO: 17261
C. VEHICLE: WATER
D. SELECTIVE AGENT: TFT 3.0 µg/ml
E. TEST DATE: 12/05/95

TEST CONDITION:	DAILY CELL COUNTS (CELLS/ML..10ES UNITS) 1	2	SUSPENSION GROWTH*	TOTAL MUTANT COLONIES	TOTAL VIABLE COLONIES	CLONING EFFICIENCY*	RELATIVE GROWTH (%)*	MUTANT FREQUENCY (10E-6 UNITS)*
S9 ACTIVATION INDUCED*	BATCH NO: 0568		AVG VEHICLE CONTROL			AVG VEHICLE CONTROL		
VEHICLE CONTROL	10.0	10.3	11.4	111	732	122.0	100.0	30.3
VEHICLE CONTROL	12.5	14.2	19.7	114	488	81.3	100.0	46.7
VEHICLE CONTROL	18.6	13.4	27.7 19.6	117	515	85.8 96.4	100.0	45.4
MCA 2 µg/ml	11.1	11.5	14.2	662	435	72.5	54.5	304.4*
MCA 4 µg/ml	9.3	11.3	11.7	787	444	74.0	45.8	354.5*
TEST COMPOUND			RELATIVE TO VEHICLE CONTROL (%)			RELATIVE TO VEHICLE CONTROL (%)		
12.5 µg/ml	12.1	15.6	107.0	132	644	111.3	119.1	41.0
25.0 µg/ml	11.6	12.2	80.2	215	622	107.5	86.2	69.1
50.0 µg/ml	6.6	9.9	37.0	399	599	103.6	38.3	133.2*
75.0 µg/ml	4.7	6.9	23.7	754	634	109.6	26.0	237.9*
100 µg/ml	7.7	8.1	35.4	710	415	71.7	25.4	342.2*
200 µg/ml	2.5*	3.4	5.8	432	214	37.0	2.1	403.7*

*SUSPENSION GROWTH = (DAY 1 COUNT/3) + (DAY 2 COUNT)/(3 OR DAY 1 COUNT IF NOT SPLIT BACK)

*CLONING EFFICIENCY = TOTAL VIABLE COLONY COUNT/NUMBER OF CELLS SEEDED * 100

*RELATIVE GROWTH = (RELATIVE SUSPENSION GROWTH * RELATIVE CLONING EFFICIENCY) / 100

*MUTANT FREQUENCY = (TOTAL MUTANT COLONIES/TOTAL VIABLE COLONIES) X 2X10E-4. DECIMAL IS MOVED TO EXPRESS THE FREQUENCY IN UNITS OF 10E-6

*VEHICLE CONTROL = 10% WATER; POSITIVE CONTROL = MCA = METHYLCHOLANTHRENE

*MUTAGENIC. EXCEEDS MINIMUM CRITERION OF 81.6 X 10E-6

* NOT SPLIT BACK

a: These tables were copied from the sponsor submission.

Chromosomal Aberrations Study In Human Whole Blood Lymphocytes With A Confirmatory Assay With Multiple Harvest (Report №:DSE:151-GLP).

This mutagenicity study was conducted at during the period of November 8, 1995 to December 27, 1995. The study was conducted in compliance with the Good Laboratory Practice Regulation. A Quality Assurance Statement was included.

Human lymphocytes collected from a single healthy male donor (30-35 years of age, non-smoker, free of all drugs, not exposed to X-rays for the previous 12 months) was used for both the mutagenicity and cytotoxicity analyses. The whole blood was cultured by adding 0.3 ml or 0.6 ml of the fresh heparinized blood to 4.7 ml or 9.4 ml of culture medium (RPMI 1640 medium, 100 units/ml penicillin, 100 μg/ml streptomycin, 2 mM L-glutamine, and 1% phytohemagglutinin), respectively. Cultures were incubated for 2 days at about 37°C ± 2°C in a humidified incubator, in an atmosphere of about 5% ± 1.5% CO_2 in air. Subsequently, the solvent or test drug was added to the cultures and incubated at 37°C for 3.6 hours (in the absence of S9) or 3.0 hours (in the presence of metabolic activation). At this time, 25.0 μM 5-bromo-2'deoxyuridine (BrdUrd) was added to the cultures and were then re-incubated for 25.5 hours at 37°C. At the 23.5 hour of this incubation period, the cells were arrested in metaphase by adding 0.1 μg/ml of Colcemid®. After which the cells were harvested. After harvesting, chromosomal and cytological preparations were done.

The preliminary cytotoxicity assay was used to determine the test range for the definitive mutagenicity analyses. In this range-finding study, the treatment medium contained oxycodone hydrochloride at concentrations of 50.0, 167.0, 500.0, 1670.0, and 5000.0 μg/ml, the positive control Mitomycin C (0.05 μg/ml in the absence of the S9 metabolic activator), the positive control cyclophosphamide (10.0 μg/ml) in the absence of the S9 metabolic activator, the negative control RPMI 1640 or the solvent control (deionized water) at a concentration of 500 μg/ml. Oxycodone HCl was studied in the presence or absence of the S9 metabolic activator. Toxicity was determine by counting 100 consecutive metaphases, if available, from the five highest doses with and without metabolic activation; and dividing cells were assessed as percentage of total lymphocytes (mitotic index).

In the chromosomal aberration study, the treatment medium contained 0.0, 250, 499, 748, 997 or 1500 μg/ml of oxycodone HCl (Trial 1: initial trial) or 500, 750, 1000, or 1500 μg/ml of oxycodone HCl (Trial 2: confirmatory assay) in the absence of metabolic activation. In the presence of S9 activation, the treatment medium contained 0, 625, 1250, 2500, 3740 or 4990 μg/ml of oxycodone HCl for Trial 1 or 1250, 2500, 3750 or 5000 μg/ml of oxycodone HCl for Trial 2. The positive controls for the assay were: 50 μg/ml cyclophosphamide (CPA) in the presence of S9 and 0.200 μg/ml mitomycin C with S9 activation. In most cases, 100 cells were scored for chromosome damage; only cells with number of centromeres equal to the modal number 46 were analyzed. To determine whether oxycodone inhibited mitosis, the mitotic index was calculated on 1000 cells per culture. Percent of polyploid (i.e., A cell containing multiple copies of the haploid number of chromosomes) and endoreduplicated cells (i.e., 4N cell in which separation of chromosomes pairs has failed.) was also estimated. An additional 10 cells per dose were evaluated for numerical aberrations.

RESULTS.

Cytotoxicity Assay. The results from the cytotoxicity study are presented in Table 3. In the absence of the metabolic activator, oxycodone caused a 25% to 66.7% suppression in mitotic indices of human lymphocytes in the concentration range of μg/ml. Oxycodone at a concentration of μg/ml was very cytotoxic in the absence of metabolic activation; mitosis was inhibited by %.

Cytotoxicity was also evident in the presence of the S9 metabolic activator; however, oxycodone HCl appeared to be slightly less toxic. At concentrations of 500.0, 1670.0, and 5000.0 μg/ml, oxycodone caused a reduction of 22.2%, 25.9%, and 81.5% in the mitotic indices as compared with the solvent control culture, respectively. The doses selected for the definitive study were based on these findings.

Initial Mutagenicity Assay. Results from the testing (initial trial) of oxycodone in the human lymphocyte for chromosomal aberrations are shown in Table 4. These results suggested that oxycodone did not possess clastogenic activity in human lymphocytes in the absence of metabolic activation. Oxycodone HCl at concentrations of 250.0, 499.0, 748.0, 997.0, and 1500.0 μg/ml did not produce any significant increase in the numbers of cells with chromosomal aberrations or in polyploid cells. Cytotoxicity was evident at the highest concentration tested; relative to solvent control (deionized water) and the negative control, 1500 μg/ml oxycodone reduced the mitotic indices by 77% and 54%, respectively.

