

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-553/S-002

PHARMACOLOGY REVIEW(S)

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCTS

REVIEW & EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

NDA 20-553 (SCF-002)

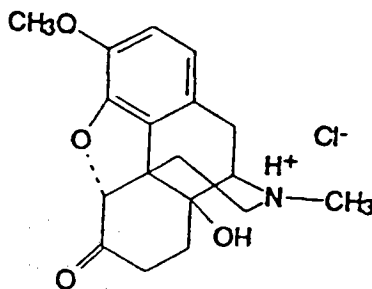
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SPONSOR: Purdue Pharma L.P.
Norwalk, Connecticut

PRODUCT: OxyContin[™]
DRUG: Oxycodone Hydrochloride
CHEMICAL NAME: Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-17-methyl-hydrochloride, (5 α).;
4,5 α -epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride
CAS REGISTRY N^o: 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), 4,5 α -Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-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 genotoxicity 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 WP2uvrA 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 $\mu\text{g}/\text{plate}$. 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 $\mu\text{g}/\text{plate}$. 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 $\mu\text{g}/\text{ml}$) induced resistant mutants at 400 and 500 $\mu\text{g}/\text{ml}$. 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 ($\mu\text{g}/\text{ml}$) 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 $\mu\text{g}/\text{ml}$. At a concentration of $\mu\text{g}/\text{ml}$, 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 $\mu\text{g}/\text{ml}$, 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 $\mu\text{g}/\text{ml}$) 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 N^o: 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 WP2uvrA; 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 _____ $\mu\text{g}/\text{plate}$. 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 $\mu\text{g}/\text{plate}$ 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 $\mu\text{g}/\text{plate}$) for TA98, TA100, TA1535, TA1537 and WP2uvrA with S9 activation; 2-nitrofluorene (1.0 $\mu\text{g}/\text{plate}$) for TA98 without the S9 metabolic activator; sodium azide (2.0 $\mu\text{g}/\text{plate}$) for TA100 and TA1534 without the S9 activator; ICR-191 (2.0 $\mu\text{g}/\text{plate}$) for TA1539 without the S9 activator and 4-nitroquinole-N-oxide (1.0 $\mu\text{g}/\text{plate}$) for WP2uvrA 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 $\mu\text{g}/\text{plate}$) 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 WP2uvrA *Escherichia coli* tester strain tested with or without S9.

L5178Y TK +/- Mouse Lymphoma Forward Mutation Assay With Oxycodone Hydrochloride (With Confirmatory Assay) (Report N^o: 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 $\mu\text{g/ml}$) 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 then 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 (6×10^6 cells/tube) in the logarithmic growth phase were treated with 100, 150, 200, 300, 400, and 500 $\mu\text{g/ml}$ of oxycodone HCl in the absence of metabolic activation, and with 50, 75, 100, 150, 200 and 250 $\mu\text{g/ml}$ of oxycodone HCl in the presence of the S9 metabolic activator. In the second mutagenicity assay, duplicate cultures of L5178Y mouse lymphoma cells (6×10^6 cells/tube) in the logarithmic growth phase were treated with 12.5, 25.0, 50.0, 75.0, 100.0, and 200.0 $\mu\text{g/ml}$ 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 $\mu\text{g/ml}$) 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 1×10^6 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 $\mu\text{g/ml}$. Oxycodone was cytotoxic at 625, 1250, 2500, and 5000 $\mu\text{g/ml}$ in the presence and absence of metabolic activation; these concentrations killed % of the cells during the 4 hour incubation period. 625 $\mu\text{g/ml}$ 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 $\mu\text{g/ml}$ and higher. A weak to moderate cytotoxic response was observed at concentrations of $\mu\text{g/ml}$; relative to the vehicle control the percent relative growth was %. The $\mu\text{g/ml}$ concentrations of oxycodone was very toxic; the observed percent relative growth was %, respectively. Mutagenicity activity was observed following treatment with $\mu\text{g/ml}$ of oxycodone in the absence of metabolic activation. However, since these 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 $\mu\text{g/ml}$. Weak to moderate cytotoxic activity was observed at concentrations ranging from $\mu\text{g/ml}$. Oxycodone was very cytotoxic in the concentration range of $\mu\text{g/ml}$. 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 $\mu\text{g/ml}$ 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 $\mu\text{g/ml}$ 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 small-colony mutants and large-colony mutants. As expected, the positive control treatments induced the characteristic 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)		SUSPENSION GROWTH*	TOTAL MUTANT COLONIES	TOTAL VIABLE COLONIES	CLONING EFFICIENCY*	RELATIVE GROWTH (%) ^b	MUTANT FREQUENCY (10E-6 UNITS) ^c
	1	2						
NONACTIVATION CONTROLS^d								
			AVG VEHICLE CONTROL				AVG VEHICLE CONTROL	
VEHICLE CONTROL	20.3	20.9	47.1	114	559	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	139	494	82.3	85.8	56.3
MMS 5 n1/ml	12.5	16.0	22.2	341	483	86.5	58.3	141.2 ^e
MMS 10 n1/ml	13.8	12.6	19.3	485	275	45.8	26.9	352.7 ^e
MMS 15 n1/ml	10.4	10.1	11.7	435	159	26.5	10.1	547.2 ^e
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 ^e
500 µg/ml	3.2 ^e	7.8	7.3	291	438	85.1	6.2	132.9 ^e

