CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-011

PHARMACOLOGY REVIEW(S)

REVIEW & EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

KEY WORDS: Roxicodone Tablets (IR), Oxycodone, Reproductive Studies Final Report

REVIEWER: **BeLinda A. Hayes, Ph.D.**
DIVISION: Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD #: 170
REVIEW COMPLETION DATE: July 18, 2000

NDA NUMBER: 21-011
SERIAL N°/DATE/TYPE OF SUBMISSION: Amendment No. 12.01/June 29, 2000/ Final reports
INFORMATION TO SPONSOR: YES (x) N0 ( )

SPONSOR (OR AGENT):

Roxane Laboratories, Inc.
P.O. Box 1653
Columbus, OH 43216-6532

MANUFACTURER FOR DRUG SUBSTANCE: [redacted]

DRUG:

GENERIC NAME: Oxycodone HCl
TRADE NAME: Roxicodone Tablets [redacted]
CHEMICAL NAME: Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-17-methyl hydrochloride; 4,5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride

RELEVANT INDs/NDAs/DMFs: NDA 20-932; IND 46, 618

DRUG CLASS: Opioid Narcotics
INDICATION: Management of moderate to severe pain where use of an opioid analgesic is appropriate
CLINICAL FORMULATION (AND COMPONENTS): Tablet (15 and 30 mg);
Inactive Ingredients Include: microcrystalline cellulose; sodium starch glycolate; corn starch; lactose; stearic acid; D&C Yellow No. 10 (5 mg tablet); and FD&C Blue No. 2 (15 mg and 30 mg tablets)
ROUTE OF ADMINISTRATION: Oral

Disclaimer: No material was taken directly from the sponsor's submission.

INTRODUCTION.

NDA 21-011/Amendment 7.01, for Roxicodone IR (Oxycodone HCL Tablets USP Immediate Release 15 and 30 mg), was initially submitted to the agency on February 28, 2000 for the treatment of moderate to severe pain in patients for whom oral opiates are indicated for more than a few days. Within that submission, four reproductive toxicity studies were submitted for review:

1.	Study Report # XIRT0199:	Oral Gavage Dosage-Range Developmental Toxicity Study Of Oxycodone In Rats. Final Pilot Report
2.	Study Report # XIRT0299:	Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of Oxycodone In Rabbits. Final Pilot Report
3.	Study Report # XIRT0399:	Oral (gavage) Developmental Toxicity Study Of Oxycodone In Rats. Final Draft Report
4.	Study Report # XIRT0499:	Oral (Stomach Tube) Developmental Toxicity Study of Oxycodone In Rabbits. Final Draft Report

The reports for the dose-range finding studies in rats (Study Report XIRT0199) and rabbits (Study Report XIRT0299) were the final audited reports. However, the definitive developmental toxicity studies in rats (Study Report XIRT0399) and rabbits (Study Report XIRT0499) were draft reports. In respond to the agency request for the final Quality Assurance reports of the definitive reproductive studies in rats and rabbits, the sponsor has submitted Amendment 12.01.

Studies Reviewed Within This Submission.

•	Study Report # XIRT0399:	Oral (gavage) Developmental Toxicity Study Of Oxycodone In Rats.
•	Study Report # XIRT0499:	Oral (Stomach Tube) Developmental Toxicity Study of Oxycodone In Rabbits.

Studies Not Reviewed Within This Submission. None

REPRODUCTIVE TOXICOLOGY

The draft reports of the following studies were initially reviewed. Review of the final audited reports of these studies did not note any changes in the protocol or the data. Hence, review of this submission has not change the reviewer initial evaluation of the data in Study Reports XIRT0399 and XIRT0499 as reported in the Pharmacology/Toxicology Review dated June 12, 2000.

Sponsor ID#:	XIRT0399
Title:	Oral (Gavage) Developmental Toxicity Study Of Oxycodone In Rats.
Amendment #, Vol. #, and page #:	Amendment # 12.01, Volume 1 pages 1 to 256
Conducting Laboratory:	
Date of Study Initiation:	November 9, 1999
GLP Compliance:	Yes (X) No ( )
QA Report:	Yes (X) No ( )

Sponsor ID#:	XIRT0499
Title:	Oral (Stomach Tube) Developmental Toxicity Study Of Oxycodone In Rabbits.
Amendment #, Vol. #, and page #:	Amendment # 12.01, Volume 1, pages 257 to 518
Conducting Laboratory:	
Date of Study Initiation:	November 12, 1999
GLP Compliance:	**Yes** (X) **No** ( )
QA Report:	**Yes** (X) **No** ( )

OVERALL SUMMARY AND EVALUATION.

The current submission is a response to the agency request for the final Quality Assurance reports for Studies XIRT0399 and XIRT0499. No changes in the protocol, raw data or conclusions were noted after review of these final reports. Hence, there are no changes to the initial pharmacology/toxicology review of Study Reports XIRT0399 and XIRT0499.
Refer to the pharmacology/toxicology review of Amendment 7.01 dated June 12, 2000 for details.

CONCLUSION AND RECOMMENDATION.

The Conclusions and Recommendations were not changed following review of these two audited final reports. The NDA is approvable, with minor labeling revisions as described in the section title Labeling Review.

Refer to the pharmacology/toxicology review of Amendment 7.01 dated June 12, 2000 for labeling revisions.

[/S/]
BeLinda A. Hayes, Ph.D.
July 19, 2000
Date

Concurred by Team Leader:

[/S/]
Dou (Lucy) Jean, Ph.D.
July 19, 2000
Date

CC: NDA# 21-011/Amendment 12.01
HFD-170/Div File
HFD-170/BHayes
HFD-170/JMilstein
F/T by: BHayes/07-18-00

APPEARS THIS WAY
ON ORIGINAL

REVIEW & EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

KEY WORDS: Roxicodone Tablets (IR), Oxycodone, Reproductive Studies,

REVIEWER: **BeLinda A. Hayes, Ph.D.**
DIVISION: Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD #: 170
REVIEW COMPLETION DATE: June 12, 2000

NDA NUMBER: 21-011
SERIAL N°/DATE/TYPE OF SUBMISSION: Amendment No. 7.0/February 28, 2000/response to approvable letter
INFORMATION TO SPONSOR: YES (X) N0 ( )

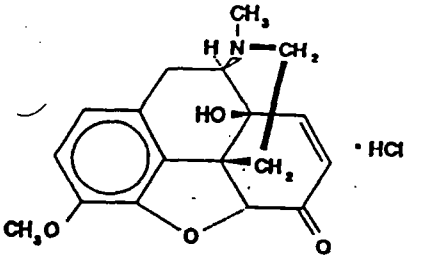
SPONSOR (OR AGENT):

Roxane Laboratories, Inc.
P.O. Box 1653
Columbus, OH 43216-6532

MANUFACTURER FOR DRUG SUBSTANCE: [———————]

DRUG:

GENERIC NAME: Oxycodone HCl
TRADE NAME: Roxicodone
CHEMICAL NAME: Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-17-methyl hydrochloride;
4,5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride
CAS REGISTRYN°: CAS 124-90-3
MOLECULAR FORMULA/MOLECULAR WEIGHT: $C_{18}H_{21}NO_4 \cdot HCl/351.83$
STRUCTURE:



RELEVANT INDs/NDAs/DMFs: NDA 20-932; IND 46, 618
DRUG CLASS: Opioid Narcotics
INDICATION: Management of moderate to severe pain where use of an opioid analgesic is appropriate
CLINICAL FORMULATION (AND COMPONENTS): Tablet (15 and 30 mg);
Inactive Ingredients Include: microcrystalline cellulose; sodium starch glycolate; corn starch; lactose; stearic acid; D&C Yellow No. 10 (5 mg tablet); and FD&C Blue No. 2 (15 mg and 30 mg tablets)
ROUTE OF ADMINISTRATION: Oral

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PROPOSED CLINICAL USE. Roxicodone ™ immediate release tablets are indicated for the management of moderate to severe pain where the use of an opioid analgesic is appropriate. The dosage of Roxicodone will be individualized based on the severity of the patients pain, the patient response and the patient body weight. It is recommended that the appropriate dose of Roxicodone be administered every 4 - 6 hours.

PREVIOUS CLINICAL EXPERIENCE. Oxycodone hydrochloride is an opioid analgesic indicated for the treatment of pain. Oxycodone has been available clinically in many forms since the 1920's and has proven to be an effective analgesic agent for the management of pain associated with cancer, lower back problems, and osteoarthritis.

DISCLAIMER. Some material from the sponsor has been reproduced in this review.

INTRODUCTION/DRUG HISTORY.

Oxycodone hydrochloride, 4, 5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride, a semisynthetic derivative of thebaine has been used clinically as a narcotic analgesic in many forms since the 1920's for the treatment of moderate to moderately severe pain. Oxycodone is available in the United States, Austria, Canada, Columbia, Czechoslovakia, Finland, Germany, Hungary, Japan, New Zealand and Switzerland in oral formulations as the hydrochloride and terephthalate sulfate either alone or in combination with aspirin or acetaminophen. In Finland, it is commonly used intramuscularly for premedication before anesthesia and severe postoperative pain. As an analgesic, oxycodone hydrochloride is approximately equipotent with morphine in the dose range of 5-10 mg (every 6 hours).

Roxane has marketed three formulations of oxycodone in the United States since the 1980's. The three Roxane's formulations currently available are: 5-mg Roxicodone™ tablets, 5 mg/5 mL Roxicodone™ oral solution and Roxicodone Intensol™ a 20 mg/mL concentrated oral solution. The sponsor has developed two new dosage strength (15-mg and 30 mg tablets) of an immediate-release oxycodone hydrochloride tablets for the conveniences of patients requiring high total daily oral doses of oxycodone, thus facilitating the accurate titration of oxycodone doses.

NDA 21-011, for Roxicodone IR (Oxycodone HCl Tablets USP Immediate Release 15 and 30 mg) was initially submitted to the agency on September 30, 1998 for the treatment of moderate to severe pain in patients for whom oral opiates are indicated for more than a few days. On September 23, 1999 an approvable letter was issued to the sponsor. A meeting was held on December 15, 1999 and a telconference on February 11, 2000 between the Agency and the sponsor was held to discuss the action plan to respond to the Agency's approvable letter. Amendment 7.01 is the sponsor complete response to the Approvable letter.

Actions items pertinent to nonclinical issues:

- The following agreements were reached between the Agency and the sponsor during the December 15, 1999 meeting and February 11, 2000 teleconference:
  - Segment II Reproductive Studies in two species (i.e., rats and rabbits) will be required prior to approval.
  - The standard battery of genotoxicity testing will be required. FDA agrees that the mutagenicity studies can be conducted as a Phase 4 commitment, although FDA would like to see them earlier.

- The carcinogenicity studies requirement can be linked to the SR application, and that it could be a Phase 4 commitment, but advised them to start the studies as soon as possible.

Studies Reviewed Within This Submission.

- Study Report # XIRT0199: Oral Gavage Dosage-Range Developmental Toxicity Study Of Oxycodone In Rats. Final Pilot Report
- Study Report # XIRT0299: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of Oxycodone In Rabbits. Final Pilot Report
- Study Report # XIRT0399: Oral (gavage) Developmental Toxicity Study Of Oxycodone In Rats. Final Draft Report
- Study Report # XIRT0499: Oral (Stomach Tube) Developmental Toxicity Study of Oxycodone In Rabbits. Final Draft Report

Studies Not Reviewed Within This Submission. None

PHARMACOLOGY.

Oxycodone hydrochloride, a semisynthetic derivative of thebaine, is an opioid agonist that is pharmacologically similar to morphine. Preclinical studies have shown that oxycodone is a weak mμ opioid agonist with potent analgesic activity in a variety of preclinical antinociceptive assays. Oxycodone also has the typical opioid-like CNS depressant activity.