However, in the presence of metabolic activation, oxycodone (625, 1250, 2500, 3740, and 4990 μg/ml) possessed clastogenic activity. A weakly significant ($p<0.05$) increased in the number of cells with chromosomal aberrations was observed at 2500.0 μg/ml. The clastogenic activity observed with 3740 and 4990 μg/ml was stronger; a significant ($p<0.01$) increase in cells with chromosomal aberrations was observed. Oxycodone did not produce a significant increase in polyploidy at any of the concentrations evaluated.

Confirmatory Trial. Results (Tables 5 and 6) from the confirmatory assays are consistent with the initial trials. Oxycodone was void of clastogenic activity in the absence of metabolic activation. As depicted in Table 3, no signficant chromosomal aberrations were observed in human lymphocytes exposed to oxycodone HCl for 24 hours or 48 hours at concentrations up to μg/ml. Clastogenic activity was observed in the presence of the metabolic activator. However, clastogenic activity was observed in the presence of the metabolic activator in the 24 hour harvest assay but not during the 48 hour harvest assay (Table 6). As expected, human lymphocytes exposed to the positive control mitomycin C induced a significant increase in the frequency of aberrations in the human lymphocytes. Oxycodone, also, did not produce any significant increase in the number of polyploidy or endoreduplication cells.

In the presence of metabolic activation, oxycodone (1250, 2500, 3750,or 5000 μg/ml) produced significant clastogenic activity in human lymphocytes in the 24 hour assay but not in the 48 hour assay (Table 4). Oxycodone at a concentration of μg/ml possessed weak clastogenic activity ($p<0.05$). Significant clastogenic activity was observed following treatment with 3750 and 5000 μg/ml. No significant increase in polyploidy or endoreduplicated cells was observed.

Table 3. Cytotoxic Effects of Oxycodone on Human Lymphocytes In Vitro.

TREATMENT: CONC (μg/ml)	MITOTIC INDEX (M.I.) (%)		M.I. SUPPRESSION[a] (%)	
	- S9	+ S9	- S9	+ S9
POSITIVE CONTROL - MMC: 0.05	0.8	NT	33.3	NT
POSITIVE CONTROL - CP: 10.0	NT	1.6	NT	40.7
NEGATIVE CONTROL - RPMI 1640	1.5	2.0	NS	25.9
SOLVENT CONTROL - Deionized Water: 50 μl/ml	1.2	2.7	0	0
OXYCODONE: 50.0	1.3	2.3	NS	14.8
OXYCODONE: 167.0	0.9	1.4	25.0	48.1
OXYCODONE: 500.0	0.4	2.1	66.7	22.2
OXYCODONE: 1670.0	0.4	2.0	66.7	25.9
OXYCODONE: 5000.0	0.0	0.5	100.0	81.5

a: M.I. suppression (%) expressed as the percent reduction of the treated mitotic index compared to the mitotic index of the solvent control.
NS: No suppression occurred.
MMC: Mitomycin C
RPMI 1640: Culture medium
CP: Cyclophosphamide
NT: Not Tested

Table 4. Sponsor's Chromosomal Aberration Analysis of The Initial Trial in Human Lymphocytes *In Vitro*.

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES
24 Hour Treatment and Harvest

Assay No.: 17261 Trial #: 1 Lab #: CY11295 Metabolic Activation: -S9
Compound: Oxycodone hydrochloride Date: 11/30/95

				CELLS SCORED	% MITOTIC INDEX	No. ENDOREDUPLICATED CELLS	No. POLYPLOID CELLS	JUDGEMENT (+/-) **	NUMBERS AND PERCENTAGES (%) OF CELLS SHOWING STRUCTURAL CHROMOSOMAL ABERRATIONS: GAP g	CHROMATID TYPE csb	CHROMATID TYPE csc	CHROMOSOME TYPE csb	CHROMOSOME TYPE csc	GT	TOTALS* -g	TOTALS* +g	JUDGEMENT (+/-) ***
CONTROLS																	
NEGATIVE:	RPMI 1640[a]		A	100	2.0	0.0	0.0								0	0	
			B	100	2.7	0.0	0.0								0	0	
			TOTAL	200											0	0	
			%		2.4	0.0	0.0	-							0.0	0.0	-
SOLVENT:	Deionized water	15.0 µl/ml	A	100	1.6	0.0	0.0				1				1	1	
			B	100	1.3	0.0	0.0								0	0	
			TOTAL	200							1				1	1	
			%		1.5	0.0	0.0	-			0.5				0.5	0.5	-
POSITIVE:	MMC[b]	0.200 µg/ml		25					1	1	7			1	7	1	
			%		1.7	0.0	0.0	-	4.0	4.0	28.0			4.0	>28.0	>32.0	+
TEST ARTICLE		250 µg/ml****	A	0	1.1												
			B	0	2.3												
			TOTAL	0													
			%		1.7												
		499 µg/ml	A	100	1.7	0.0	1.0								0	0	
			B	100	1.6	0.0	0.0								0	0	
			TOTAL	200											0	0	
			%		1.7	0.0	0.5	-							0.0	0.0	-
		748 µg/ml	A	100	2.1	0.0	1.0								0	0	
			B	100	1.4	0.0	0.0								0	0	
			TOTAL	200											0	0	
			%		1.8	0.0	0.5	-							0.0	0.0	-
		997 µg/ml	A	100	2.1	0.0	0.0			1					1	1	
			B	100	2.4	0.0	0.0								0	0	
			TOTAL	200						1					1	1	
			%		2.3	0.0	0.0	-		0.5					0.5	0.5	-
		1500 µg/ml	A	100	1.4	0.0	0.0								0	0	
			B	100	0.8	0.0	0.0								0	0	
			TOTAL	200											0	0	
			%		1.1	0.0	0.0	-							0.0	0.0	-

csb: chromatid break csc: chromatid exchange csb: chromosome break csc: chromosome exchange GT: greater than 10 aberrations
* -g: no. or % of cells with chromosome aberrations; +g: no. or % of cells with chromosome aberrations + no. or % of cells with gaps.
[a] RPMI 1640 = Culture medium
** Significantly greater in % polyploidy and % endoreduplication than the solvent control, $p < 0.01$.
[b] MMC = Mitomycin C
*** Significantly greater in -g than the solvent control, $p < 0.01$.
**** Chromosome aberrations not analyzed due to higher dose concentrations available for analysis.

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES
3 Hour Treatment, 24 Hour Harvest

Assay No.: 17261 Trial #: 1 Lab #: CY11295 Metabolic Activation: +S9
Compound: Oxycodone hydrochloride Date: 11/30/95

				CELLS SCORED	% MITOTIC INDEX	No. ENDOREDUPLICATED CELLS	No. POLYPLOID CELLS	JUDGEMENT (+/-) **	NUMBERS AND PERCENTAGES (%) OF CELLS SHOWING STRUCTURAL CHROMOSOMAL ABERRATIONS: GAP g	CHROMATID TYPE csb	CHROMATID TYPE csc	CHROMOSOME TYPE csb	CHROMOSOME TYPE csc	GT	TOTALS* -g	TOTALS* +g	JUDGEMENT (+/-) ***
CONTROLS																	
NEGATIVE:	RPMI 1640[a]		A	100	3.6	0.0	0.0								0	0	
			B	100	3.2	0.0	0.0								0	0	
			TOTAL	200											0	0	
			%		3.4	0.0	0.0	-							0.0	0.0	-
SOLVENT:	Deionized water	30.0 µl/ml	A	100	3.2	0.0	1.0								0	0	
			B	100	4.1	0.0	0.0								0	0	
			TOTAL	200											0	0	
			%		3.7	0.0	0.5	-							0.0	0.0	-
POSITIVE:	CP[b]	30.0 µg/ml		25						9	6	1			13	13	
			%		1.6	0.0	0.0	-		36.0	24.0	4.0			52.0	52.0	+
TEST ARTICLE		625 µg/ml****	A	0	3.1												
			B	0	2.7												
			TOTAL	0													
			%		2.9												
		1250 µg/ml	A	100	3.0	0.0	1.0								0	0	
			B	100	2.7	0.0	1.0			2					2	2	
			TOTAL	200						2					2	2	
			%		2.9	0.0	1.0	-		1.0					1.0	1.0	-
		2500 µg/ml	A	100	2.7	0.0	0.0		3	3	1				4	5	
			B	100	2.9	0.0	0.0		1	2		1			3	4	
			TOTAL	200					4	5	1	1			7	9	
			%		2.8	0.0	0.0	-	2.0	2.5	0.5	0.5			3.5	4.5	↵
		3748 µg/ml	A	100	3.7	0.0	0.0		2	5	1	1			6	9	
			B	100	3.8	0.0	0.0		4	7		1			8	9	
			TOTAL	200					6	15	1	2			16	18	
			%		3.8	0.0	0.0	-	3.0	7.5	0.5	1.0			8.0	9.0	+
		4990 µg/ml	A	100	3.9	0.0	0.0		3	23	4	4			24	25	
			B	100	3.3	0.0	0.0		7	20	2	2			20	23	
			TOTAL	200					10	43	6	6			44	48	
			%		3.6	0.0	0.0	-	5.0	21.5	3.0	3.0			22.0	24.0	+