*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 - 10X 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)		SUSPENSION GROWTH*	TOTAL MUTANT COLONIES	TOTAL VIABLE COLONIES	CLONING EFFICIENCY*	RELATIVE GROWTH (%) ^b	MUTANT FREQUENCY (10E-6 UNITS) ^c
	1	2						
S9 ACTIVATION INDUCED^d								
	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	142	529	88.2	86.8	53.7
MCA 2 µg/ml	12.8	16.0	22.8	766	484	67.3	42.6	379.2 ^e
MCA 4 µg/ml	11.5	13.5	17.3	789	444	74.0	39.8	355.4 ^e
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 ^e
75.0 µg/ml	11.1	13.4	44.5	584	535	102.7	45.7	218.3 ^e
100 µg/ml	9.2	14.6	40.2	621	438	84.1	33.8	283.6 ^e
150 µg/ml	4.0 ^e	12.2	11.0	594	337	64.7	7.1	352.5 ^e
200 µg/ml	3.8 ^e	9.8	8.8	586	258	49.5	4.4	454.3 ^e
250 µg/ml	2.1 ^e	5.6	5.0	268	274	52.6	2.6	195.6 ^e

*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 - 10X 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/PL. 10ES UNITS)		SUSPENSION GROWTH ^b	TOTAL MUTANT COLONIES	TOTAL VIABLE COLONIES	CLONING EFFICIENCY ^c	RELATIVE GROWTH (%) ^d	MUTANT FREQUENCY (10E-6 UNITS) ^e
	1	2						
INACTIVATION CONTROLS ^f								
ANG VEHICLE CONTROL								
VEHICLE CONTROL	17.6	11.1	21.7	83	429	71.5	100.0	43.4
VEHICLE CONTROL	13.2	14.9	21.9	97	549	91.5	100.0	35.3
VEHICLE CONTROL	17.0	13.8	25.1	23.2	107	74.8	79.3	44.1
ANG VEHICLE CONTROL								
M/S 5 ml/ml	7.4	14.4	11.8	394	240	40.0	25.7	328.3 ^g
M/S 10 ml/ml	8.0	8.2	7.3	454	92	15.3	6.1	987.8 ^g
M/S 15 ml/ml	6.4	4.6	3.3	264	46	7.7	1.4	1147.8 ^g
TEST COMPOUND								
RELATIVE TO VEHICLE CONTROL (%)								
200 µg/ml	18.4	9.9	49.3	112	529	111.2	54.8	42.3
300 µg/ml	9.3	7.8	31.2	144	470	98.8	30.8	61.3
350 µg/ml	8.1	7.2	27.9	184	645	135.6	37.8	57.1
400 µg/ml	4.9	10.5	24.6	169	392	82.4	20.3	86.2 ^g
450 µg/ml	4.5	9.6	20.7	142	413	86.8	18.0	68.8
500 µg/ml	2.7 ^h	8.8	12.6	314	512	107.6	13.6	122.7 ^g