The analgesic activity of oxycodone has been evaluated in rats (Carter, 1991; Pöyhiä and Kalso, 1992; Leow and Smith, 1994) and mice (Weinstein and Gaylord, 1979; Swedberg, 1994). The analgesic activity of oxycodone was compared to that of morphine and codeine in the rat 55 ° hot plate assay using hind paw lick and hind paw-lick-or jump as the endpoint (Carter, 1991). Oxycodone's analgesic activity was qualitatively similar to morphine and codeine regardless of the endpoint measured. Oxycodone (p.o.) was more potent than codeine (p.o.) but less potent than morphine (i.p., s.c.).

The antinociceptive activity of oxycodone hydrochloride was compared to that of morphine hydrochloride in the rat tail flick and hot plate nociceptive test following intraperitoneal, intrathecal and subcutaneous administrations (Pöyhiä and Kalso, 1992). Pöyhiä and Kalso (1992) reported that the strength of oxycodone's analgesic activity is route-dependent. Oxycodone was more potent than morphine in both thermal nociceptive tests following systemic administration; oxycodone was 2 and 4 times more potent than morphine following subcutaneous and intraperitoneal administration, respectively. However, weak antinociceptive effects were observed following intrathecally administered oxycodone; it was approximately 14 times less potent than morphine. Plummer *et al.* (1990) and Pöyhiä *et al.* (1989) have also reported similar findings in rats using the hot plate and tail flick assays.

Pöyhiä and Kalso (1992) also compared the onset and duration of oxycodone's analgesic activity to that of morphine following intraperitoneal, intrathecal and subcutaneous administrations. In the rat tail flick and hot plate nociceptive assays, the antinociceptive effects of oxycodone (2.5-5.0 mg/kg) had a significant ($P<0.05$) faster onset (mean = 15 min) in comparison to morphine (5-10 mg/kg) which had a mean onset of 30 minutes following both subcutaneous and

intraperitoneal administrations. In contrast to the onset of antinociceptive effects observed with the lower doses, the highest dose of oxycodone (10 mg/kg) and morphine (20 mg/kg) had similar onset of analgesic activity following both routes of administration. The duration of action was similar for both drugs following subcutaneous administration; whereas, intraperitoneal oxycodone had a significantly ($P<0.05$) longer duration of action in comparison to intraperitoneal morphine. Intrathecal oxycodone had a shorter onset and duration of action in comparison to morphine. Plummer *et al.* (1990) postulated that the weak antinociceptive effects, fast onset and short duration of action, observed following intrathecal administration are due to its low polarity in comparison to the high polarity of morphine.

The antinociceptive activity of oxycodone was compared to morphine and its metabolite noroxycodone in Sprague Dawley rats following intracerebroventricular (ICV) administration (Leow and Smith, 1994). Oxycodone and its metabolite noroxycodone were effective analgesics following ICV administration. Relative to morphine, oxycodone and noroxycodone were 2.3 and 5.9 times less potent than morphine, respectively. Oxycodone's analgesic activity had a more rapid onset than morphine or noroxycodone. Oxycodone's maximum antinociception occurred at 9.3 mins ($p\leq0.05$) post-injection; whereas morphine's and noroxycodone's antinociceptive effects occurred at 31.8 and 34.6 minutes post-dosing, respectively. Consistent with morphine-induced analgesia, the analgesic effects of oxycodone and noroxycodone are mediated by opioid receptors. Naloxone pre-administration (55 nmol, icv, 15 min pre) abolished the antinociceptive effects of oxycodone (227 nmol) and reduced the antinociceptive effects of both noroxycodone (332 nmol) and morphine (93 nmol).

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

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

Oxycodone produces opioid-type CNS depression (i.e., loss of righting, placing and corneal reflexes and catalepsy) in rats. The CNS depressant effects of oxycodone was compared to those of morphine following subcutaneous, intraperitoneal and intrathecal administration (Pöyhiä and Kalso, 1992). Consistent with its analgesic properties, its CNS depressant effects are route-dependent. Oxycodone (2.5-10.0 mg/kg) was more potent than morphine in eliciting CNS depressant effects following both subcutaneous and intraperitoneal administrations. Subcutaneously and intraperitoneally administered oxycodone caused a dose-dependent loss in all reflexes measured and induced catalepsy; whereas subcutaneously administered morphine (10 and 20 mg/kg) only affected the righting and corneal reflexes and induced catalepsy. Only the righting reflex loss and morphine-induced catalepsy were observed following the intraperitoneal administration of 20 mg/kg morphine. Neither oxycodone (12.5 and 100 μg) nor morphine (6.25 and 50 μg) elicited any CNS depressant activity following intrathecal administration.

The binding profile of oxycodone has been evaluated in rats brain (Pert and Synder, 1973; Chen *et al.*, 1991). Using ^{3}H-naloxone or ^{3}H-DAMGO as the ligand for the mμ opioid receptors both group of investigators demonstrated that oxycodone binds to the mμ opioid receptors with weak affinity. These results were surprising considering that oxycodone was a potent analgesic agent in rats and has an analgesic potency approximately 0.7 fold that of morphine in humans (Ross, *et al.*, 1993). These findings suggest that oxycodone's analgesic efficacy may be due to the formation of an active metabolite or metabolites. Beaver (1977), Kalso (1990) and Inturrisi (1990) have suggested that part of the analgesic effects of oxycodone can be attributes to active metabolites. In a clinical study comparing the pharmacokinetic profile of oxycodone after intramuscular and oral administrations, Pöyhiä (1992) reported that noroxycodone and oxymorphone are two major metabolites of oxycodone.

REPRODUCTIVE TOXICOLOGY

Sponsor ID#: XIRTO199
Title: Oral (Gavage) Dosage-Range Developmental Toxicity Of Oxycodone In Rats.
Amendment #, Vol. #, and page #: Amendment # 7, Volume 3, pages 5 to 99
Conducting Laboratory: [redacted]
Date of Study Initiation: September 29, 1999
GLP Compliance: Yes (X) No ( )
QA Report: Yes (X) No ( )

METHODS:

Species: Sprague-Dawley Rat (Crl:CD®BR VAF/Plus®)
#/sex/group: 8/mated females/group
Age: At least 60 days of age upon receipt
Weight: At day 0 of the study, the mean body weight was approx. 235 g.
Study Design: Rats will be dosed with the test article or vehicle once daily on days 7 through 17 of presumed gestation.
Doses:

DOSE GROUP	DOSAGE (mg/kg/day)	CONCENTRATION (mg/mL)	VOLUME	BATCH N°
I	0 (Diluent)	0	17.5	B-1418-001P-A
II	3	1	3	B-1418-001P-B
III	15	1	15	B-1418-001P-B
IV	75	20	3.75	B-1418-001P-C
V	350	20	17.5	B-1418-001P-C

Route, Form, and Volume: Oral, Solution, See above table

Drug, Lot #: Oxycodone Hcl, See above table

Formulation/Vehicle: Solution/R.O Deionized Water

STUDY PARAMETERS:

Viability: Twice Daily
Clinical Signs: **Dosing Period:** Daily before and 60 ± 10 min post-dosing; **Postdosage Period:** Daily
Body Weights: **Acclimation Period:** Weekly; **Predosage Period:** Day 0 of presumed gestation; **Dosage and Postdosage Periods:** Daily
Food Consumption: **Predosage Period:** Day 0 of presumed gestation, **Dosage Period:** Days 7, 10, 12, and 15; **Postdosage Period:** Days 18 and 21
At Necropsy: All surviving rats were sacrificed on gestation day 21 and examined with respect to: number of corpora lutea, number and distribution of implantation sites and uterine contents.
Examination of Fetuses: Fetuses were weighed, sexed, and examined for gross external alterations

Gross Pathology: Thoracic, abdominal and pelvic viscera were examined

RESULTS.

Clinical Signs In Dosed Animals. Oxycodone-induced clinical signs were observed in the dams. The clinical signs that appeared to be treatment-related are presented in Table 1. The number of subjects presenting these clinical signs were dose-dependent. With the exception of excess salivation in one dam, no treatment-related clinical signs were observed in the low dose group (3.0 mg/kg/day). In the high dose group, all the subjects displayed muscle rigidity, loss of righting reflex, and decreased motor activity.

Table 1. Clinical Signs observed in the dams following oxycodone treatment during day 7 thru 17 of gestation.

CLINICAL SIGN	Nº SUBJECTS WITH SIGN/TOTAL Nº SUBJECTS				
	DOSE (mg/kg/day)				
	0	3	15	75	150
Muscle Rigidity	0/8	0/8	1/8	8/8	8/8
Impaired Righting Reflex	0/8	0/8	0/8	8/8	8/8
↓ Motor Activity	0/8	0/8	0/8	4/8	8/8
Excess Salivation	0/8	1/8	0/8	1/8	2/8
Bradypnea	0/8	0/8	0/8	1/8	1/8
Lacrimation	0/8	0/8	2/8	8/8	7/8
Chromorhinorrhea	0/8	0/8	0/8	1/8	5/8
Chromodacyorrhea	0/8	0/8	0/8	2/8	4/8
Death	0/8	0/8	0/8	0/8	3/8

Mortality. Deaths occurred in three rats in the high dose group during the first two days of dosing. These deaths were associated with the initial high dosage level being too high; the original high dosage level was 350 mg/kg/day. After the death of one rat, the dosage level was lowered to 250 mg/kg/day. This dose of oxycodone resulted in the death of two rats. Subsequently the dosage level was reduced to 150 mg/kg/day. Summary of these deaths are presented in Table 2. As indicated in Table 2, the following overt signs of toxicity were observed in all rats prior to their death: decreased motor activity, loss of righting reflex, muscle rigidity throughout the entire body, and lacrimation. Necropsy revealed that all 3 females were pregnant and the conceptuses appeared normal for their developmental age.

Table 2. Summary Of Oxycodone-Related Deaths.

RAT No.	DOSE (mg/kg/day)	DAY OF DEATH	OBSERVED CLINICAL SIGNS PRIOR TO DEATH	NECROPSY RESULTS
12383	350	Prior to dosing on Day 8	Day 7: Loss of righting reflex; ↓ motor activity; muscle rigidity throughout entire body; lacrimation; bradypnea	**Tissue:** Normal **Pregnant:** Yes **Conceptuses:** 13, Normal
12384	250	Prior to dosing on Day 8	Day 7: Loss of righting reflex; ↓ motor activity; muscle rigidity throughout the entire body; lacrimation; excess salivation	**Stomach:** Red areas (0.1 cm in diameter) on the mucosal surface **Pregnant:** Yes **Conceptuses:** 14, Normal;
12387	250	6 hrs 56 mins after dosing on Day 7	Day 7: Loss of righting reflex; ↓ motor activity; muscle rigidity throughout the entire body; lacrimation	**Stomach:** Numerous red areas (1.0 cm in diameter) on the glandular surface **Pregnant:** Yes **Conceptuses:** 14, Normal

Body Weight. As depicted in Figure 1 (copied from the sponsor's submission) the body weight of the oxycodone-treated rats were lower than the controls during the dosage (days 7 through 17) and postdosage (days 18 through 21) periods. The reduced body weight gain became evident on days 11, 10, 9, and 8 for the 3, 15, 75 and 150 mg/kg/day treatment groups, respectively, and remained reduced for the remainder of the study. This observed reduced body weight gains were dose-dependent. The body weight gain observed in the groups was 15%, 33.4%, 56.5%, and 65.4% less than the control in the 3.0, 15.0, 75.0 and 150.0 mg/kg/day groups, respectively.

Food Consumption. Poor appetite was observed in the oxycodone-treated rats. In comparison to the control rats, the oxycodone-treated rats, absolute (g/day) and relative (g/kg/day) food consumption were reduced during the dosing period. Food consumption was also reduced during the postdosing period, with the exception of the relative food consumption of the high dose group.

Embryo-Fetal Development. No treatment-related effects on the number of corpora lutea, and implantation sites were observed (Table 3). The number of corpora lutea and implantation sites were comparable among the five treatment groups.