csb: chromatid break csc: chromatid exchange csc: chromosome break csc: chromosome exchange GT: greater than 10 aberrations
* -g: no. or % of cells with chromosome aberrations; +g: no. or % of cells with chromosome aberrations + no. or % of cells with gaps.
[a] RPMI 1640 = Culture medium
** Significantly greater in % polyploidy and % endoreduplication than the solvent control, $p < 0.01$.
[b] CP = Cyclophosphamide
*** Significantly greater in -g than the solvent control, $p < 0.01$.
↵ Weakly significantly greater in -g than the solvent control, $p < 0.05$.
**** Chromosome aberrations not analyzed due to higher dose concentrations available for analysis.

Table 5. Sponsor's Chromosomal Aberration Analysis of The Confirmatory Trial in Human Lymphocytes *In Vitro*.

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES
24 Hour Treatment and Harvest

Assay No.: 17261 Trial #: 2 Lab #: CY12085 Metabolic Activation: -S9

Compound: Oxycodone hydrochloride Date: 12/06/95

				CELLS SCORED	% MITOTIC INDEX	No. ENDORE-DUPLICATED CELLS	No. POLY-PLOID CELLS	JUDGE-MENT (+/-) **	NUMBERS AND PERCENTAGES (%) OF CELLS SHOWING STRUCTURAL CHROMOSOMAL ABERRATIONS							
									GAPS	CHROMATID TYPE		CHROMOSOME TYPE		GT	TOTALS*	
										csb	cse	csb	csc		-g	+g
CONTROLS																
NEGATIVE:	RPMI 1640[a]		A	100	3.3	0.0	0.0			1					1	1
			B	100	3.5	0.0	0.0								0	0
			TOTAL	200						1					1	1
				%	3.4	0.0	0.0	-		0.5					0.5	0.5 -
SOLVENT:	Deionized water	15.0 µl/ml	A	100	4.2	0.0	0.0				1				1	1
			B	100	2.1	0.0	0.0								0	0
			TOTAL	200							1				1	1
				%	3.2	0.0	0.0	-			0.5				0.5	0.5 -
POSITIVE:	MMC[b]	0.200 µg/ml		25						2	5	3			8	8
				%	1.6	0.0	0.0	-		8.0	20.0	12.0			32.0	32.0 +
TEST ARTICLE		500 µg/ml	A	100	3.0	0.0	1.0		1						0	1
			B	100	3.4	0.0	0.0								0	0
			TOTAL	200					1						0	1
				%	3.2	0.0	0.5	-	0.5						0.0	0.5 -
		750 µg/ml	A	100	2.4	0.0	0.0								0	0
			B	100	2.8	0.0	0.0		2						0	2
			TOTAL	200					2						0	2
				%	2.6	0.0	0.0	-	1.0						0.0	1.0 -
		1000 µg/ml	A	100	3.6	0.0	0.0								0	0
			B	100	3.9	0.0	0.0			1	1				2	2
			TOTAL	200						1	1				2	2
				%	3.8	0.0	0.0	-		0.5	0.5				1.0	1.0 -
		1500 µg/ml	A	100	1.6	1.0	0.0								0	0
			B	100	1.8	0.0	0.0								0	0
			TOTAL	200											0	0
				%	1.7	0.5	0.0	-							0.0	0.0 -

csb: chromatid break csc: chromatid exchange csb: chromosome break csc: chromosome exchange GT: greater than 10 aberrations

* -g: no. or % of cells with chromosome aberrations; +g: no. or % of cells with chromosome aberrations + no. or % of cells with gaps.

** Significantly greater in % polyploidy and % endoreduplication than the solvent control, $p < 0.01$.

*** Significantly greater in -g than the solvent control, $p < 0.01$.

[a] RPMI 1640 = Culture medium

[b] MMC = Mitomycin C

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES
48 Hour Treatment and Harvest

Assay No.: 17261 Trial #: 2 Lab #: CY12085 Metabolic Activation: -S9

Compound: Oxycodone hydrochloride Date: 12/06/95

				CELLS SCORED	% MITOTIC INDEX	No. ENDORE-DUPLICATED CELLS	No. POLY-PLOID CELLS	JUDGE-MENT (+/-) **	NUMBERS AND PERCENTAGES (%) OF CELLS SHOWING STRUCTURAL CHROMOSOMAL ABERRATIONS							
									GAPS	CHROMATID TYPE		CHROMOSOME TYPE		GT	TOTALS*	
										csb	cse	csb	csc		-g	+g
CONTROLS																
NEGATIVE:	RPMI 1640[a]		A	100	3.4	0.0	0.0					1			1	1
			B	100	3.4	0.0	0.0								0	0
			TOTAL	200								1			1	1
				%	3.4	0.0	0.0	-				0.5			0.5	0.5 -
SOLVENT:	Deionized water	15.0 µl/ml	A	100	4.4	0.0	0.0								0	0
			B	100	3.3	1.0	0.0								0	0
			TOTAL	200											0	0
				%	3.9	0.5	0.0	-							0.0	0.0 -
TEST ARTICLE		500 µg/ml	A	100	1.6	0.0	0.0								0	0
			B	100	1.9	0.0	0.0		1	1		1			1	1 -
			TOTAL	200					1	1		1			1	1
				%	1.8	0.0	0.0	-	0.5	0.5		0.5			0.5	0.5 -
		750 µg/ml****	B	200					1	2	1				3	3
				%	1.2	0.0	0.0	-	0.5	1.0	0.5				1.5	1.5 -
		1000 µg/ml	A	100	1.2	0.0	0.0		1						0	1
			B	100	2.3	0.0	0.0								0	0
			TOTAL	200					1						0	1
				%	1.8	0.0	0.0	-	0.5						0.0	0.5 -
		1500 µg/ml	A	100	1.5	0.0	0.0								0	0
			B	100	1.9	0.0	0.0		1						0	1
			TOTAL	200					1						0	1
				%	1.7	0.0	0.0	-	0.5						0.0	0.5 -

csb: chromatid break csc: chromatid exchange csb: chromosome break csc: chromosome exchange GT: greater than 10 aberrations

* -g: no. or % of cells with chromosome aberrations; +g: no. or % of cells with chromosome aberrations + no. or % of cells with gaps.

** Significantly greater in % polyploidy and % endoreduplication than the solvent control, $p < 0.01$.

*** Significantly greater in -g than the solvent control, $p < 0.01$.

**** Only B culture available for counting.

[a] RPMI 1640 = Culture medium

Table 6. Sponsor's Chromosomal Aberration Analysis of The Confirmatory Trial in Human Lymphocytes *In Vitro*.