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

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

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

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

^fVEHICLE CONTROL = 10E WATER; POSITIVE CONTROL = M/S - METHYL METHANESULFONATE

^gMUTAGENIC, EXCEEDS MINIMUM CRITERION OF 84.3 X 10E-6

^hNOT 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/PL. 10ES UNITS)		SUSPENSION GROWTH ^b	TOTAL MUTANT COLONIES	TOTAL VIABLE COLONIES	CLONING EFFICIENCY ^c	RELATIVE GROWTH (%) ^d	MUTANT FREQUENCY (10E-6 UNITS) ^e
	1	2						
S9 ACTIVATION INDUCED ^f								
ANG 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	137	515	85.8	96.4	45.4
ANG VEHICLE CONTROL								
MCA 2 µg/ml	11.1	11.5	14.2	662	435	72.5	54.5	304.4 ^g
MCA 4 µg/ml	9.3	11.3	11.7	787	444	74.0	45.8	354.5 ^g
TEST COMPOUND								
RELATIVE TO VEHICLE CONTROL (%)								
12.5 µg/ml	12.1	15.6	187.8	132	644	111.3	119.1	41.8
25.0 µg/ml	11.6	12.2	88.2	215	622	107.5	86.2	69.1
50.0 µg/ml	6.6	9.9	37.8	399	599	103.6	38.3	133.2 ^g
75.0 µg/ml	4.7	8.9	23.7	754	634	109.6	26.0	237.9 ^g
100 µg/ml	7.7	8.1	35.4	710	415	71.7	25.4	342.2 ^g
200 µg/ml	2.5 ^h	3.4	5.8	432	214	37.0	2.1	403.7 ^g

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

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

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

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

^fVEHICLE CONTROL = 10E WATER; POSITIVE CONTROL = MCA - METHYLOLANTHRENE

^gMUTAGENIC, EXCEEDS MINIMUM CRITERION OF 81.6 X 10E-6

^hNOT 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 N^o: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 μ g/ml streptomycin, 2 mM L-glutamine, and 1% phytohemagglutinin), respectively. Cultures were incubated for 2 days at about $37^{\circ}\text{C} \pm 2^{\circ}\text{C}$ in a humidified incubator, in an atmosphere of about $5\% \pm 1.5\%$ 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 $\mu\text{g}/\text{ml}$ 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 $\mu\text{g}/\text{ml}$, the positive control Mitomycin C (0.05 $\mu\text{g}/\text{ml}$ in the absence of the S9 metabolic activator), the positive control cyclophosphamide (10.0 $\mu\text{g}/\text{ml}$) in the absence of the S9 metabolic activator, the negative control RPMI 1640 or the solvent control (deionized water) at a concentration of 500 $\mu\text{g}/\text{ml}$. 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 $\mu\text{g}/\text{ml}$ of oxycodone HCl (Trial 1: initial trial) or 500, 750, 1000, or 1500 $\mu\text{g}/\text{ml}$ 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 $\mu\text{g}/\text{ml}$ of oxycodone HCl for Trial 1 or 1250, 2500, 3750 or 5000 $\mu\text{g}/\text{ml}$ of oxycodone HCl for Trial 2. The positive controls for the assay were: 50 $\mu\text{g}/\text{ml}$ cyclophosphamide (CPA) in the presence of S9 and 0.200 $\mu\text{g}/\text{ml}$ 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 $\mu\text{g/ml}$. Oxycodone at a concentration of $\mu\text{g/ml}$ 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 $\mu\text{g/ml}$, 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 $\mu\text{g/ml}$ 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 $\mu\text{g/ml}$ oxycodone reduced the mitotic indices by 77% and 54%, respectively.