Treatment-related effects on the litter size, number of live fetuses, number of dams with viable fetuses, number of total and early resorptions, the percent resorbed conceptuses and fetal body weight were noted. As depicted in Table 4, these parameters in the 3.0, 15.0, and 75.0 mg/kg/day treated dams were comparable to those in the control dams. However, the litter size, the number of live fetuses and the number of dams with viable fetuses were reduced in the high dose (150 mg/kg/day)group. Also, in the high dose group, the number of total and early resorptions and the percentage of resorbed conceptuses were increased. The fetal body weight were reduced at all doses of oxycodone. Relative to the control, the mean fetal body weight (g) per litter was 4.5%, 9.5%, 7.6%, and 6.4% less for the 3.0, 15.0, 75.0, and 150.0 mg/kg/day groups.

Figure 1. Maternal Body Weight (copied from the sponsor submission.).

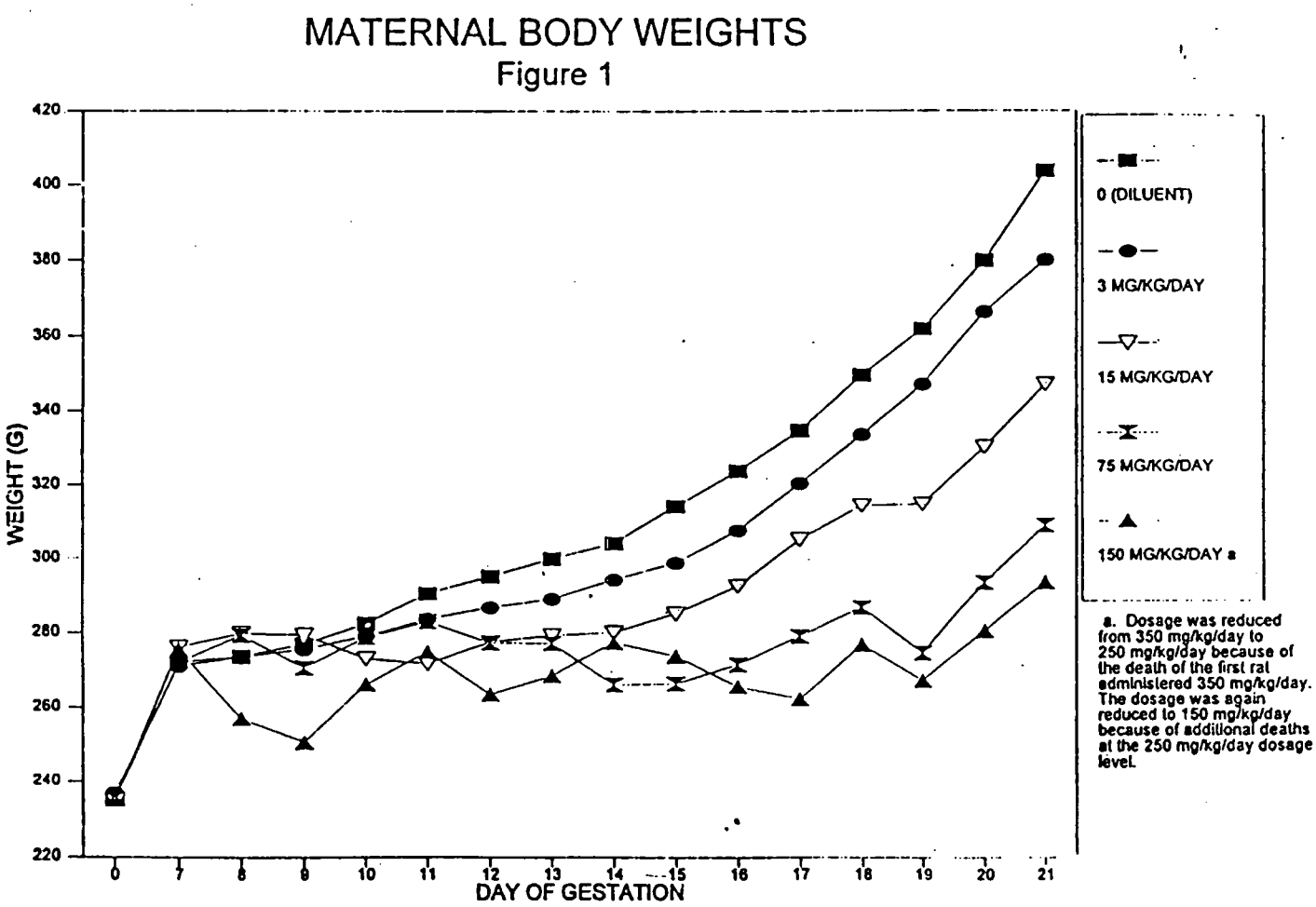

Table 3. **Effects oxycodone on the mean number of corpora lutea, implantation site, percent of rats pregnant and placenta appearance.**

DOSE (mg/kg/day)	# PREGNANT/TOTAL (%)	MEAN (± S.D.)		# TESTED (%)
		CORPORA LUTEA	IMPLANTATION SITE	NORMAL PLACENTAE
0.0	8/8 (100.0 %)	15.4 (1.2)	13.8 (1.0)	8 (100.0)
3.0	8/8 (100.0 %)	17.8 (2.5)	14.8 (2.1)	8 (100.0)
15.0	8/8 (100.0 %)	17.8 (2.6)	14.9 (1.6)	8 (100.0)
75.0	6/8 (75.0 %)	14.5 (2.9)	13.5 (1.9)	6 (100.0)
150.0	6/8 (75.0 %)	16.3 (5.1)	16.3 (5.1)	2 (100.0)

Table 4. **Litter, and resorption data.**

DOSE (mg/kg/day)	LITTER DATA : MEAN (± S.D.)			RESORPTION DATA: MEAN (± S.D.)		% DAMS WITH (#/TOTAL EXAMINED)		
	SIZE	LIVE FETUSES	DEAD FETUSES	EARLY	LATE	ANY RESORPTIONS	ALL CONCEPTUSES RESORBED	VIABLE FETUSES
0.0	13.2 (1.4)	13.2 (1.4)	0	0.5 (0.5)	0	50.0 (4/8)	0.0 (0/8)	100.0 (8/8)
3.0	13.9 (2.9)	13.9 (2.9)	0	0.9 (1.2)	0	37.5 (3/8)	0 (0/8)	100.0 (8/8)
15.0	14.1 (2.4)	14.1 (2.4)	0	0.8 (1.4)	0	37.5 (3/8)	0 (0/8)	100.0 (8/8)
75.0	12.8 (2.6)	12.8 (2.6)	0	0.7 (1.2)	0	33.3 (2/6)	0 (0/6)	100.0 (6/6)
150.0	7.3 (7.0)	7.3 (7.0)	0	6.7 (5.8)	0	66.7 (2/3)	33.3 (1/3)	66.7 (2/3)

Gross Examination of fetus. No treatment-related gross abnormalities were reported. It was reported that one fetus in the 150 mg/kg/day group had a thread-like tail.

CONCLUSION.

In this dose-range finding study, oxycodone (0, 3, 15, 75, and 150 mg/kg/day) was administered orally to pregnant rats from days 7 to 17 of pregnancy. The effects of orally administered oxycodone on both dams and fetuses were evaluated.

The key findings of this study were:

1. **Maternal NOAEL** could not be determined in this study since reduction in body weight and food consumption were observed in the dams in the lowest dose of 3.0 mg/kg/day. **The NOAEL was less than 3.0 mg/kg/day.**

2. Oral administration of oxycodone to pregnant female rats was tolerated up to 150 mg/kg/day without deaths. Deaths were observed at 250 and 350 mg/kg/day.

3. The litter size, number of live fetuses, and the number of dams with viable fetuses were reduced in the high dose group (150 mg/kg/day group).

4. The number of total and early resorptions and the percent resorbed conceptuses per litter were increased in the high dose group.

5. A decrease in fetal body weight was observed at all oxycodone treatment groups. This decrease fetal body weight is probably related to the reduced body weight and food consumption observed in the female rats in all treatment groups.

6. No treatment-related gross abnormalities in dams and fetuses..

7. **Developmental NOEL** could not be determined since the fetal body weight was decreased relative to the control in all oxycodone treatment groups. Relative to the control, the mean fetal body weight (g) per litter was 4.5%, 9.5%, 7.6%, and 6.4% less for the 3.0, 15.0, 75.0, and 150.0 mg/kg/day groups. **The NOEL was less than 3.0 mg/kg/day.**

Based on these results, the sponsor stated that in the definitive developmental toxicity study in rats that oxycodone would be evaluated at 0, 3, and 15 mg/kg/day and a dose lower than 3.0 mg/kg. The reviewer feels that these doses will produce no effects to some measurable toxicity in the female rats along with minimal developmental toxicity; this is acceptable.

Sponsor ID#: XIRTO399
Title: Oral (Gavage) Developmental Toxicity Study Of Oxycodone In Rats.
Amendment #, Vol. #, and page #: Amendment # 7, Volume 4, pages 1 to 261
Conducting Laboratory:
Date of Study Initiation: November 9, 1999
GLP Compliance: Yes (X) No ( )
QA Report: **It was stated that the study underwent Quality Assurance Audit; the report was not signed.**

METHODS:

Species: Sprague-Dawley Rat (Crl:CD®(SD)IGSBR VAF/Plus®)
#/sex/group: 25/mated females/group
Age: Approximately 66 days of age upon receipt
Weight: At day 0 of the study, the mean body weight ranged between 200 g to 225 g at receipt
Study Design: Rats were dosed with the test article or vehicle once daily on days 7 through 17 of presumed gestation. All surviving rats were sacrificed on Day 21.

Doses:

DOSE GROUP	DOSAGE (mg/kg/day)	CONCENTRATION (mg/mL)	VOLUME (mL/kg)
I	0 (Diluent)	0	4.0
II	1.0	1.0	1.0
III	4.0	1.0	4.0
IV	16.0	5.0	3.2

Route, Form, and Volume: Oral (gavage), Solution, See above table

Drug, Lot #: Oxycodone HCl, Lot No. 991321A

Formulation/Vehicle: Solution/Reverse Osmosis Membrane Processed Deionized Water

STUDY PARAMETERS:

Viability: Twice Daily
Clinical Signs: **Dosing Period:** Daily, before dosing, 60 ± 10 min and 3 hours ± 10 min post-dosing and at the end of the workday; **Postdosage Period:** Daily
Mortalities: **Dosing Period:** Daily, before dosing, 60 ± 10 min and 3 hours ± 10 min post-dosing and at the end of the workday; **Postdosage Period:** Daily
Abortions & Premature Deliveries: **Dosing Period:** Daily, before, 60 ± 10 min and 3 hours ± 10 min post-dosing and at the end of the workday; **Postdosage Period:** Daily
Body Weights: **Acclimation Period:** Weekly; **Predosage Period:** Day 0 of presumed gestation; **Dosage and Postdosage Periods:** Daily
Food Consumption: **Predosage Period:** Day 0 of presumed gestation, **Dosage Period:** Days 7, 10, 12, and 15; **Postdosage Period:** Days 18 and 21

STUDY PARAMETERS (CONT.):

At Necropsy: All surviving rats were sacrificed by carbon dioxide asphyxiation on gestation day 21 and examined with respect to: number of corpora lutea, sign of pregnancy, number and distribution of implantation sites, early and late resorptions, live and dead fetuses.
Examination of Fetuses: Fetuses were weighed, sexed, and examined for gross external alterations. Approx. half of the fetuses in each litter were examined for soft tissue alteration. The remaining fetuses were examined for skeletal alterations.
Gross Pathology: Thoracic, abdominal and pelvic viscera were examined

RESULTS.