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES
3 Hour Treatment, 24 Hour Harvest

Assay No.: 17261 Trial #: 2 Lab #: CY12085 Metabolic Activation: +S9

Compound: Oxycodone hydrochloride Date: 12/06/95

					CELLS SCORED	% MITOTIC INDEX	No. ENDORE-DUPLICATED CELLS	No. POLY-PLOID CELLS	JUDGE-MENT (+/-) **	NUMBERS AND PERCENTAGES (%) OF CELLS SHOWING STRUCTURAL CHROMOSOMAL ABERRATIONS								JUDGE-MENT (+/-) ***
										GAP g	CHROMATID TYPE ctb	CHROMATID TYPE ctc	CHROMOSOME TYPE csb	CHROMOSOME TYPE csc	GT	TOTALS* -g	TOTALS* +g	
CONTROLS																		
NEGATIVE:	RPMI 1640 [a]		A	100	3.2	0.0	0.0								0	0	
			B	100	3.2	1.0	0.0								0	0	
			TOTAL												0	0	
				%	3.2	0.5	0.0	-							0.0	0.0	-
SOLVENT:	Deionized water	50.0 µl/ml	A	100	3.1	0.0	0.0								0	0	
			B	100	3.1	0.0	0.0								0	0	
			TOTAL	200											0	0	
				%	3.1	0.0	0.0	-							0.0	0.0	-
POSITIVE:	CP [b]	50.0 µg/ml		25							11	1	5	1	12	12	
				%	1.5	0.0	0.0	-			44.0	4.0	20.0	4.0	48.0	48.0	+
TEST ARTICLE		1250 µg/ml	A	100	3.1	0.0	0.0				2		1		2	2	
			B	100	1.5	0.0	0.0		1		3	1			4	5	
			TOTAL	200					1		5	1	1		6	7	
				%	2.3	0.0	0.0	-	0.5		2.5	0.5	0.5		3.0	3.5	+'
		2500 µg/ml	A	100	2.9	0.0	0.0		1		1		1		2	3	
			B	100	3.0	0.0	0.0				1		2		3	3	
			TOTAL	200					1		2		3		5	6	
				%	3.0	0.0	0.0	-	0.5		1.0		1.5		2.5	3.0	-
		3750 µg/ml	A	100	2.9	0.0	0.0		1		14	1	3		15	15	
			B	100	2.7	0.0	0.0		4		5	2	2	1	8	12	
			TOTAL	200					5		19	3	5	1	23	27	
				%	2.8	0.0	0.0	-	2.5		9.5	1.5	2.5	0.5	11.5	13.5	+
		5000 µg/ml	A	100	1.9	0.0	0.0				10	1	3		12	12	
			B	100	2.2	0.0	0.0		2		10		2		11	12	
			TOTAL	200					2		20	1	5		23	24	
				%	2.1	0.0	0.0	-	1.0		10.0	0.5	2.5		11.5	12.0	+

ctb: chromatid break ctc: chromatid exchange csb: chromosome break csc: chromosome exchange GT: greater than 10 aberrations

* -g: no. or % of cells with chromosome aberrations; +g: no. or % of cells with chromosome aberrations + no. or % of cells with gaps. [a] RPMI 1640 = Culture medium

** Significantly greater in % polyploidy and % endoreduplication than the solvent control, $p < 0.01$. [b] CP = Cyclophosphamide

*** Significantly greater in -g than the solvent control, $p < 0.01$. +' Weakly significantly greater in -g than the solvent control, $p < 0.05$.

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES
3 Hour Treatment, 48 Hour Harvest

Assay No.: 17261 Trial #: 2 Lab #: CY12085 Metabolic Activation: +S9

Compound : Oxycodone hydrochloride Date: 12/06/95

					CELLS SCORED	% MITOTIC INDEX	No. ENDORE-DUPLICATED CELLS	No. POLY-PLOID CELLS	JUDGE-MENT (+/-) **	NUMBERS AND PERCENTAGES (%) OF CELLS SHOWING STRUCTURAL CHROMOSOMAL ABERRATIONS								JUDGE-MENT (+/-) ***
										GAP g	CHROMATID TYPE ctb	CHROMATID TYPE ctc	CHROMOSOME TYPE csb	CHROMOSOME TYPE csc	GT	TOTALS* -g	TOTALS* +g	
CONTROLS																		
NEGATIVE:	RPMI 1640 [a]		A	100	5.0	0.0	0.0								0	0	
			B	100	6.9	0.0	1.0								0	0	
			TOTAL	200											0	0	
				%	6.0	0.0	0.5	-							0.0	0.0	-
SOLVENT:	Deionized water	50.0 µl/ml	A	100	3.5	0.0	0.0				2				2	2	
			B	100	4.0	0.0	0.0								0	0	
			TOTAL	200							2				2	2	
				%	3.8	0.0	0.0	-			1.0				1.0	1.0	-
TEST ARTICLE		1250 µg/ml	A	100	7.0	0.0	0.0		1			1			1	2	
			B	100	3.9	0.0	1.0				1		2		3	3	
			TOTAL	200					1		1	1	2		4	5	
				%	5.5	0.0	0.5	-	0.5		0.5	0.5	1.0		2.0	2.5	-
		2500 µg/ml	A	100	2.3	0.0	1.0					2	1	1	4	4	
			B	100	2.5	0.0	0.0				1		3		4	4	
			TOTAL	200							1	2	4	1	8	8	
				%	2.4	0.0	0.5	-			0.5	1.0	2.0	0.5	4.0	4.0	-
		3750 µg/ml	A	100	2.4	0.0	0.0		1						0	1	
			B	100	2.1	0.0	1.0		1		2	2			3	4	
			TOTAL	200					2		2	2			3	5	
				%	2.3	0.0	0.5	-	1.0		1.0	1.0			1.5	2.5	-
		5000 µg/ml	A	100	1.9	0.0	1.0		1		2	2			4	5	
			B	100	2.6	0.0	0.0				2		2		4	4	
			TOTAL	200					1		4	2	2		8	9	
				%	2.3	0.0	0.5	-	0.5		2.0	1.0	1.0		4.0	4.5	-

ctb: chromatid break ctc: chromatid exchange csb: chromosome break csc: chromosome exchange GT: greater than 10 aberrations

* -g: no. or % of cells with chromosome aberrations; +g: no. or % of cells with chromosome aberrations + no. or % of cells with gaps. [a] RPMI 1640 = Culture medium

** Significantly greater in % polyploidy and % endoreduplication than the solvent control, $p < 0.01$.

*** Significantly greater in -g than the solvent control, $p < 0.01$.

In Vivo (Oral Dosing) Mouse Micronucleus Assay With Oxycodone Hydrochloride (Report №: DSE-152).

The mouse micronucleus assay was conducted at during November 8, 1995 to December 28, 1995. The assay was conducted in accordance to the guidelines and governmental standards of the GLP. A signed Quality Assurance Statement was submitted.

The micronucleus test was conducted in young (approximately 8 weeks of age at time of dosing) male and female Crl:CD-1®(ICR)BR mice. Oxycodone HCl was administered orally at single doses of 87.5, 175.0, and 350.0 mg/kg in the male and at single doses of 150.0, 300.0, and 600.0 mg/kg in the female mice. Cyclophosphamide, served as a positive reference compound, was administered orally into a group of 10 mice (5 males and 5 females) at a single dose of 80.0 mg/kg. Another group of 10 mice (5 ♂ and 5 ♀), receiving deionized water (10 ml/kg) served as vehicle control. The vehicle was administered orally.

Oxycodone HCl-treated mice, 5 males and 5 females per time point, were euthanized with CO_2 at 24, 48, and 72 hours after the acute dose. Cyclophosphamide-treated mice were analyzed 24 hours after dosing. Bone marrow cells were aspirated from the epiphyses of both femora. The bone marrow cells were centrifuged in 3-5 ml of bovine serum; the supernatant was removed by aspiration and portions of the pellet were spread on slides and air dried. Slides were fixed in methanol and stained according to the procedures of Schmid (1975)I that is, the slides were stained in May-Grunwald solution followed by Giemsa.