However, in the presence of metabolic activation, oxycodone (625, 1250, 2500, 3740, and 4990 $\mu\text{g/ml}$) possessed clastogenic activity. A weakly significant ($p < 0.05$) increase in the number of cells with chromosomal aberrations was observed at 2500.0 $\mu\text{g/ml}$. The clastogenic activity observed with 3740 and 4990 $\mu\text{g/ml}$ 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 significant chromosomal aberrations were observed in human lymphocytes exposed to oxycodone HCl for 24 hours or 48 hours at concentrations up to $\mu\text{g/ml}$. 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 $\mu\text{g/ml}$) 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 $\mu\text{g/ml}$ possessed weak clastogenic activity ($p < 0.05$). Significant clastogenic activity was observed following treatment with 3750 and 5000 $\mu\text{g/ml}$. No significant increase in polyploidy or endoreduplicated cells was observed.

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

TREATMENT: CONC ($\mu\text{g/ml}$)	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 $\mu\text{l/ml}$	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

CONTROLS		CELLS SCORED	% INDEX	No. ENDOPOLY-DUPPLICATED CELLS	No. POLY-PLOID CELLS	JUDGEMENT (+/-) ***	NUMBERS AND PERCENTAGES (%) OF CELLS SHOWING STRUCTURAL CHROMOSOMAL ABERRATIONS					JUDGEMENT (+/-) ***			
							GAP %	CHROMATID TYPE		CHROMOSOME TYPE			GT	TOTALS*	
								cb	cc	cb	cc			-	+
NEGATIVE: RPMI 1640 ^b	A 100		2.0	0.0	0.0										
	B 100		2.7	0.0	0.0										
	TOTAL 200														
	%		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 ^c	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	>28.0		
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	
	746 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	1	
		B 100		2.4	0.0	0.0							0	0	
		TOTAL 200								1		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		

cb: chromatid break cc: chromatid exchange cb: chromosome break cc: 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. ^b RPMI 1640 - Culture medium
** Significantly greater in % polyploidy and % endoreduplication than the solvent control, p < 0.01. ^c 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

CONTROLS		CELLS SCORED	% INDEX	No. ENDOPOLY-DUPPLICATED CELLS	No. POLY-PLOID CELLS	JUDGEMENT (+/-) ***	NUMBERS AND PERCENTAGES (%) OF CELLS SHOWING STRUCTURAL CHROMOSOMAL ABERRATIONS					JUDGEMENT (+/-) ***			
							GAP %	CHROMATID TYPE		CHROMOSOME TYPE			GT	TOTALS*	
								cb	cc	cb	cc			-	+
NEGATIVE: RPMI 1640 ^b	A 100		2.6	0.0	0.0										
	B 100		3.2	0.0	0.0										
	TOTAL 200														
	%		3.4	0.0	0.0							0.0	0.0		
SOLVENT: Deionized water 98.0 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		7	9		
		%		2.8	0.0	0.0		2.0	2.5	0.5		3.5	4.5		
	3750 µg/ml	A 100		3.7	0.0	0.0		2	8	1		4	9		
		B 100		3.8	0.0	0.0		4	7	1		8	9		
		TOTAL 200						6	15	1		16	18		
		%		3.8	0.0	0.0		3.0	7.5	0.5		8.0	9.0		
4990 µg/ml	A 100		3.9	0.0	0.0		3	23	4		34	25			
	B 100		3.3	0.0	0.0		7	30	2		39	23			
	TOTAL 200						10	43	6		44	41			
	%		3.6	0.0	0.0		5.0	21.5	3.0		22.0	24.0			

cb: chromatid break cc: chromatid exchange cb: chromosome break cc: 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. ^b RPMI 1640 - Culture medium
** Significantly greater in % polyploidy and % endoreduplication than the solvent control, p < 0.01. ^c 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 #: CY12083 Metabolic Activation: -S9
Compound: Oxycodone hydrochloride Date: 12/06/93