Clinical Signs In Dosed Animals. Oxycodone-induced clinical signs were observed in the dams (Table 1). The following clinical signs appeared to be treatment-related: repetitive chewing, decreased motor activity, soft or liquid feces, bradypnea, and lacrimation. The incidence of repetitive chewing in the mid- and high-dose group was statistically significant ($p \leq 0.05$ or $p \leq 0.01$). The incidences of soft or liquid feces, decreased motor activity, lacrimation, and bradypnea observed in the high dose group were statistically significant ($p \leq 0.01$)

Table 1. Clinical Signs observed in the dams following oxycodone treatment during day 7 thru 17 of gestation.

CLINICAL SIGN	Nº SUBJECTS WITH SIGN/TOTAL Nº SUBJECTS			
	DOSE (mg/kg/day)			
	0	1.0	4.0	16.0
Repetitive Chewing	0/25	0/25	14/25	22/25
Localized Alopecia	1/25	2/25	4/25	4/25
Generalized Alopecia	0/25	0/25	1/25	0/25
↓ Motor Activity	0/25	0/25	0/25	13/25
Soft or Liquid Feces	0/25	1/25	1/25	13/25
Bradypnea	0/25	0/25	0/25	8/25
Lacrimation	0/25	0/25	0/25	6/25
Chromodacyorrhea	0/25	0/25	1/25	0/25
Death	0/25	0/25	0/25	0/25

Mortality. No treatment-related deaths occurred.

Body Weight. Treatment-related effects on body weight gain were observed. During the dosing period (days 7-17), the body weight gain observed in the low-, mid-, and high-dose groups was approximately 8.6, 27.3, and 40.6% less than that of the control group (Table 2). These reductions were statistically significant ($p \leq 0.01$ or $p \leq 0.05$) for the mid- and high-dose groups. During the post-dosing period (days 18 to 21), both the low- and mid-dose groups mean body weight gain was approximately 9.2% and 8.5% higher than that of the control group This rebound effect did not occur in the high-dose group. The mean body weight gain in the high-dose group remained significantly reduced during the post-dosing period.

Food Consumption. Treatment-related effects on food consumption were observed (Table 3). Both absolute (g/day) and relative (g/kg/day) food consumptions were significantly ($p \leq 0.01$) reduced in the mid- and high-dose groups throughout the dosing period. Absolute food intake, relative to the control group, was reduced by 15.7% and 27.6% in the mid- and high-dose groups, respectively. During the post-dosing period, the absolute food consumption in the high dose group remained significantly reduced (28.4%) relative to the control group. Reduced food intake (absolute) was evidence throughout the entire gestation period; food intake was 13.7% and 27.7% lower than the control in the mid- and high-dose groups, respectively.

Premature Delivery. One dam (#13692) in the high dose group prematurely delivered on day 21 of gestation. This dam displayed the following overt signs of toxicity prior to this premature delivery, swollen right forepaw on days 8 to 12 of gestation, soft or liquid feces on days 11 to 16 of gestation, bradypnea on day 14 of gestation, and repetitive chewing on days 15 to 17 of gestation. Necropsy did not reveal any abnormalities. This dam had 17 pups. Examination of the pups revealed that three pups had wavy ribs; the other pups appeared normal.

Embryo-Fetal Development. No treatment-related effects on the number of corpora lutea, and implantation sites were observed (Table 4). The number of corpora lutea and implantation sites were comparable among the four treatment groups.

No treatment-related effects on litter size, number of live fetuses, number of dead fetuses, number of dams with viable fetuses, number of early and late resorptions and the percent resorbed conceptuses were observed. As depicted in Table 5, these parameters in the 1.0, 4.0 and 16.0 mg/kg/day oxycodone treatment groups were comparable to those in the control dams. No treatment-related effects were observed on litter size, live and dead fetuses, percent dead or resorbed conceptuses and percent live male (Table 5). In comparison to the control fetuses, the body weight of the female and male fetuses in the low and high-dose groups was significantly lower and higher, respectively, than those of the control fetuses (Table 6).

Findings from gross external, soft tissue and skeletal examinations are presented in Tables 7, 8, and 9 respectively. One gross abnormality was observed; a fetus in the 1.0 mg/kg/day oxycodone group had a cleft palate. No treatment-related malformations in soft tissues were observed. However, several non treatment-related soft tissue variations were observed. These soft tissues variations included: 1) Descendation of the umbilical artery to the left of the urinary bladder in 2 fetuses, 1 fetus, and 1 fetus in the 0, 4.0, and 16.0 mg/kg/day group, respectively. 2) A significant ($p \leq 0.01$) increase in the number of fetuses with the innominate artery in 4 fetuses from 3 litters in the 1.0 mg/kg/day group and 2 fetuses from 2 litters in the 16.0 mg/kg/day group. Because no dose-dependent trend in the incidence of this variation was observed, this variation is not considered to be treatment-related. 3) A slight or moderate dilation of the pelvis of one kidney in 1 fetus, and 1 fetus in the 0 and 16 mg/kg/day groups.

Skeletal examinations detected 1 skeletal malformation and 2 skeletal variations among the fetuses examined. The one fetus in the 1.0 mg/kg/day group with the cleft palate also had an incompletely ossified palate in the skull. The skeletal variations included: 1) A significant reduction in the incidence of a cervical rib at the 7th cervical vertebra in the 1, 4, and 16 mg/kg/day groups. 2) An asymmetric 2nd and 3rd sternal centra in 1 fetus in the 4.0 mg/kg/day group.

No significant differences in the average numbers of ossification per fetus for the hyoid, vertebrae, ribs, sternum, forelimbs or hindlimbs were observed among the four treatment groups.

Table 2. **Mean body weight changes for rats orally dosed with oxycodone relative to the control group.**

DOSE (mg/kg/day)	BODY WEIGHT CHANGE (G)				BODY WEIGHT CHANGE RELATIVE TO CONTROL (%)			
	DAYS 0 - 7	DAYS 7 - 18	DAYS 18 - 21	DAYS 0 - 21	DAYS 0 - 7	DAYS 7 - 18	DAYS 18 - 21	DAYS 0-21
Control	+44.0 ± 8.1	+87.5 ± 9.4	+54.1 ± 10.2	+ 185.6 ± 22.0	100	100	100	100
1.0	+45.1 ± 6.5	+80.0 ± 10.7	+59.1 ± 8.7	+184.1 ± 16.8	↑ 2.5%	↓ 8.6%	↑ 9.2	↓ 0.8%
4.0	+ 41.3 ± 9.6	+63.6 ± 15.6[A]	+ 58.7 ± 8.6	+ 1163.8 ± 23.0[A]	↓ 6.1%	↓ 27.3%	↑ 8.5%	↓11.9%
16.0	+ 43.2 ± 7.6	+35.5 ± 14.4[A]	+47.5 ± 11.7[B,C]	+127.2 ±21.5[A,C]	↓ 1.8%	↓ 40.6%	↓12.29%	↓ 31.5%

A: Significantly different from the control group ($p \leq 0.01$)
B: Significantly different from the control group ($p \leq 0.05$)
C: The average of 23 subjects; dam 13692 delivered prematurely on gestation day 21, her data was not included in the analysis.

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Table 3. Effect of oxycodone on average absolute and relative food intake.

GROUP	CONTROL	1.0	4.0	16.0
MEAN ABSOLUTE FOOD INTAKE (G/DAY)				
Mean Intake During Dosing Period: Days 7-18	26.8 ± 3.1	25.2 ± 1.5[A]	22.6 ± 1.7[B]	19.4 ± 1.5[B]
Change Relative To Control (%)	100%	↓ 6.0%	↓15.7%	↓ 27.6%
Means Intake Post-Dosage Period: Days 18-21	28.5 ± 4.9	27.1 ± 2.3	26.4 ± 2.3	20.4 ± 3.4[B]
Change Relative To Control (%)	100 %	↓ 4.9%	↓ 7.4%	↓ 28.4%
Mean Intake Entire Gestation Period: Days 7-21	27.1 ± 2.8	25.7 ± 1.4[C]	23.4 ± 1.5[B]	19.6 ± 1.7[B]
Change relative To Control (%)	100%	↓ 5.2%	↓ 13.7%	↓ 27.7%
MEAN RELATIVE FOOD INTAKE (G/KG/DAY)				
Mean Intake During Dosing: Days 7-18	85.8 ± 9.3	82.2 ± 4.6[A]	76.6 ± 4.2[B]	69.2 ± 5.0[B]
Change Relative To Control (%)	100%	↓4.2%	↓10.7%	↓ 19%
Means Intake Post-Dosage Period: Days 18-21	73.0 ± 13.3	70.2. ± 5.3	72.2 ± 6.9	61.9 ± 8.6[B,D]
Change Relative To Control (%)	100%	↓ 3.8%	↓ 1.1%	↓ 15%
Mean Intake Entire Gestation Period: Days 7-21	82.4 ± 7.9	79.0 ± 4.1	75.2 ± 3.8[B]	67.4 ± 4.9[B,D]
Change Relative To Control (%)	100%	↓ 4.1%	↓ 8.7%	↓ 18.2%

A: Excludes values that appeared incorrectly recorded as well as those associated with spillage.
B: Significantly different from the control group ($p \leq 0.01$)
C: Significantly different from the control group ($p \leq 0.05$)
D: Excludes values for dam 13692, which prematurely delivered on gestation day 21.

Table 4. **Effects of oxycodone on the mean number of corpora lutea, implantation site, percent of rats pregnant and presenting with normal placenta.**

DOSE (mg/kg/day)	# PREGNANT/TOTAL (%)	MEAN (± S.D.)		# EXAMINED (%)
		CORPORA LUTEA	IMPLANTATION SITE	NORMAL PLACENTAE
0.0	25/25 (100.0 %)	17.7 (1.8)	16.0 (1.7)	25 (100.0)
1.0	24/25 (96.0 %)	17.2 (1.7)	15.4 (2.1)	24 (100.0)
4.0	25/25 (100.0 %)	17.0 (2.7)	15.2 (3.2)	25 (100.0)
16.0	24/25(96.0 %)	17.9 (2.0)	16.5 (1.8)	23 (100.0)

Table 5. **Litter, and resorption data.**

DOSE (mg/kg/day)	LITTER DATA : MEAN (± S.D.)			RESORPTION DATA: MEAN (± S.D.)		% DAMS WITH (#/TOTAL EXAMINED)		
	SIZE	LIVE FETUSES	DEAD FETUSES	EARLY	LATE	ANY RESORPTIONS	ALL CONCEPTUSES RESORBED	VIABLE FETUSES
0.0	15.6 (1.8)	15.6 (1.8)	0	0.4 (0.6)	0	36.0 (9/25)	0 (0/25)	100.0 (25/25)
1.0	14.8 (2.0)	14.8 (2.0)	0	0.5 (1.0)	0	37.5 (9/24)	0 (0/24)	100.0 (24/24)
4.0	14.6 (3.0)	14.6 (3.0)	0	0.5 (0.6)	0 (0.2)	48.0 (12/25)	0 (0/25)	100.0 (25/25)
16.0	15.6 (1.9)	15.6 (1.9)	0 (0.2)	0.9 (1.2)	0	47.8 (11/23)	0 (0/23)	100.0 (23/23)

Table 6. Litter Data.

DOSE (mg/kg/day)	LITTER DATA					MEAN BODY WEIGHTS (GRAMS)/LITTER (±S.D.)		
	NO. OF LIVE FETUSES	MEAN % DEAD OR RESORBED CONCEPTUSES/LITTER (±S.D.)	No. OF LIVE MALE FETUSES	MEAN %LIVE MALE FETUSES/LITTER (±S.D.)	No. OF LIVE FEMALE FETUSES	LIVE FETUSES	LIVE MALE FETUSES	LIVE FEMALE FETUSES
0.0	390	2.6 (3.6)	204	51.8 (14.7)	186	5.20 (0.26)	5.33 (0.28)	5.07 (0.27)
1.0	356	3.5 (5.8)	177	49.4 (11.8)	179	5.41 (0.32)[a]	5.58 (0.36)[a]	5.25 (0.33)[a]
4.0	366	3.4 (3.9)	180	48.8 (12.2)	186	5.22 (0.29)	5.38 (0.37)	5.07 (0.28)
16.0	358	5.5 (7.2)	190	52.8 (11.2)	168	4.93 (0.27)[b]	5.06 (0.29)[b]	4.79 (0.26)[b]

a: Significantly different from the control value ($p \leq 0.05$).
b: Significantly different from the control value ($p \leq 0.01$).