The slides were analyzed by scoring 1000 polychromatic erythrocytes (PCE) from each animal. The polychromatic erythrocytes (PCE) to normochromatic erythrocyte (NCE) cell ratio and the frequency of micronucleated cells (% micronucleated cells based on the total PCEs) were calculated. According to the sponsor, the normal frequency of micronuclei in the Crl:CD-1®(ICR)BR strain is about 0.0 -0.4% for their laboratory.

Results. Results of the micronucleus assay are presented in Tables 7 and 8. The frequency of PCEs versus NCEs are presented in Table 7. There was no indication of reduction in PCE to NCE in the oxycodone-treated mice; the ratios for treated groups fell within the observed range of the vehicle control group. This indicated no oxycodone-induced bone marrow toxicity in males or females.

The frequency of micronucleated cells are presented in Table 8. As expected, Cyclophosphamide (CPA) clearly increased the numbers of micronucleated polychromatic erythrocytes (MN-PCE) was statistically ($p<0.05$) increased in both the male and female mice following treatment with CPA. Oxycodone, at all dose levels tested or bone marrow collection time, did not significantly increase the number of micronucleated polychromatic erythrocytes per 1000 polychromatic erythrocytes analyzed in either the male or female mice.

Table 7. Measure of Oxycodone-Induced Bone Marrow Toxicity.

Treatment: Dose (mg/kg)	Sex	Mean Ratio PCE/NCE (± S.E.)[a]		
		24 hr	48 hr	72 hr
CPA: 80.0 mg/kg	M	0.48 ± 0.01	NT	NT
	F	0.61 ± 0.10	NT	NT
Deionized H_2O 10 ml/kg	M	0.46 ± 0.10	0.54 ± 0.02	0.65 ± 0.01
	F	0.49 ± 0.09	0.41 ± 0.04	057 ± 0.12
Oxycodone: 87.5 (M); 150 (F)	M	0.51 ± 0.08	0.53 ± 0.06	0.59 ± 0.09
	F	0.59 ± 0.06	0.59 ± 0.07	0.56 ± 0.06
Oxycodone: 175 (M); 300 (F)	M	0.51 ± 0.07	0.50 ± 0.06	0.62 ± 0.07
	F	0.46 ± 0.05	0.54 ± 0.12	0.59 ± 0.11
Oxycodone: 350 (M); 600 (F)	M	0.55 ± 0.07	0.48 ± 0.06	0.71 ± 0.15
	F	0.46 ± 0.07	0.51 ± 0.11	0.78 ± 0.14

a: Calculated from total number of PCE and NCE for each animal.
NT: Not Tested
CPA: Cyclophosphamide

Table 8. Effect of Oxycodone on the Frequency of Micronucleated Polychromatic (MN-PCEs) in The Mouse Bone Marrow Assay.

Treatment: Dose (mg/kg)	Sex	24 HOURS	48 HOURS	72 HOURS
		Mean Frequency of MN-PCE Formation (%)	Mean Frequency of Formation of MN-PCE (%)	Mean Frequencies of Formation of MN-PCE (%)
Oxycodone: 0.0	M	0.14 ± 0.04	0.18 ± 0.06	0.10 ± 0.03
	F	0.08 ± 0.06	0.14 ± 0.05	0.10 ± 0.06
	M,F	0.11 ± 0.03	0.16 ± 0.04	0.10 ± 0.03
Oxycodone: 87.5 (M); 150 (F)	M	0.14 ± 0.04	0.22 ± 0.09	0.10 ± 0.04
	F	0.08 ± 0.05	0.20 ± 0.09	0.14 ± 0.12
	M,F	0.11 ± 0.03	0.21 ± 0.06	0.12 ± 0.06
Oxycodone: 175 (M); 300 (F)	M	0.24 ± 0.09	0.12 ± 0.04	0.08 ± 0.04
	F	0.06 ± 0.04	0.02 ± 0.02	0.08 ± 0.02
	M,F	0.15 ± 0.06	0.07 ± 0.03	0.08 ± 0.02
Oxycodone: 350 (M); 600 (F)	M	0.18 ± 0.04	0.14 ± 0.04	0.08 ± 0.04
	F	0.12 ± 0.04	0.10 ± 0.06	0.13 ± 0.03
	M,F	0.15 ± 0.03	0.13 ± 0.03	0.10 ± 0.02
CPA: 80.0	M	4.16 ± 0.94[a]	NT	NT
	F	2.16 ± 0.30[a]		
	M,F	3.16 ± 0.57[a]		

a: Significantly greater than vehicle controls, $p<0.05$ (Dunnett's t-test).
CPA: Cyclophosphamide

LABELING REVIEW.

The proposed draft labeling has been reviewed. In conformance with 21CFR201.56 General Requirements on Content and Format of Labeling for Human Prescription Drugs, the subsection of the Precautions should be Carcinogenesis, Mutagenesis, Impairment of Fertility instead of Mutagenicity/Carcinogenicity. From the standpoint of pharmacology, the Mutagenicity/Carcinogenicity section should be amended as follows based on the available data:

Sponsor's Proposed Section:

Mutagenicity/Carcinogenicity:

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. Coli test with and without metabolic activation at doses up to 5000 μg, chromosomal aberration test in human lymphocytes (in the absence of metabolic activation and with activation after 48 hours of exposure) at doses up to 1500 μg/ml, and in the in vivo bone 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 hour but not 48 hours of exposure and 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. The doses/concentrations used are well beyond those that would likely be attainable in humans. Therefore, the data from these tests indicate that oxycodone hydrochloride would not pose a genotoxic risk to humans.

Studies of oxycodone in animals to evaluate its carcinogenic potential have not been conducted owing to the length of clinical experience with the drug substance.

Replacement:

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Studies of oxycodone in animals to evaluate its carcinogenic potential have not been conducted.

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. Coli test with and without metabolic activation at doses up to 5000 μg, chromosomal aberration test in human lymphocytes (in the absence of metabolic activation and with activation after 48 hours of exposure) at doses up to 1500 μg/ml, and in the in vivo bone 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) and 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.

RECOMMENDATIONS.

We have no objections to the approval of this NDA supplement, based on the submitted information. However, the suggested labelling revisions will be necessary prior to approval.

External Recommendation. The suggested labeling changes discussed in the "Labeling Review" Section should be forwarded to the sponsor prior to approval of this NDA Supplement.

BeLinda A. Hayes
BeLinda A. Hayes, Ph.D., Pharmacologist

12/18/96
Date

Concurred by Team Leader:

Dou Huey (Lucy) Jean
Dou Huey (Lucy) Jean, Ph.D., Pharmacologist

Dec. 18, 1996
Date

CC: Orig NDA# 20-553
HFD-170/Div File
HFD-170/BHayes
HFD-170/BMcNeal
F/T by:BHayes/12-13/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-553/S-002

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JUL 29 1996

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-553 **SUPPLEMENT NO.:** 002
NAME: Oxycontin™ 80 mg
SPONSOR: Purdue Pharma L.P., 100 Connecticut Avenue, Norwalk, CT 06850
SUBMISSION DATE: June 24, 1996 **REVIEW DATE:** July 8, 1996
TYPE OF SUBMISSION: Bioequivalency Study Report
REVIEWER: Suresh Doddapaneni, Ph.D.

SYNOPSIS

The Purdue Fredrick Company has developed oxycodone hydrochloride in an oral controlled release tablet form in a range of dosage strengths (10, 20, and 40 mg) to be taken on a q12h basis. These strengths were approved on December 21, 1995 for use in the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days. The sponsor is proposing to market a new strength Oxycontin™ 80 mg controlled release tablet as a line extension to the already approved strengths for use in patients tolerant to opioids (requiring more than 160 mg). The section 6 of this submission consists of a single pharmacokinetic study conducted to assess the bioequivalence of the new Oxycontin™ 80 mg strength tablet relative to the currently marketed Oxycontin™ 40 mg tablet (two 40 mg tablets).