CONTROLS		CELLS SCORED	% MICRO INDEX	No. ENDORE-DUPLICATED CELLS	No. POLY-PLOID CELLS	RIDGE-MENT (++)	NUMBERS AND PERCENTAGES (%) OF CELLS SHOWING STRUCTURAL CHROMOSOMAL ABERRATIONS						RIDGE-MENT (++)			
							CHROMATID TYPE			CHROMOSOME TYPE				GT	TOTALS*	
							GAP	cb	cc	cb	cc	-g			+g	
NEGATIVE: RPM 1640 ^b	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: Distilled water 15.0 µg/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			
	%	3.2	0.0	0.0			0.5					0.5	0.5			
POSITIVE: MMC ^c 0.200 µg/ml	A 25	1.6	0.0	0.0		1	1	3				1	1			
	B 25	1.6	0.0	0.0		0.0	20.0	12.0				32.0	32.0			
	%	1.6	0.0	0.0		0.0	20.0	12.0				32.0	32.0			
TEST ARTICLE	300 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	2.1	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			1	1			0	0			
		B 100	3.0	0.0	0.0			1	1			2	2			
		TOTAL 200						1	1			2	2			
		%	3.3	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				

cb: chromatid break cc: chromatid exchange cb: chromosome break cc: chromosome exchange GT: greater than 10 aberrations
* -g: no. or % of cells with chromosome aberrations; +g: no. or % of cells with chromosome aberrations + an. or % of cells with gaps. ^b RPM 1640 - Culture medium
** Significantly greater in % polyploidy and % endoreduplication than the solvent control, p < 0.01. ^c MMC - Mitomycin C
*** Significantly greater in -g than the solvent control, p < 0.01.

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES
48 Hour Treatment and Harvest

Assay No.: 17261 Trial #: 2 Lab #: CY12083 Metabolic Activation: -S9
Compound: Oxycodone hydrochloride Date: 12/06/93

CONTROLS		CELLS SCORED	% MICRO INDEX	No. ENDORE-DUPLICATED CELLS	No. POLY-PLOID CELLS	RIDGE-MENT (++)	NUMBERS AND PERCENTAGES (%) OF CELLS SHOWING STRUCTURAL CHROMOSOMAL ABERRATIONS						RIDGE-MENT (++)			
							CHROMATID TYPE			CHROMOSOME TYPE				GT	TOTALS*	
							GAP	cb	cc	cb	cc	-g			+g	
NEGATIVE: RPM 1640 ^b	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: Distilled water 15.0 µg/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	300 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	A 200	3.2	0.0	0.0		1	3	1			3	3			
		B 200	3.2	0.0	0.0		0.5	1.0	0.5			1.5	1.5			
		%	3.2	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							0	0			
		B 100	2.3	0.0	0.0							0	0			
		TOTAL 200										0	0			
		%	1.8	0.0	0.0							0.0	0.0			
	1500 µg/ml	A 100	1.5	0.0	0.0							0	0			
B 100		1.9	0.0	0.0							0	0				
TOTAL 200											0	0				
	%	1.7	0.0	0.0							0.0	0.0				

cb: chromatid break cc: chromatid exchange cb: chromosome break cc: chromosome exchange GT: greater than 10 aberrations
* -g: no. or % of cells with chromosome aberrations; +g: no. or % of cells with chromosome aberrations + an. or % of cells with gaps. ^b RPM 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.
**** Only B culture available for counting.