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Table 7. Fetal Gross Abnormalities.

	NUMBER FETUSES WITH ABNORMALITY (PERCENTAGE)			
DOSE (MG/KG/DAY)	**0.0**	**1.0**	**4.0**	**16.0**
No. LITTERS EVALUATED	25	24	25	23
No. FETUSES EVALUATED	390	356	366	359
No. LIVE FETUSES EVALUATED	390	356	366	358
No. DEAD FETUSES EVALUATED	0	0	0	1[a]
PALATE: CLEFT				
LITTER INCIDENCE	0 (0)	1 (4.2)	0 (0)	0 (0)
FETAL INCIDENCE	0 (0)	1 (0.3)	0 (0)	0 (0)

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Table 8. Fetal soft tissue alterations.

	NUMBER FETUSES WITH SOFT TISSUE ABNORMALITY (PERCENTAGE)			
DOSE (MG/KG/DAY)	**0.0**	**1.0**	**4.0**	**16.0**
No. LITTERS EVALUATED	25	24	25	23
No. FETUSES EVALUATED	187	171	177	173
No. LIVE FETUSES EVALUATED	187	171	177	173
KIDNEYS (LEFT): PELVIS, MODERATE DILATION				
LITTER INCIDENCE	1 (4.0)	0 (0))	0 (0)	0 (0)
FETAL INCIDENCE	1 (0.5)	0 (0)	0 (0)	0 (0)
KIDNEYS (RIGHT): PELVIS, SLIGHT DILATION				
LITTER INCIDENCE	0 (0)	0 (0)	0 (0)	1 (4.3)
FETAL INCIDENCE	0 (0)	0 (0)	0 (0)	1 (0.6)
VESSELS: UMBILICAL ARTERY DESCENDED TO THE LEFT OF THE URINARY BLADDER				
LITTER INCIDENCE	2 (8.0)	0 (0)	1 (4.0)	1 (4.3)
FETAL INCIDENCE	2 (1.1)	0 (0)	1 (0.6)	1 (0.6)
VESSELS: INOMINATE, ABSENT				
LITTER INCIDENCE	0 (0)	3 (12.5)	0 (0)	2 (8.7)
FETAL INCIDENCE	0 (0)	4 (2.3)	0 (0)	2 (1.2)

a: Dead fetus was excluded from group average and statistical analyses.
b: Significantly different from the 0.0 mg/kg group value ($p \leq 0.05$)
c: Significantly different from the 0.0 mg/kg group value ($p \leq 0.01$)

Table 9. Fetal skeletal alterations.

	NUMBER FETUSES WITH SKELETAL ABNORMALITY (PERCENTAGE)			
DOSE (MG/KG/DAY)	**0.0**	**1.0**	**4.0**	**16.0**
No. LITTERS EVALUATED	25	24	25	23
No. FETUSES EVALUATED	203	185	189	186
No. LIVE FETUSES EVALUATED	203	185	189	185
No. DEAD FETUSES EVALUATED	0	0	0	1[a]
CERVICAL VERTEBRAE: CERVICAL RIB PRESENT AT 7th CERVICAL VERTEBRA				
LITTER INCIDENCE	8 (32.0)	1 (4.2)[b]	2 (8.0)[b]	4 (17.4)[c]
FETAL INCIDENCE	9 (4.4)	1 (0.5)[b]	2 (1.0)[b]	8 (4.3)
RIBS: WAVY, RIGHT 6th-12th, LEFT 9th-11th				
LITTER INCIDENCE	1 (4.0)	0 (0)	0 (0)	0 (0)
FETAL INCIDENCE	1 (0.5)	0 (0)	0 (0)	0 (0)
SKULL: PALATE, INCOMPLETELY OSSIFIED, MEDIAL				
LITTER INCIDENCE	0 (0)	1 (4.2)	0 (0)	0 (0)
FETAL INCIDENCE	0 (00	1 (0.5)	0 (0)	0 (0)
STERNAL CENTRA: ASYMMETRIC, 2nd AND 3rd				
LITTER INCIDENCE	0 (0)	0 (0)	1 (4.0)	0 (0)
FETAL INCIDENCE	0 (0)	0 (0)	1 (0.5)	0 (0)

a: Dead fetus was excluded from group average and statistical analyses.
b: Significantly different from the 0.0 mg/kg group value ($p \leq 0.05$)

CONCLUSION.

In this segment II study, oxycodone (0, 1.0, 4.0, and 16.0 mg/kg/day) was administered orally to pregnant rats from days 7 to 17 of pregnancy. The primary objective of this study was to detect adverse effects of orally administered oxycodone on the pregnant female and on the development of the embryo and fetus.

1. **NOAEL**could not be determined since the low dose did produce an effect on body weight gain; the body weight gain was 8.6% less than the control. The **NOAEL was less than 1.0 mg/kg/day**

2. Oral administration of oxycodone to pregnant female rats was tolerated up to 16.0 mg/kg/day without deaths, but clinical signs and significant effects on body weight and food consumption were observed.

3. No treatment-related effects on the development of the embryo was observed. Oxycodone had no effects on the litter size, number of fetuses, number of dams with viable fetuses, number of late and early resorptions and the percent resorbed conceptuses.

4. No treatment-related effects on the development of the fetus was observed. Oxycodone did not produce any gross, soft tissue or skeletal abnormalities.

5. A decrease in fetal body weight was observed in the 16.0 mg/kg group. This decrease in fetal body weight may be due to maternal toxicity, that is decreased body weight and food consumption, observed in the high dose group.

6. Oxycodone was not teratogenic or embryo-fetal toxic in rats at oral doses up to 16 mg/kg or 2 times the daily oral dose of 90 mg/day on a mg/m^2 basis.

Sponsor ID#: XIRTO299
Title: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study Of Oxycodone In Rabbits.
Amendment #, Vol. #, and page #: Amendment # 7, Volume 3 pages 100 to 188
Conducting Laboratory:
Date of Study Initiation: October 1, 1999
GLP Compliance: Yes (X) No ( )
QA Report: Yes (X) No ( )

METHODS:

Species: New Zealand White [Hra:(NZW)SPF] Rabbit
#/sex/group: 5 timed-pregnant females/group
Age: Approximately 5 to 7 months of age at the time of the study
Weight: At the time of the study, the body weight range between 2.5 kg to 5.5 kg.
Study Design: Rabbits will be dosed with the test article or vehicle once daily on days 6 through 18 of presumed gestation, the period of organogenesis.

Doses:

DOSE GROUP	No. OF FEMALE RABBITS	DOSAGE (mg/kg/day)	CONCENTRATION (mg/mL)	VOLUME (mL/kg)
I	5	0.0	0.0	12.0
II	5	4.0	20.0	0.2
III	5	15.0	20.0	0.75
IV	5	60.0	20.0	3.0
V	5	240	20.0	12.0

Route, Form, and Volume: Oral (Stomach Tube), Solution, See above table

Drug, Lot #: Oxycodone HCl, Lot No. 991321A

Formulation/Vehicle: Solution/Reverse Osmosis Membrane Processed Deionized Water

STUDY PARAMETERS:

Viability: Twice Daily
Clinical Signs: **Predosage Period:** Once; **Dosing Period:** Daily, before dosing, 60 ± 10 min post-dosing; **Postdosage Period:** Daily
Mortalities: **Dosing Period:** Daily, before dosing, 60 ± 10 min post-dosing; **Postdosage Period:** Daily
Abortions & Premature Deliveries: **Dosing Period:** Daily, before, 60 ± 10 min and 3 hours ± 10 min post-dosing and at the end of the workday; **Postdosage Period:** Daily
Body Weights: **Predosage Period:** Day 0 of presumed gestation and on the day of arrival to the Testing Facility; **Dosage and Postdosage Periods:** Daily
Food Consumption: **Predosage Period:** Daily after arrival to the Testing Facility; **Dosage Period:** Daily; **Postdosage Period:** Daily

STUDY PARAMETERS (CONT.):

At Necropsy: All surviving rabbits and live fetuses were euthanized with [redacted] (Dams: via intravenous injections; Fetuses: via intraperitoneal injection injection) on presumed gestation day 29. Dams was Cesarean-sectioned and a gross necropsy was performed.

Gross Pathology: Thoracic, abdominal and pelvic viscera were examined.

Caesarean-Sectioning Observation. Rabbits was examined for number and distribution of:

- Corpora Lutea
- Implantation Sites
- Live and dead fetuses.
- Early and late resorptions

Fetal Observations:

- Body weight of live fetuses
- Sex
- Gross external alteration
- Representative photographs of fetal gross alterations will be taken.

RESULTS.

Clinical Signs In Dosed Animals. Oxycodone-induced clinical signs were observed in the does in the high dose group. The clinical signs that appear to be treatment-related are presented in Table 1. Clinical signs were only observed in the does in the high dose group. Decreased motor activity was observed in the does during the first three days of dosing. Due to the severity of this overt sign of toxicity, the sponsor lowered the dose to 150 mg/kg/day for the remainder of the study. The main clinical sign observed in the does at a dose of 150 mg/kg/day was ataxia; many of the does presented with these clinical signs during days 9 thru 17 of the study.

Mortality. No treatment-related deaths occurred; all dams survived to the scheduled sacrificed day.

Body Weight. Treatment-related effects on body weight were observed. As depicted in Figure 1 (copied from the sponsor submission), a dose-dependent reduction in body weight gains occurred. The body weight and body weight gains of the dams in the low dose group (4.0 mg/kg/day) were comparable to the controls. Dose-related body weight loss was observed in the 15.0, 60.0, and 240/150 mg/kg/day groups. Mean body weights in the 15.0, 60.0, and 240/250 mg/kg/day groups were approximately 6.0%, 11.0%, and 15.0% lower, respectively, than those of the control group on the last day (day 18) of dosing (Table 2). Even though the mean weight of these groups were less than those of controls, the mean body weight was not significantly different. Some recovery in body weight loss was evidence on day 29 (9 days after dosing was terminated) of the study; the mean body weights in the 15.0, 60.0, and 240/150 mg/kg/day groups were approximately 4.1%, 8.4%, and 11% lower, respectively, than those of the control group.

Food Consumption. Dose-dependent reduction in both absolute and relative food consumptions occurred (Table 3). As depicted in Table 3, relative to the control group, the absolute food intake was dose-dependent in all oxycodone groups during the dosing period. During the post-dosing period, food intake in the 60 and 240/150 mg/kg/day group were generally comparable to the control group. When food intake was expressed as relative food consumption, a dose-dependent reduction in food consumption was observed in the 15, 60, and 240/150 mg/kg/day groups. The low dose group relative food intake was similar to the control group.

Table 1. **Clinical Signs observed in the dams following oxycodone treatment during days 7 thru 17 of gestation.**

CLINICAL SIGN	Nº SUBJECTS WITH SIGN/TOTAL Nº SUBJECTS				
	DOSE (mg/kg/day)				
	0	4.0	15.0	60.0	240/150[A]
↓ Motor Activity	0/5	0/5	0/5	0/5	D6: 4/5 D7: 4/5 D8: 4/5
Ataxia	0/5	0/5	0/5	0/5	D9: 3/5 D10: 3/5 D11: 3/5 D12: 1/5 D13: 2/5 D16:2/5 D17: 2/5
Impaired Righting Reflex	0/5	0/5	0/5	0/5	D6: 2/5

A: Due to severity of the overt signs of toxicity on days 6-8, the dose was decreased to 150 mg/kg/day for the remainder of the study.