Oxycontin™ 80 mg tablet was found to be bioequivalent to two Oxycontin™ 40 mg tablets with respect to both C_{max} and AUC.

RECOMMENDATION

The supplement 002 to NDA 20-553 is acceptable from the viewpoint of Office of Clinical Pharmacology and Biopharmaceutics and the proposed labeling changes to the pharmacokinetics section by the sponsor can be approved.

DSoush 7/29/96
Suresh Doddapaneni, Ph.D.
Pharmacokineticist

RD initialed by Dale Conner, PharmD on 7/19/96
FT initialed by Dale Conner, PharmD. DC 7/29/96

CC:

NDA 20-553, HFD-170 (Division files, McNeal), HFD-850 (Lesko), HFD-860 (Malinowski), HFD-870 (Doddapaneni, Mei-Ling Chen, Conner, Chron, Drug, Reviewer), HFD-880 (Fleischer), HFD-340 (Viswanathan), HFD-205 (FOI)
R/D by: DConner/7-19-96
F/T by: PO'Connor/7-30-96

1.0. BACKGROUND

Oxycodone is a semi-synthetic opioid agonist that has been available for clinical use since 1917. Oral oxycodone is approximately twice as potent as oral morphine on a milligram basis. Therepeutic application of oxycodone for the most part has been as a combination ingredient with aspirin or acetaminophen for the treatment of moderate to moderately severe pain. Oxycodone hydrochloride is also available as a single ingredient oral analgesic in tablet and solution formulations for the management of moderate to severe pain. The Purdue Fredrick Company has developed oxycodone hydrochloride in an oral controlled release tablet form in a range of dosage strengths (10, 20, and 40 mg) to be taken on a q12h basis. These strengths were approved on December 21, 1995 for use in the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days. The sponsor is proposing to market a new strength of 80 mg Oxycontin™ controlled release tablet as a line extension to the already approved strengths for use in patients tolerant to opioids (requiring more than 160 mg). The sponsor believes increased compliance can be obtained with the availability of the 80 mg strength with the advantage of taking fewer tablets for higher doses. The 80 mg strength has been approved for use in Canada in January 1996. This submission consists of a single pharmacokinetic study conducted to assess the bioequivalence of the proposed to be marketed 80 mg Oxycontin™ tablet relative to the currently marketed Oxycontin™ 40 mg (2 tablets).

2.0. STUDY DESIGN

This was an open label, randomized, analytically blinded, single dose, two-way cross-over study in twenty-four young, normal, healthy, opioid naive fasted (8 hours pre- and 4 hours post-dose) males and females (protocol No. OC94-0703). Since 80 mg oxycodone can cause opioid related side effects the subjects were administered Trexan™ 50 mg (naltrexone hydrochloride) to minimize the occurrence of the adverse effects (2 tablets each 24 hours prior to dosing, along with dose, and 24 hours after the administration of the oxycodone dose). A washout period of 1 week separated the two treatments. The two treatments were;

Test: One Oxycontin™ 80mg controlled release tablet.
Reference: Two Oxycontin™ 40 mg controlled release tablets.

C_{max}, t_{max}, AUC (AUC_{0-48} and $AUC_{0-\infty}$), $t_{1/2}$ abs, $t_{1/2}$ elm, W_{50}, and Wagner-Nelson percent drug absorbed (k_a was obtained from a 10 mg IR tablet treatment in a previous study). ANOVA with factors for sequence, period, treatment, and subject (sequence) was used to test the statistical significance of the parameter estimates. ANOVA analysis was also performed after separation of the data based on gender to examine the treatment differences within the same sex. Ninety percent (90%) confidence intervals were constructed for C_{max} and AUC using the two one-sided t-tests procedure to test the bioequivalence of the two treatments.

3.0. RESULTS AND DISCUSSION

ANOVA analysis of all the pharmacokinetic parameters of oxycodone evaluated in this study excepting t_{max} were statistically insignificant between Oxycontin™ 80 mg tablet and two Oxycontin™ 40 mg tablets overall and within both male and female subject groups. For C_{max} and

AUC (both AUC_{0-48} and $AUC_{0-\infty}$), the 90% confidence intervals were within the FDA acceptable limits (Table 1). This was verified by this reviewer by analyzing the C_{max} and AUC data on SAS and constructing the 90% confidence intervals.

Dose-proportionality between 10, 20, and 40 mg strengths was demonstrated in the original NDA. To find out if the 80 mg strength is dose-proportional with the other strengths, a rough analysis of the mean C_{max} and $AUC_{0-\infty}$ values of oxycodone for the Oxycontin™ 40 mg tablet with Oxycontin™ 80 mg tablet was performed by this reviewer. A slightly more than proportional increase in C_{max} (2.5 fold) and $AUC_{0-\infty}$ (2.5 fold) for the Oxycontin™ 80 mg tablet over the Oxycontin™ 40 mg tablet was found. In a published report, naltrexone was demonstrated to increase the C_{max} (15%) and AUC_{0-24} (23%) of controlled release morphine tablets in its presence. Since the current study was also conducted in subjects treated with naltrexone, presumably the 25% increase seen in C_{max} and $AUC_{0-\infty}$ with Oxycontin™ 80 mg tablet is a result of the effect of naltrexone on oxycodone's absorption (naltrexone reverses the reduction of gastric emtying caused by oxycodone). Therefore, Oxycontin™ 80 mg can be considered to be dose-proportional to the other strengths.

The effect of food was not studied for Oxycontin™ 80 mg tablet. However, it may not be necessary to study it separately for the following reasons;

(1) Food effect (old FDA high fat breakfast) was studied for the Oxycontin™ 40 mg tablet in the original NDA and it was concluded that meals would not have a significant clinical effect *in vivo*.

(2) The Oxycontin™ 80 mg tablet formulation is similar to the Oxycontin™ 40 mg tablet and is essentially a proportionate scale up of the Oxycontin™ 40 mg tablet in terms of the active and inactive ingredients.

(3) Currently, the package insert allows doses up to 120 mg to be used using any combination of 10, 20, and 40 mg depending upon the dose.

(4) The *in vitro* dissolution data for the Oxycontin™ 80 mg tablet is within the specifications set for the 10, 20, and 40 mg strengths in the original NDA.

4.0. PROPOSED PACKAGE INSERT

The following relevant changes were made in the pharmacokinetics and metabolism section of the proposed package insert by incorporation of the information for the 80 mg strength obtained from this study to that of the currently marketed strengths of Oxycontin™.

5.0. CONCLUSIONS

Based on the 90% confidence interval analysis, the controlled release Oxycontin™ 80 mg tablet is bioequivalent with repect to AUC_{0-24} and C_{max} of absorption to controlled release Oxycontin™ 2 x 40 mg tablets. The labeling changes proposed by the sponsor as discussed above are reasonable.

STUDY SUMMARY

NDA/IND# 20-553 Suppl/Amend.# 078 (6/2/93) Submission Date: Volume:

Study Type: Bioequivalency Study #: OC94-0703

Study Title: A Single Dose, Two-Way, Randomized, Crossover, Analytically Blinded, Bioequivalence Study of Two (2) Controlled-Release Oxycodone 40 mg Tablets and One (1) Controlled-Release Oxycodone 80 mg Tablet Each Give with Naltrexone in Fasted Normal Volunteers

Clinical Investigator:

Site:

Analytical Investigator:

Site:

Single Dose: X Multiple Dose: __ Washout Period: 7 days

Cross-Over: X Parallel: __ Other Design:

Fasted: X Food Study: __ FDA High Fat Breakfast:

If fasted, how long (hrs)? 8 hrs pre- and 4 hrs post-dose

Subject Breakdown

Normal: 24 Patients: __ Young: 24 Elderly: __ Renal: __ Hepatic: __

Subject Type: Male

Weight Mean 78.03 kg Range

Age Mean 30.75 yr Range

Subject Type: Female

Weight Mean 66.24 kg Range

Age Mean 30.92 yr Range

Group	N= 24	M= 12	F= 12
Group	N=	M=	F=
Group	N=	M=	F=
Group	N=	M=	F=
Group	N=	M=	F=
Group	N=	M=	F=

Treatment Group	Dose	Dosage Form	Strength	Lot #	Lot Size
CR Oxycodone	2 x 40 mg	Tablets	40 mg	4C	902,507 tabs
CR Oxycodone	80 mg	Tablet	80 mg	6E	532,777 tabs

Sampling Times

Plasma: 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 18, 24, 30, 36, 48 hrs.