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	% METRIC INDEX	No. ENDORE-DUPLICATED CELLS	No. POLY-PLOID CELLS	JUDGE-MENT (++)	NUMBERS AND PERCENTAGES (%) OF CELLS SHOWING STRUCTURAL CHROMOSOMAL ABERRATIONS						GT	TOTALS*		JUDGE-MENT (+++)	
							GAP	CHROMATID TYPE		CHROMOSOME TYPE		-		%			
								cb	cc	cb	cc						
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 200												0	0		
		%	3.2	0.5	0.0									0.0	0.0		
SOLVENT:	Distilled water 30.0 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 30.0 µg/ml	25															
		%	1.3	0.0	0.0				11	1	5	1	48.0	4.0	12	12	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	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	

cb: chromatid break cc: chromatid exchange cb: chromosome break cc: 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	% METRIC INDEX	No. ENDORE-DUPLICATED CELLS	No. POLY-PLOID CELLS	JUDGE-MENT (++)	NUMBERS AND PERCENTAGES (%) OF CELLS SHOWING STRUCTURAL CHROMOSOMAL ABERRATIONS						GT	TOTALS*		JUDGE-MENT (+++)	
							GAP	CHROMATID TYPE		CHROMOSOME TYPE		-		%			
								cb	cc	cb	cc						
CONTROLS																	
NEGATIVE:	RPMI 1640 ^a	A 100	5.0	0.0	0.0												
		B 100	6.9	0.0	1.0												
		TOTAL 200															
		%	6.0	0.0	0.5										0.0	0.0	
SOLVENT:	Distilled 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	
		%	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	1	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	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						1	2	2		4	4	
		TOTAL 200									1	4	2		8	9	
		%	2.3	0.0	0.5						0.5	2.0	1.0		4.0	4.5	

cb: chromatid break cc: chromatid exchange cb: chromosome break cc: 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 Nº: 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 CO₂ 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) 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 (\pm S.E.) ^a		
		24 hr	48 hr	72 hr
CPA: 80.0 mg/kg	M	0.48 \pm 0.01	NT	NT
	F	0.61 \pm 0.10	NT	NT
Deionized H ₂ O 10 ml/kg	M	0.46 \pm 0.10	0.54 \pm 0.02	0.65 \pm 0.01
	F	0.49 \pm 0.09	0.41 \pm 0.04	0.57 \pm 0.12
Oxycodone: 87.5 (M); 150 (F)	M	0.51 \pm 0.08	0.53 \pm 0.06	0.59 \pm 0.09
	F	0.59 \pm 0.06	0.59 \pm 0.07	0.56 \pm 0.06
Oxycodone: 175 (M); 300 (F)	M	0.51 \pm 0.07	0.50 \pm 0.06	0.62 \pm 0.07
	F	0.46 \pm 0.05	0.54 \pm 0.12	0.59 \pm 0.11
Oxycodone: 350 (M); 600 (F)	M	0.55 \pm 0.07	0.48 \pm 0.06	0.71 \pm 0.15
	F	0.46 \pm 0.07	0.51 \pm 0.11	0.78 \pm 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 F M,F	0.14 ± 0.04 0.08 ± 0.06 0.11 ± 0.03
Oxycodone: 87.5 (M); 150 (F)	M F M,F	0.14 ± 0.04 0.08 ± 0.05 0.11 ± 0.03	0.22 ± 0.09 0.20 ± 0.09 0.21 ± 0.06	0.10 ± 0.04 0.14 ± 0.12 0.12 ± 0.06
Oxycodone: 175 (M); 300 (F)	M F M,F	0.24 ± 0.09 0.06 ± 0.04 0.15 ± 0.06	0.12 ± 0.04 0.02 ± 0.02 0.07 ± 0.03	0.08 ± 0.04 0.08 ± 0.02 0.08 ± 0.02
Oxycodone: 350 (M); 600 (F)	M F M,F	0.18 ± 0.04 0.12 ± 0.04 0.15 ± 0.03	0.14 ± 0.04 0.10 ± 0.06 0.13 ± 0.03	0.08 ± 0.04 0.13 ± 0.03 0.10 ± 0.02
CPA: 80.0	M F M,F	4.16 ± 0.94 ^a 2.16 ± 0.30 ^a 3.16 ± 0.57 ^a	NT	NT