Figure 1. **Maternal Body Weight.**

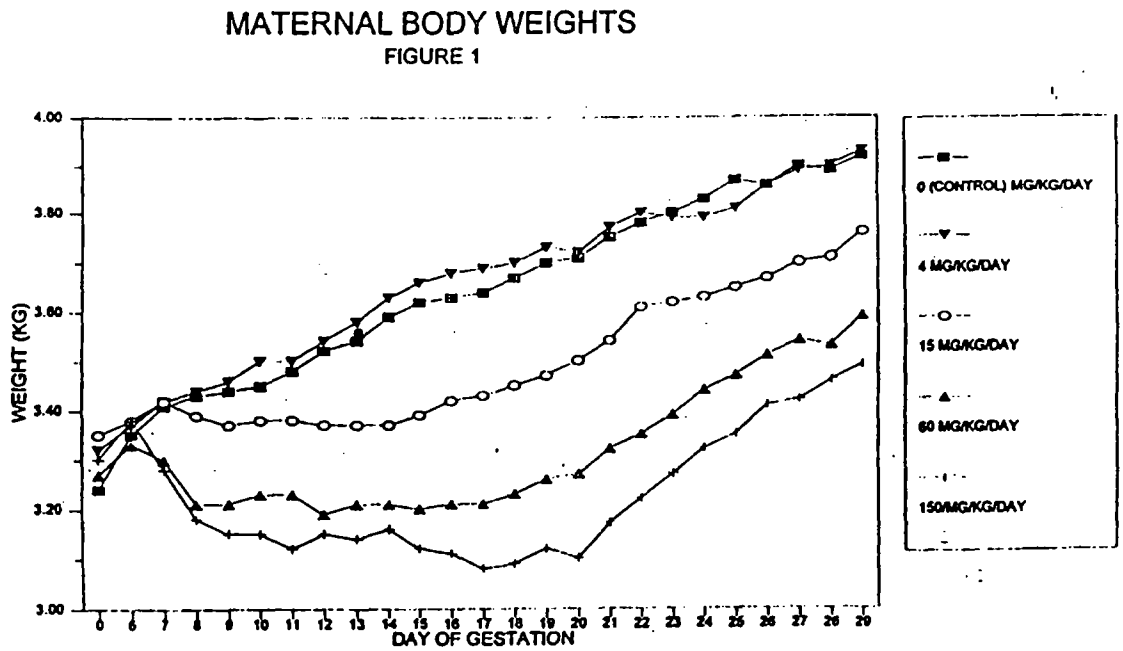

Table 2. **Mean body weight changes for rabbits orally dosed with oxycodone relative to the control group.**

DOSE (mg/kg/day)	MEAN BODY WEIGHT (KG)			BODY WEIGHT CHANGE RELATIVE TO CONTROL (%)		
	DAY 0	DAY 18	DAY 29	DAY 0	DAY 18	DAY 29
Control	3.24 ± 0.22	3.67 ± 0.19	3.92 ± 0.23	100	100	100
4.0	3.23 ± 0.35	3.70 ± 0.37	3.93 ± 0.35	↑ 3%	↑ 0.8%	↑ 0.3%
15.0	3.35 ± 0.26	3.45 ± 0.39	3.76 ± 0.29	↑ 3.4%	↓ 6%	↓ 4.1%
60.0	3.27 ± 0.23	3.26 ± 0.30	3.59 ± 0.25	↑ 0.9%	↓ 11%	↓ 8.4%
240/150	3.0 ± 0.18	3.12 ± 0.18	3.49 ± 0.15	↑ 0.9%	↓ 15%	↓ 11%

Table 3. **Effect of oxycodone on average absolute and relative food intake.**

GROUP	CONTROL	4.0	15.0	60.0	240/150
MEAN ABSOLUTE FOOD INTAKE (G/DAY)					
Mean Intake During Dosing: Days 6-19	170 ± 21.1	167.2 ± 10.4[A]	95.7 ± 56.5	56.0 ± 29.5	32.7 ± 6.0
Change Relative To Control (%)	100%	↓ 22%	↓ 44%	↓ 67%	↓ 80%
Means Intake Post-Dosage Period: Days 19-29	151.9 ± 21.4	132.1 ± 19.8	130.6 ± 20.5	148.4 ± 21.6	147.3 ± 16.8
Change Relative To Control (%)	100 %	↓ 13%	↓ 14%	↓ 2.3%	↓ 3.0%
MEAN RELATIVE FOOD INTAKE (G/KG/DAY)					
Mean Intake During Dosing: Days 6-19	48.3 ± 4.4	48.8 ± 4.2[A]	27.5 ± 15.5	17.1 ± 9.1	10.3 ± 1.7
Change Relative To Control (%)	100%	↓ 1%	↓ 43%	↓ 65%	↓ 79%
Means Intake Post-Dosage Period: Days 19-29	39.8 ± 5.4	35.1 ± 7.5	36.2 ± 6.5	43.6 ± 7.3	44.7 ± 4.8
Change Relative To Control (%)	100%	↓ 12%	↓ 9%	↓ 10%	↓ 12%

A: **Is the mean of four rabbits.**

Embryo-Fetal Development. No treatment-related effects on the number of corpora lutea and implantation sites were observed (Table 4). The number of corpora lutea and implantation sites were comparable among the five treatment groups. Does dosed with oxycodone during organogenesis also did not show a treatment-related effect on the litter size, number of live and dead fetuses, number of early and late resorptions, and percent resorbed conceptuses. As depicted in Table 5, these parameters in the 4.0, 15.0, 60.0, and 240/150 mg/kg/day groups were comparable to those in the control does. No treatment-related effects were observed in litter size, live and dead fetuses, fetal body weight and percent live male (Table 6).

Gross external examination of the fetuses revealed one fetus in the 60 mg/kg/day group had thoracogastroschisis and medial flexion of a forelimb. No gross alterations were noted in any of the fetuses in the other treatment groups.

Table 4. Effects of oxycodone on the mean number of corpora lutea, implantation site, percent of rats pregnant and presenting with normal placenta.

DOSE (mg/kg/day)	# PREGNANT/TOTAL (%)	MEAN (± S.D.)		# EXAMINED (%)
		CORPORA LUTEA	IMPLANTATION SITE	NORMAL PLACENTAE
0.0	5/5 (100.0 %)	10.2 (1.9)	9.2 (2.2)	5 (100.0)
4.0	5/5 (100.0 %)	9.6 (1.8)	9.2 (2.2)	5 (100.0)
15.0	5/5 (100.0 %)	9.8 (1.1)	9.0 (1.0)	5 (100.0)
60.0	5/5(100.0 %)	10.0 (2.0)	9.0 (2.4)	5 (100.0)
240/150	5/5 (100.0%)	8.4 (0.5)	7.6 (0.9)	5 (100.0)

Table 5. Litter, and resorption data.

DOSE (mg/kg/day)	LITTER DATA : MEAN (± S.D.)			RESORPTION DATA: MEAN (± S.D.)		% DAMS WITH (#/TOTAL EXAMINED)		
	SIZE	LIVE FETUSES	DEAD FETUSES	EARLY	LATE	ANY RESORPTIONS	ALL CONCEPTUSES RESORBED	VIABLE FETUSES
0.0	8.6 (1.7)	8.4 (1.5)	0.2 (0.4)	0 0 (0.0)	0.6 (0.5)	60% (3/5)	0% (0/5)	100% (5/5)
4.0	9.2 (2.2)	9.2 (2.2)	0 (0.0)	0.0 (0.0)	0.0 (0.0)	0% (0/5)	0% (0/5)	100% (5/5)
15.0	9.0 (1.0)	9.0 (1.0)	0 (0.0)	0.0 (0.0)	0.0 (0.0)	0% (0/5)	0% (0/5)	100% (5/5)
60.0	8.6 (2.4)	8.6 (2.4)	0 (0.0)	0.2 (0.4)	0.2 (0.4)	40% (2/5)	0% (0/5)	100% (5/5)
240/150	7.4 (1.1)	7.4 (1.1)	0.0 (0.0)	0.2 (0.4)	0.0 (0.0)	20% (1/5)	0% (0/5)	100% (5/5)

Table 6. Litter Data.

DOSE (mg/kg/day)	LITTER DATA					MEAN BODY WEIGHTS (GRAMS)/LITTER (±S.D.)		
	No. OF LIVE FETUSES	No. OF DEAD FETUSES	No. OF LIVE MALE FETUSES	MEAN %LIVE MALE FETUSES/LITTER (±S.D.)	No. OF LIVE FEMALE FETUSES	LIVE FETUSES	LIVE MALE FETUSES	LIVE FEMALE FETUSES
0.0	42	1	23	54.0% (9.8)	19	45.0 (5.13)	46.25 (4.85)	43.0 (6.17)
6.0	46	0	27	58.3% (11.4)	19	44.9 (44.57)	45.74 (4.31)	43.81 (5.04)
15.0	45	0	25	56.1% (20.0)	20	42.62 (5.09)	42.52 (44.46)	42.29 (5.92)
60.0	43	0	31	72.3 (15.5)	12	43.86 (4.47)	43.54 (44.85)	42.08 (8.65)
240/150	37	0	19	48.7 (27.9)	18	40.67 (3.39)	41.84 (4.17)	39.91 (3.70)

KEY STUDY FINDINGS:

1. **Maternal NOAEL** = 4.0 mg/kg/day. At 15.0 mg/kg/day, the body weight was 6% lower than that of the control on the last day of dosing and absolute food consumption was 22% lower than that of the control during the dosing period (days 6-19).

2. Oral administration of oxycodone to pregnant rabbits was tolerated up to 150 mg/kg/day; no deaths occurred. Oxycodone-induced clinical signs were observed in the high dose group; the main clinical sign observed was ataxia. Dose-dependent reduction in both absolute and relative food consumption during the dosing period was observed. Relative to control, a 22%, 44%, 67% and 80% decrease in absolute food consumption was observed in the 4, 15, 60, and 150 mg/kg/day groups, respectively. This treatment-related effect on food consumption was reversible; during the post-dosing period the absolute food consumption of the mid- and high-dose was comparable to the control group.

3. No organ toxicity was observed.

4. No treatment-related effects on the development of the embryo were observed. Oxycodone had no effects on litter size, number of fetuses, number of live fetuses, number of dams with viable fetuses, number of early and late resorptions, fetal body weight, and the percent resorbed conceptuses.

5. **Developmental NOEL was at 150.0 mg/kg/day, the highest dose tested.**

6. Based on the results from this study, the sponsor selected doses of 0, 1, 5, and 25 mg/kg/day for developmental toxicity study in rabbits. These doses are acceptable; 1.0 mg/kg/day should be the NOEL dose and 25 mg/kg/day should produce some maternal toxicity (such as decrease body weight gain).

Sponsor ID#: XIRTO499 (Draft Final Report)
Title: Oral (Stomach Tube) Developmental Toxicity Study Of Oxycodone In Rabbits.
Amendment #, Vol. #, and page #: Amendment # 7, Volume 5, pages 1 to 258
Conducting Laboratory: [redacted]
Date of Study Initiation: November 12, 1999
GLP Compliance: Yes (X) No ( )
QA Report: **It was stated that the study underwent Quality Assurance Audit; the report was not signed.**

METHODS:

Species: New Zealand White [Hra:(NZW)SPF] Rabbit
#/sex/group: 20 timed-pregnant females/group
Age: Approximately 5 to 7 months of age at the time of the study.
Weight: At the time of the study, the body weight ranged from 2.5 to 5.5 kg.
Study Design: Rabbits were dosed with the test article or vehicle once daily on days 6 through 18 of presumed gestation, the period of organogenesis.

Doses: These doses were selected based on the results from the dose-range finding study (Study Report XIRTO299).