Urine: N/A

Feces: N/A

Assay Method: High Performance Liquid Chromatography (HPLC)

Assay Sensitivity: 5 ng/mL

Assay Accuracy: -4.40 to 2.3% over range of standard curve (5-200 ng/mL)
Mean %CV of low control (10 ng/mL): 0.80%
Mean %CV of high control (150 ng/mL): 1.55%

Labeling Claims From Study: The 80 mg oxycodone CR tablet (The Purdue Frederick Company) is bioequivalent to 2 x 40 mg oxycodone CR tablets.

Table 1. Pharmacokinetic parameters of oxycodone following dosing with Oxycontin™ 80 mg CR tablet and Oxycontin™ 2 x 40 mg CR tablets

Parameter	CR Oxy 80mg	CR Oxy 2x40mg	Ratio(%)* CR Oxy 80mg / CR Oxy 2x40mg	90% CI Lower	90% CI Upper
AUC (0-48hrs)					
Arithmetic Mean(SD)	1081.7(343.51)	1076.1(346.27)	100.52	91.19	109.77
Geometric Mean	1031.5	1019.7	101.16	91.38	112.10
AUC (0-Infinity)					
Arithmetic Mean(SD)	1085.5(350.77)	1093.6(376.59)	99.26	89.67	108.74
Geometric Mean	1033.8	1030.4	100.33	90.44	111.41
Cmax (ng/mL)					
Arithmetic Mean(SD)	98.46(31.55)	99.07(28.17)	99.39	88.82	108.80
Geometric Mean	94.02	95.54	98.40	89.13	107.51
T 1/2 Abs. (hrs)					
Arithmetic Mean(SD)	0.79(0.62)	1.07(0.92)	73.91	40.68	107.40
T 1/2 Elim. (hrs)					
Arithmetic Mean(SD)	6.41(1.82)	6.26(2.24)	102.47	88.43	117.30
Tmax (hrs)					
Arithmetic Mean(SD)	2.07(1.14)	3.00(1.61)	68.84	49.21	89.48
Curve Width @50% Cmax					
Arithmetic Mean(SD)	7.80(2.14)	8.67(2.83)	89.90	76.44	104.31
Wag-Nel 50% (hrs)					
Arithmetic Mean(SD)	3.64(1.49)	4.04(1.97)	85.33	63.70	109.06

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Note: Ratio and 90% CI are based on least squares means
* Ratio(%): (Test mean / Reference mean)*100%

JAN - 8 1997

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-553 **SUPPLEMENT NO.:** 002 **NAME:** Oxycontin™ 80 mg
SPONSOR: Purdue Pharma L.P., 100 Connecticut Avenue, Norwalk, CT 06850
SUBMISSION DATE: June 24, 1996
REVIEWER: Suresh Doddapaneni, Ph.D. **REVIEW DATE:** December 19, 1996

Addendum to the Primary Review

Subsequent to the completion of the review of this supplement, DSI conducted an audit of the bioequivalency study (protocol C94-0703) and concluded that the integrity of the data are questionable due to several problems identified with the analytical methodology employed in this study. Form 483 was issued to the sponsor (see attachment). Upon review of the DSI findings, this reviewer concurs with the overall conclusion of the DSI and recommends that the bioequivalency data from this study should not be used as a basis for approval of this supplement.

DSuresh 1/8/97

Suresh Doddapaneni, Ph.D.
Pharmacokineticist
DPE II/OCPB

FT initialed by Dale Conner, PharmD. 1/8/97

CC:
Orig. NDA 20-553/S-002
Div. Files
HFD-170/SDoddapaneni
HFD-170/DConner/BMcNeal

20-553

DEC
FEB 13 1997

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-553 **SUPPLEMENT NO.:** B-001
TRADE NAME: Oxycontin™ 10 mg, 20 and 40 mg **DRUG NAME:** Oxycodone HCL
SPONSOR: Purdue Pharma L.P., 100 Connecticut Avenue, Norwalk, CT 06850
TYPE OF SUBMISSION: Bioavailability Study Report **SUBMISSION DATE:** October 25, 1996
REVIEWER: Suresh Doddapaneni, Ph.D. **REVIEW DATE:** November 26, 1996

SYNOPSIS

The Purdue Frederick Company has developed oxycodone hydrochloride in an oral controlled release tablet form in a range of dosage strengths (10, 20, and 40 mg) to be taken on a q12h basis. These strengths were approved on December 21, 1995 for use in the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days. In addition, the sponsor has submitted a SNDA on July 8, 1996 proposing to market a new strength Oxycontin™ 80 mg controlled release tablet as a line extension to the already approved strengths for use in patients tolerant to opioids (requiring more than 160 mg). The current submission consists of a single comparative bioavailability study of the 10 mg strength controlled release tablet with two 5 mg tablets of immediate-release oxycodone (Endone™) and 10 mL of immediate release oxycodone oral solution 5 mg/5 mL (Roxicodone™).

Oxycontin™ 10 mg tablet was found to be equally bioavailable to two 5 mg tablets of immediate-release oxycodone (Endone™) and 10 mL of immediate release oxycodone oral solution 5 mg/5 mL (Roxicodone™) with respect to the extent but not the rate of absorption.

RECOMMENDATION

No action is indicated on this supplement.

Suresh 12/5/96

Suresh Doddāpaneni, Ph.D.
Pharmacokineticist
DPE II/OCPB

RD initialed by Dale Conner, PharmD
FT initialed by Dale Conner, PharmD.

12/5/96

CC:

NDA 20-553, HFD-170 (Division files, McNeal), HFD-850 (Lesko), HFD-870 (Doddapaneni, Mei-Ling Chen, Conner, Chron, Drug, Reviewer), HFD-340 (Viswanathan)

BACKGROUND

Oxycodone is a semi-synthetic opioid agonist that has been available for clinical use since 1917. Oral oxycodone is approximately twice as potent as oral morphine on a milligram basis. Therapeutic application of oxycodone for the most part has been as a combination ingredient with aspirin or acetaminophen for the treatment of moderate to moderately severe pain. Oxycodone hydrochloride is also available as a single ingredient oral analgesic in tablet and solution formulations for the management of moderate to severe pain. The Purdue Frederick Company has developed oxycodone hydrochloride in an oral controlled release tablet form in a range of dosage strengths (10, 20, and 40 mg) to be taken on a q12h basis. These strengths were approved on December 21, 1995 for use in the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days. In addition, the sponsor has submitted a SNDA on July 8, 1996 proposing to market a new strength Oxycontin™ 80 mg controlled release tablet as a line extension to the already approved strengths for use in patients tolerant to opioids (requiring more than 160 mg) to increase compliance. The current submission consists of a single comparative bioavailability study of the 10 mg strength controlled release tablet with two 5 mg tablets of immediate-release oxycodone (Endone™) and 10 mL of immediate release oxycodone oral solution 5 mg/5 mL (Roxicodone™).

OBJECTIVES:

To characterize the pharmacokinetic profile of oxycodone when administered as a single controlled-release (Oxycontin™) 10 mg tablet compared with two 5 mg tablets of immediate-release (IR) oxycodone (Endone™) and 10 mL of immediate-release oxycodone oral solution (Roxicodone™) 5 mg/ 5 mL given as a single oral dose.