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 $\mu\text{g}/\text{ml}$, and in the in vivo bone micronucleus assay in mice (at plasma levels of up to 48 $\mu\text{g}/\text{ml}$). Mutagenic results occurred in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 $\mu\text{g}/\text{ml}$) at 24 hour but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 $\mu\text{g}/\text{ml}$ or greater with metabolic activation and at 400 $\mu\text{g}/\text{ml}$ 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 $\mu\text{g}/\text{ml}$, and in the in vivo bone micronucleus assay in mice (at plasma levels of up to 48 $\mu\text{g}/\text{ml}$). Mutagenic results occurred in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 $\mu\text{g}/\text{ml}$) and in the mouse lymphoma assay at doses of 50 $\mu\text{g}/\text{ml}$ or greater with metabolic activation and at 400 $\mu\text{g}/\text{ml}$ 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.

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

RD initialed by Dale Conner, PharmD on 7/19/96

FT initialed by Dale Conner, PharmD.

DK 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. 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. 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_{el} 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 emptying 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 respect 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:

Analytical Investigator:

Site:

Site:

Single Dose: Multiple Dose: Washout Period: 7 days

Cross-Over: Parallel: Other Design:

Fasted: 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: <u>Male</u>	Group	N= 24	M= 12	F= 12
Weight	Mean <u>78.03 kg</u>	Range	Group	N=	M=	F=
Age	Mean <u>30.75 yr</u>	Range	Group	N=	M=	F=
		Subject Type: <u>Female</u>	Group	N=	M=	F=
Weight	Mean <u>66.24 kg</u>	Range	Group	N=	M=	F=
Age	Mean <u>30.92 yr</u>	Range	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(%)*	90% CI	
			CR Oxy 80mg / CR Oxy 2x40mg	Lower	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.

Suresh 1/8/97

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

FT initialed by Dale Conner, PharmD.

DMC 1/8/97

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

20-553

DEC 3 1996

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.

APC 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 (AUC₀₋₃₆ and AUC_{0-∞}), $t_{1/2abs}$, $t_{1/2elim}$, 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 $t_{1/2}(elim)$, t_{max} , 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 $t_{1/2}(abs)$ 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,∞} (ng-hr/mL)	113.42	111.93	101.22	96.33-106.37
C _{max} (ng/mL)	9.18	29.00	31.53	27.67-35.92
t _{1/2} (abs) (hrs)	0.94	0.99	94.34	72.24-121.03
t _{1/2} (elim) (hrs)	6.44	1.97	326.34	299.54-350.78
T _{max} (hrs)	2.33	0.83	280.95	235.57-325.76
Peak width @ 50% C _{max} (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,∞} (ng-hr/mL)	113.42	109.26	104.29	99.24-109.59
C _{max} (ng/mL)	9.18	25.99	35.14	30.84-40.05
t _{1/2} (abs) (hrs)	0.94	0.48	193.71	144.66-242.38
t _{1/2} (elim) (hrs)	6.44	2.09	308.11	285.48-334.31
T _{max} (hrs)	2.33	0.76	305.71	262.13-362.50
Peak width @ 50% C _{max} (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,∞} (ng-hr/ml)	111.93	109.26	103.03	98.04-108.26
C _{max} (ng/ml)	29.00	25.99	111.48	97.83-127.02
t _{1/2} (abs) (hrs)	0.99	0.48	205.35	151.39-249.11
t _{1/2} (elim) (hrs)	1.97	2.09	94.41	70.89-119.72
T _{max} (hrs)	0.83	0.76	108.62	61.09-161.46
Peak width @ 50% C _{max} (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) × 100%

b Ratio (%) = (IR mean/IR Solu mean) × 100%

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