DOSE GROUP	No. OF FEMALE RABBITS	DOSAGE (mg/kg/day)	CONCENTRATION (mg/mL)	VOLUME (mL/kg)
I	20	0.0	0	5.0
II	20	1.0	1.0	1.0
III	20	5.0	1.0	5.0
IV	20	25.0	5.0	5.0

Route, Form, and Volume: Oral (Stomach Tube), Solution, See above table

Drug, Lot #: Oxycodone HCl, Lot No. 991321A

Formulation/Vehicle: Solution/Reverse Osmosis Membrane Processed Deionized Water

STUDY PARAMETERS:

Viability: Twice Daily
Clinical Signs: **Predosage Period:** Once; **Dosing Period:** Daily, before dosing, 60 ± 10 min post-dosing; **Postdosage Period:** Daily
Mortalities: **Dosing Period:** Daily, before dosing, 60 ± 10 min post-dosing; **Postdosage Period:** Daily
Abortions & Premature Deliveries: **Dosing Period:** Daily, before, 60 ± 10 min and 3 hours ± 10 min post-dosing and at the end of the workday; **Postdosage Period:** Daily
Body Weights: **Predosage Period:** Day 0 of presumed gestation and on the day of arrival to the Testing Facility; **Dosage and Postdosage Periods:** Daily
Food Consumption: **Predosage Period:** Daily after arrival to the Testing Facility; **Dosage Period:** Daily; **Postdosage Period:** Daily

STUDY PARAMETERS (CONT.):

At Necropsy: All surviving rabbits and live fetuses were euthanized with [redacted] (Dams: via intravenous injections; Fetuses: via intraperitoneal injection injection) on presumed gestation day 29. Dams was n Caesarean-sectioned and a gross necropsy was performed.

Gross Pathology: Thoracic, abdominal and pelvic viscera were examined.

Caesarean-Sectioning Observation. Rabbits was examined for number and distribution of:

- Corpora Lutea
- Implantation Sites
- Live and dead fetuses.
- Early and late resorptions

Fetal Observations:

- Body weight of live fetuses
- Sex
- Gross external alteration
- Soft tissue examination: 1) Cavitated organs was evaluated in all fetus by dissections.; 2) A single cross-section will be made between the parietal and frontal bones, and the brain will be examined *in situ*.
- Skeletal examination : Skeletal alterations was assessed after staining with alizarin red S.
- Representative photographs of fetal gross alterations was taken.

RESULTS.

Clinical Signs. Clinical signs observed included: scant feces (1.0 and 5.0 mg/kg/day groups), soft or liquid feces (significantly reduced), localized alopecia of the back or underside, ungroomed coat and red substance in the cage pan. These clinical signs were not considered to be treatment-related.

Mortality. No treatment-related deaths occurred.

Body Weight. Treatment-related effects on bodyweight were observed in the high dose group (Figure 1 as copied from the sponsor's submission). During the dosing period (days 6-19), the body weight gain observed in the high dose group was approximately 44% less than that of the control group. The body weight gain observed in the low and mid-dose groups was slightly greater than that of the controls (Table 1). During the post-dosing period (days 19-29) the body weight gain in the low and mid dose groups were comparable to that of the control. The high dose group showed some recovery in body weight gain; the body weight gain during this period was slightly lower than that of the controls. At the end of the study, the body weight gain in high dose group was significantly less than the control group from days 6-29; it was 27% lower (Table 1).

Food Consumption. Treatment-related effects on food consumption were observed in the 25.0 mg/kg/day treatment group (Table 2). Both the absolute (g/day) and relative (g/kg/day) food consumptions were significantly reduced during the dosing period (Days 6-19). Relative to the control group, the absolute and relative food intake were reduced by 19% and 17%, respectively. A rebound phenomenon was observed during the post-dosing period (days 19-29); both relative and absolute food consumptions were increased over that of the control group. No treatment-related effects on food consumption were observed in the 1.0 and 5.0 mg/kg/day groups. The absolute and relative food intake in the low- and mid- dose groups were greater than that of the control group during the dosing and post-dosing periods.

Table 1. **Mean body weight changes for rabbits orally dosed with oxycodone relative to the control group.**

DOSE (mg/kg/day)	BODY WEIGHT CHANGE (KG)				BODY WEIGHT CHANGE RELATIVE TO CONTROL (%)			
	DAYS 0 - 6	DAYS 6 - 19	DAYS 19 - 29	DAYS 6 - 29	DAYS 0 - 6	DAYS 6 - 19	DAYS 19 - 29	DAYS 6-29
Control	+0.07 ± 0.08	+0.25 ± 0.13	+0.23 ± 0.10	+0.48 ± 0.19	100	100	100	100
1.0	+0.08 ± 0.07	+0.32 ± 0.07	+0.23 ± 0.08[A]	+0.54 ± 0.12[A]	↑ 14%	↑ 28%	100	↑ 13%
5.0	+0.04 ± 0.08	+0.32 ± 0.06	+0.24 ± 0.11	+0.56 ± 0.12	↓ 43%	↑ 28%	↑ 4%	↑ 17%
25.0	+0.07 ± 0.07	+0.14 ± 0.17	+0.21 ± 0.14	+0.35 ± 0.19[B]	100	↓ 44%	↓ 9%	↓ 27%[B]

A: Represent the average of 17 values; does not include the weight of doe 1435 which aborted on day 28 of gestation.
B: Significantly different from the control group ($p \leq 0.05$)

Table 2. **Effect of oxycodone on average absolute and relative food intake.**

GROUP	CONTROL	1.0	5.0	25.0
MEAN ABSOLUTE FOOD INTAKE (G/DAY)				
Mean Intake During Dosing: Days 6-19	156.4 ± 33.0	175.4 ± 12.7	175.6 ± 12.7[A]	126.6 ± 36.4[A]
Change Relative To Control (%)	**100%**	**↑ 12%**	**↑ 12%**	**↓ 19%**
Means Intake Post-Dosage Period: Days 19-29	143.19 ± 28.1	153.5 ± 22.7[B,C]	153.6 ± 22.4	155.3 ± 22.7
Change Relative To Control (%)	**100 %**	**↑ 7%**	**↑ 7%**	**↑ 8%**
Mean Intake Entire Gestation Period: Days 6-29	150 .8 ± 27.7	165.6 ± 14.7 [C]	166.0 ± 14.2	138.9 ± 25.9
Change Relative To Control (%)	**100%**	**↑ 10%**	**↑ 11%**	**↓ 8%**
MEAN RELATIVE FOOD INTAKE (G/KG/DAY)				
Mean Intake During Dosing: Days 6-19	42.2 ± 7.5	47.3 ± 5.1	47.8 ± 4.6[A]	34.9 ± 9.8[A]
Change Relative To Control (%)	**100%**	**↑ 12%**	**↑ 13%**	**↓ 17%**
Means Intake Post-Dosage Period: Days 19-29	36.4 ± 5.9	38.7 ± 5.9[C]	39.1 ± 6.4	41.0 ± 6.8
Change Relative To Control (%)	**100%**	**↑ 6%**	**↑ 7%**	**↑ 13%**
Mean Intake Entire Gestation Period: Days 6-29	**39.6 ± 5.6**	**43.4 ± 4.9[B,C]**	**43.8 ± 4.8[A]**	**37.5 ± 6.8**
Change Relative To Control (%)	**100%**	**↑ 10%**	**↑ 11%**	**↓ 6%**

A: **Significantly different from control group ($p \leq 0.05$)**
B: **Represent the average of 17 values**
C: **Value for doe 1435 was not included; this doe aborted on day 28 of gestation.**

Embryo-Fetal Development. No treatment-related effects on the number of corpora lutea and implantation sites were observed (Table 3). The number of corpora lutea and implantation sites were comparable among the four groups. All placentas examined in the control group and mid-dose group (5.0 mg/kg/day) appeared normal; in the 1.0 and 25.0 mg/kg/day treatment group, one placenta in each group did not appear normal. As depicted in Table 4, no treatment-related effects on the litter size, number of live fetuses, number of late resorptions, and percent resorbed conceptuses; these parameters in the 1.0, 5.0, and 25.0 mg/kg/day groups were comparable to those in the control does . No treatment-related effects were observed in litter size, live and dead fetuses, fetal body weight and percent live male (Table 5).

No treatment-related gross abnormalities were observed. Several non-treatment gross abnormalities were observed: 1) One fetus in the low-dose group presented with meningocele in the lumbar region and fore and/or hindlimb was rotated medially.; 2) One fetus in the mid-dose group had open eye lids and abdominal distension. No treatment-related malformations or variations in soft tissues were observed. Several non treatment-related soft tissue malformations or variations were observed (Table 6). A significant increase ($p \leq 0.01$) in the number of fetuses observed without the intermediate lobe of the lung were detected in the low dose group.

Skeletal examination did not detect any significant treatment-related skeletal variations or malformations among the fetuses examined. Some skeletal malformations of the skull, vertebrae/ribs and lumbar vertebrae; and variations of the skull, hyoid, ribs, and sternum were reported. These malformations and variations were within the range of the historical control and the incidence level was not dose-dependent.

Table 3. Effects oxycodone on the mean number of corpora lutea, implantation site, percent of rats pregnant and presenting with normal placenta.

DOSE (mg/kg/day)	# PREGNANT/TOTAL (%)	MEAN (± S.D.)		# EXAMINED (%)
		CORPORA LUTEA	IMPLANTATION SITES	NORMAL PLACENTAE
0.0	20/20 (100.0 %)	10.1 (2.9)	8.6 (1.8)	20 (100.0)
1.0	20/20 (100.0 %)	10.0 (2.8)	8.1 (1.8)	17 (94.1)
5.0	20/20 (100.0 %)	11.4 (2.6)	9.2 (2.7)	19 (100.0)
25.0	20/20 (100.0 %)	9.9 (2.5)	8.6 (2.7)	19 (94.7)

Table 4. Litter, and resorption data.

DOSE (mg/kg/day)	LITTER DATA : MEAN (± S.D.)			RESORPTION DATA: MEAN (± S.D.)		% DAMS WITH (#/TOTAL EXAMINED)		
	SIZE	LIVE FETUSES	DEAD FETUSES	EARLY	LATE	ANY RESORPTIONS	ALL CONCEPTUSES RESORBED	VIABLE FETUSES
0.0	8.4 (1.8)	8.4 (1.8)	0 (0.0)	0 0 (0.2)	0.0 (0.2)	10% (2/20)	0% (0/20)	100% (20/20)
1.0	7.6 (2.4)	7.6 (2.4)	0 (0.0)	0.04(1.0)	0.0 (0.2)	29.4% (5/17)	5.9% (1/17)	94.1% (16/17)
5.0	8.6 (3.0)	8.6 (3.0)	0 (0.0)	0.4 (010)	0.3 (0.6)	31.6% (6/19)	0% (0/19)	100% (19/19)
25.0	7.7 (3.3)	7.7 (3.3)	0 (0.0)	0.8 (3.0)	0.1 (0.3)	26.3% (5/19)	5.3% (1/19)	94.7% (18/19)

Table 5. Litter Data.

DOSE (mg/kg/day)	LITTER DATA					MEAN BODY WEIGHTS (GRAMS)/LITTER (±S.D.)		
	No. OF LIVE FETUSES	No. OF DEAD FETUSES	No. OF LIVE MALE FETUSES	MEAN %LIVE MALE FETUSES/LITTER (±S.D.)	No. OF LIVE FEMALE FETUSES	LIVE FETUSES	LIVE MALE FETUSES	LIVE FEMALE FETUSES
0.0	169	0	82	47.0% (16.8)	87	44.63 (3.99)	45.64 (4.27)	43.82 (4.90)[A]
1.0	130	0	60	46.7% (15.2)	70	45.46 (3.91)	46.14 (4.50)	44.57 (3.88)
5.0	163	0	90	57.9% (13.4)	73	45.88 (4.76)	46.07 (5.16)	45.79 (5.18)
25.0	146	0	81	58.1 (233.2)	65	46.16 (5.45)	46.51 (5.31)	43.91 (5.30)[B]

A: Value is the average of 19. B: The mean of 16 because litters 1465 and 1466 had no female fetuses.