STUDY DESIGN

Study Type: Bioavailability

Study Title: A Single Dose Pharmacokinetic Study in Healthy Adult Males of One (1) Oxycodone Controlled-Release 10 mg Tablet, Two (2) Immediate-Release Oxycodone 5 mg Tablets and Immediate-Release Oxycodone Oral Solution 10 mg.

Study Features: This was an open label, randomized, analytically blinded, single dose, three-way cross-over study in twenty-two adult, healthy, opioid naive fasted (10 hours pre- and 4 hours post-dose) males (protocol No. OC94-0101). A washout period of 1 week separated the treatments.

Clinical Investigator	Analytical Investigator: Purdue Research Center Yonkers, New York

Subject Breakdown:

Weight	Mean: 76.1 kg Range:
Age	Mean: 25.1 yrs Range:

Formulation:

Treatment Group	Dose	Dosage Form	Strength	Lot Number	Lot Size
Oxycodone Controlled Release	10 mg	Tablet (Oxycontin™)	10 mg	5C	121.12 kg
Oxycodone Immediate Release	10 mg	Tablet (Endone™)	5 mg	AV4522	Unknown
Oxycodone Immediate Release	10 mg	Oral Solution (Roxicodone™)	5 mg/5 mL	940729	Unknown

Plasma Sampling Times: pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 18, 24, 30, and 36, hours post-dose.

Assay Method: Gas chromatography/mass spectrometry

Assay Sensitivity: 0.2 ng/mL

Assay Accuracy: -10.0% to 0.8% over a range of 0.2 - 100 ng/mL

Pharmacokinetic and Statistical Analysis: C_{max}, t_{max}, AUC (AUC_{0-36} and $AUC_{0-\infty}$), $t_{1/2}$abs, $t_{1/2}$elm, W_{50} (peak width at 50% C_{max}), and Wagner-Nelson percent drug absorbed (k_{el} was obtained from immediate release solution). ANOVA with factors for sequence, period, treatment, and subject (sequence) was used to test the statistical significance of the parameter estimates. Ninety percent (90%) confidence intervals were constructed for C_{max} and AUC using the two one-sided t-tests procedure to test the bioequivalence of the test treatment with the two references.

Labeling Claims: Controlled release oxycodone 10 mg tablet was equally bioavailable to immediate release oxycodone 2x5 mg tablets and to immediate release oxycodone 10 mL oral solution , with respect to the extent but not the rate of absorption. The C_{max} of the controlled release tablet was one-third that observed with the immediate release products. The plasma oxycodone concentrations of controlled release oxycodone 10 mg tablet were much lower compared to immediate release oxycodone 2x5 mg tablets and to immediate release oxycodone 10 mL oral solution for the first 5 hours and much higher after 8 hours. Minor differences in the rate of absorption of immediate release oxycodone solution and tablets were not clinically significant.

RESULTS AND DISCUSSION

The pharmacokinetic parameters and results of the statistical analysis are summarized in Table 1. Controlled release oxycodone 10 mg tablet was equally bioavailable to immediate release oxycodone 2x5 mg tablets and to IR oxycodone 10 mL oral solution with respect to the extent of absorption, based on the AUC 90% confidence intervals, but was not comparable to these products with respect to the rate of absorption, based on the C_{max} 90% confidence intervals. The C_{max} of the CR tablet was approximately one-third that observed with the IR products. Mean t1/2(elim), tmax, W_{50}, C_{max}, and Wagner-Nelson 50% drug absorbed were significantly longer for CR oxycodone 10 mg tablet than for either IR oxycodone 10 mL oral solution or IR oxycodone 2x5 mg tablets. CR oxycodone 10 mg tablet had a significantly longer $t_{1/2}$(abs) than IR oxycodone 10 mL oral solution.

IR oxycodone 2x5 mg tablets and IR oxycodone 10 mL oral solution were equally bioavailable with respect to the extent of absorption, based on the AUC 90% confidence intervals, but were not comparable with respect to the rate of absorption, based on the C_{max} 90% confidence intervals. IR oxycodone 10 mL oral solution had significantly shorter mean t1/2(abs) than IR oxycodone 2x5 mg tablets.

This reviewer was informed, during a telecon on December 5, 1996 with Lee Ann Storey of Purdue Pharma, that at the time of submission of the original NDA 20-533, results from this study were not completely available and as such the study report is submitted now to complete the pharmacokinetic information in this NDA. She further stated there are no labeling implications that arise out of this study.

CONCLUSIONS

Controlled release oxycodone 10 mg tablet was equally bioavailable to immediate release oxycodone 2x5 mg tablets and to immediate release oxycodone 10 mL oral solution with respect to the extent but not the rate of absorption. The C_{max} of the controlled release tablet was one-third that observed with the immediate release products.

Table 1. Pharmacokinetic parameters of oxycodone following dosing with Oxycontin™ CR tablet, oxycodone IR tablets, and oxycodone immediate release solution.

PK Parameters	CR Oxy 10 mg	IR Oxy 2x5 mg	Ratio (%)[a] (CR/IR)	90% Confidence Interval
$AUC_{0,36}$ (ng-hr/mL)	111.70	111.93	99.69	94.88-104.75
$AUC_{0,\infty}$ (ng-hr/mL)	113.42	111.93	101.22	96.33-106.37
Cmax (ng/mL)	9.18	29.00	31.53	27.67-35.92
t½(abs) (hrs)	0.94	0.99	94.34	72.24-121.03
t½(elim) (hrs)	6.44	1.97	326.34	299.54-350.78
Tmax (hrs)	2.33	0.83	280.95	235.57-325.76
Peak width @ 50% Cmax (hrs)	9.82	2.09	470.39	421.82-490.83
Wagner-Nelson 50% (hrs)	5.20	0.63	819.70	691.62-849.24

	CR Oxy 10 mg	IR Oxy Solu 10 mL	Ratio (%)[a] (CR/IR Solu)	90% Confidence Interval
$AUC_{0,36}$ (ng-hr/mL)	111.70	109.26	102.69	97.73-107.90
$AUC_{0,\infty}$ (ng-hr/mL)	113.42	109.26	104.29	99.24-109.59
Cmax (ng/mL)	9.18	25.99	35.14	30.84-40.05
t½(abs) (hrs)	0.94	0.48	193.71	144.66-242.38
t½(elim) (hrs)	6.44	2.09	308.11	285.48-334.31
Tmax (hrs)	2.33	0.76	305.71	262.13-362.50
Peak width @ 50% Cmax (hrs)	9.82	2.34	418.88	387.48-450.87
Wagner-Nelson 50% (hrs)	5.20	0.62	839.49	737.31-905.36

	IR Oxy 2x5 mg	IR Oxy Solu 10 mL	Ratio (%)[b] (IR/IR Solu)	90% Confidence Interval
$AUC_{0,36}$ (ng-hr/ml)	111.93	109.26	103.01	98.03-108.23
$AUC_{0,\infty}$ (ng-hr/ml)	111.93	109.26	103.03	98.04-108.26
Cmax (ng/ml)	29.00	25.99	111.48	97.83-127.02
t½(abs) (hrs)	0.99	0.48	205.35	151.39-249.11
t½(elim) (hrs)	1.97	2.09	94.41	70.89-119.72
Tmax (hrs)	0.83	0.76	108.62	61.09-161.46
Peak width @ 50% Cmax (hrs)	2.09	2.34	89.05	60.16-123.56
Wagner-Nelson 50% (hrs)	0.63	0.62	102.41	22.59-190.63

(Cross-reference: Table 18 and Appendix IV)
a Ratio (%) = (test mean/reference mean) x 100%
b Ratio (%) = (IR mean/IR Solu mean) x 100%

Note: For AUC(0,36), AUC(0,∞) and Cmax, geometric means are given. For all other parameters, arithmetic means are given.