Table 6. Fetal soft tissue alteration.

	NUMBER OF FETUSES WITH SOFT TISSUE ABNORMALITY (PERCENTAGE)			
DOSE (MG/KG/DAY)	**0.0**	**1.0**	**5.0**	**25.0**
No. LITTERS EVALUATED	20	16	19	18
No. FETUSES EVALUATED	169	130	163	146
No. LIVE FETUSES EVALUATED	169	130	163	146
EYE (S): SMALL				
LITTER INCIDENCE	1 (5.0)	1 (5.2)	0 (0)	1 (5.6)
FETAL INCIDENCE	1 (0.6)	1 (0.8)	0 (0)	1 (0.7)
EYES (S): CIRCUMCORNEAL HEMORRHAGE				
LITTER INCIDENCE	0 (0)	1 (6.2)	0 (0)	0 (0)
FETAL INCIDENCE	0 (0)	1 (0.8)	0 (0)	0 (0)
LUNGS: INTERMEDIATE LOBE ABSENT				
LITTER INCIDENCE	2 (10.0)	5 (31.2)	0 (0)	3 (16.7)
FETAL INCIDENCE	3 (1.8)	9 (6.9)[A]	0 (0)	4 (2.7)
SPLEEN: SMALL				
LITTER INCIDENCE	1(5.0)	1 (6.2)	0 (0)	0 (0)
FETAL INCIDENCE	1 (0.6)	1 (0.8)	0 (0)	0 (0)
GALLBLADDER: SMALL				
LITTER INCIDENCE	0 (0)	1 (6.2)	0 (0)	0 (0)
FETAL INCIDENCE	0 (0)	1 (0.8)	0 (0)	0 (0)

A: Significantly different from the 0.0 mg/kg group value ($p \leq 0.01$)

CONCLUSION.

In this segment II study, oxycodone (0, 1.0, 5.0, and 25.0 mg/kg/day) was administered orally to pregnant rabbits from days 6 thru 18 of gestation. The primary objective of this study was to detect adverse effects of orally administered oxycodone on the pregnant female and on the development of the embryo and fetus. **The key findings of this study were:**

1. **Maternal NOAEL** was 5.0 mg/kg/day.

2. Oral administration of oxycodone to pregnant female rabbits was tolerated up to 25.0 mg/kg/day; no treatment-related deaths or clinical signs were reported. However, some maternal toxicity was observed at the highest dose tested. During the dosing period body weight gain was 44% less than that of the control and the absolute food consumption was reduced by 19%.

3. No treatment-related effects on the development of the embryo were observed; that is no effects on corpus lutea, implantation sites, early or late resorptions. Litter size, number of fetuses, number of live fetuses, number of dams with viable fetuses, and percent males were comparable among the four treatment groups.

4. No treatment-related effects on the development of the fetuses were observed. Oxycodone did not produce any significant gross, soft tissue or skeletal abnormalities.

5. **Developmental NOEL** was 25.0 mg/kg/day. Oxycodone was not teratogenic or embryo-fetal toxic at doses up to 25 mg/kg, the highest dose tested. This " no-effect" dose is approximately 5 times the daily oral dose of 90 mg/day on a mg/m^2 basis.

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Swedberg, M.D.B., "The mouse grid-shock analgesia test:Pharmacological characterization of latency to vocalization threshold as an index of antinociception." J. Pharmacol. Exp. Ther., 269:1021-1028, 1994.

Weinstein, S.H. and Gaylord, J.C., "Determination of oxycodone in plasma and identification of a major metabolite." Journal of Pharmaceutical Sciences, 68:527-528, 1979.

OVERALL SUMMARY AND EVALUATION.

Introduction. The current submission is a response to an approvable letter for NDA 21-011 for Roxicodone™ (oxycodone hydrochloride) immediate release tablets (15 and 30 mg). Roxane Laboratories, Inc. currently has three formulations of oxycodone available in the United States; a 5-mg Roxicodone™ tablet, 5 mg/5 mL Roxicodone™ oral solution and Roxicodone Intensol™ a 20 mg/mL concentrated oral solution. Roxane Laboratories, Inc. has developed two dosage strength (15 mg and 30 mg tablets) of an immediate-release oxycodone hydrochloride tablets to extend their current IR oxycodone line. These strengths are intended for patients requiring high total daily oral doses of oxycodone for the management of moderate to severe pain. It is recommended that Roxicodone be administered every 4-6 hours at the lowest dosage level that will achieve adequate analgesia. The dosage level will be individualize; adjusted according to the severity of pain, patient response, and patient size. It is recommended that patients with no history of opioid analgesic use be started on Roxicodone in dosing range of 5 to 15 mg every 4 to 6 hours.

Oxycodone was first marketed as an analgesic prior to the requirement for extensive nonclinical testing, hence toxicity studies are limited to acute toxicity studies and some published toxicology studies in the literature. Considering that oxycodone has been marketed for approximately eighty years in many forms and that it has an adequate safety profile, an extensive preclinical safety evaluation was not required in order for the agency to evaluate its preclinical safety for this NDA. Despite its long marketing history, there are no specific data on the carcinogenicity, mutagenicity, or reproductive toxicology of oxycodone hydrochloride. An agreement was reached between the sponsor and the agency to address these preclinical toxicology areas. It was agreed that [redacted] carcinogenicity studies requirements could be Phase 4 commitments. In this NDA submission, Roxane Laboratories, Inc. submitted the results from segment II reproductive toxicology studies conducted in rats and rabbits.

Safety Evaluation. The developmental and reproductive toxicity potentials of oxycodone were evaluated in both rats and rabbits according to the standard protocol for a Segment II reproductive toxicity study. In the rat segment II study, oxycodone was administered orally to female rats during gestation days 7-17 at doses of 1.0, 4.0, and 16.0 mg/kg/day. No teratogenic effects in the offspring were observed; but some maternal toxicity were noted. Oxycodone-induced clinical signs (ie., repetitive chewing, decreased motor activity, bradypnea, lacrimation and soft or liquid feces) were noted in the high dose group (16.0 mg/kg/day) and body weight gain reduction occurred in all treatment groups. A decrease in fetal body weight was observed in the 16.0 mg/kg/day treatment group; this may be due to the observed reduction in body weight and food consumption of the maternal rats in the high dose group. There were no effects on embryo or fetal developments. Based on these results, oxycodone was not teratogenic or embryo-fetal toxic at doses up to 16 mg/kg/day.

Oxycodone (1.0, 5.0, and 25.0 mg/kg/day) administered orally to pregnant female rabbits during critical time of gestation (days 6-18) caused no teratogenic or embryo-fetal toxic effects. Oxycodone at a dose of 25.0 mg/kg/day did produce some maternal toxicity; body weight gain was significantly reduced during the dosing period. Based on the results, oxycodone was not teratogenic or embryo-fetal toxic in rabbits at doses up to 25.0 mg/kg/day.

The nonclinical studies provided indicated that oxycodone is not a reproductive toxicant in Sprague-Dawley rats or New Zealand rabbits following oral administration at doses up to 16.0 mg/kg/day (2 times the daily oral dose of 90 mg/day on a mg/m^2 basis) and 25.0 mg/kg/day (5 times the daily oral dose of 90 mg/day on a mg/m^2 basis), respectively.

Clinical Relevance of Safety Issues. The nonclinical studies appear to indicate that following oral administration oxycodone was not teratogenic or embryo-fetal toxic; however, because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed. The Pregnancy Category is B.

COMMUNICATION REVIEW:

Labeling Review (NDA)

The proposed draft labeling has been reviewed and the following changes are recommended:

Under **Pregnancy:**

This section has been rewritten as follow:

Teratogenic Effects: Category B: Reproduction studies in Sprague-Dawley rats and New Zealand white rabbits revealed that when oxycodone was administered orally at doses up to 16 mg/kg (approximately 2 times the daily oral dose 90 mg for adults on a mg/m^2 basis) and 25 mg/kg (approximately 5 times the daily oral dose of 90 mg on a mg/m^2 basis), respectively was not teratogenic or embryo-fetal toxic. There are no adequate and well-controlled studies of oxycodone in pregnant women. Because animal reproductive studies are not always predictive of human responses, Roxicodone should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

Conclusions. The NDA is approvable, with minor labeling revisions as described in the section title Labeling Review.

RECOMMENDATIONS:

Internal comments: From a pharmacology/toxicology standpoint, the NDA is approvable with the above labeling revisions.

External Recommendations (to sponsor): The following labeling revisions are recommended:

Under **Pregnancy:**

This section has been rewritten as follow:

Teratogenic Effects: Category B: Reproduction studies in Sprague-Dawley rats and New Zealand white rabbits revealed that when oxycodone was administered orally at doses up to 16 mg/kg (approximately 2 times the daily oral dose of 90 mg for adults on a mg/m^2 basis) and 25 mg/kg (approximately 5 times the daily oral dose of 90 mg on a mg/m^2 basis), respectively was not teratogenic or embryo-fetal toxic. There are no adequate and well-controlled studies of oxycodone in pregnant women. Because animal reproductive studies are not always predictive of human responses, Roxicodone should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

Pending NDA Issues:

The final Quality Assurance reports of the definitive reproductive studies in rats and rabbits are pending. The project manager contacted the sponsor on June 27, 2000; the sponsor informed the project manager that the reports will be submitted soon.

As agreed upon in the February 11, 2000 telconference, the following issues are outstanding:

1. Submissions of the [redacted] are still pending.

2. Submission of the carcinogenicity protocols for agency approval prior to their initiation are still pending. [redacted]

[/S/]
BeLinda A. Hayes, Ph.D.

June 29, 2000
Date

Concurred by Team Leader:

[/S/]
Dou (Lucy) Jean, Ph.D.

June 29, 2000
Date

CC: Orig NDA# 21-011
HFD-170/Div File

Review and Evaluation of Pharmacology/Toxicology Data
Division of Anesthetic, Critical Care & Addiction Drug Products
HFD-170 / Harry M. Geyer, III Ph.D.

NDA: **#21-011 original: September 30, 1998**

Information to sponsor **Yes (x)** **No ( )**

Completion Date: September 14, 1999

Sponsor: Roxane Laboratories, Inc.
Columbus, Ohio

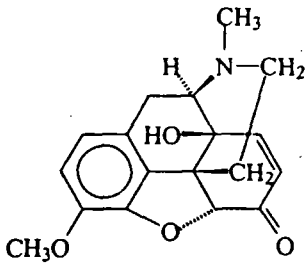
Manufacturers of Drug Substance:

[ ]

Trade Name: Roxicodone™

Drug Name: oxycodone hydrochloride - Immediate release

Chemical Name: 4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride



.HCl

Oxycodone hydrochloride
$C_{18}H_{21}NO_4.HCl$
MW 351.83

Relevant IND/NDA/DMF:

NDA 20-932 - Roxicodone SR
IND 46,618 - Roxicodone

Drug Class: narcotic analgesic

Indication: management of moderate to severe pain

Clinical Formulation (and components):
oxycodone (15mg, 30 mg), lactose NF, stearic acid NF, D&C Yellow No 10.

Route of Administration: oral tablets

Proposed Marketing/Clinical Dose: 15 mg, 30 mg

Studies Reviewed within this Submission: None submitted.

Introduction/Drug History: Oxycodone is a semi-synthetic morphine-like alkaloid which has been marketed for nearly 80 years. The analgesic activity in animals may be greater than morphine on a mg/kg basis but the effects of morphine and oxycodone are similar in the cardiovascular system, gastrointestinal tract and renal function. Oxycodone, like morphine, directly suppresses the brain stem respiratory center and reduces its reaction to blood carbon dioxide tension, producing respiratory depression. Oxycodone also depresses the cough reflex by direct action of the medullary cough center.

Comments and Evaluation: The proposed dosages and duration has been used clinically, but the genetic toxicology and reproductive safety tests in animals have not been done. The deficience are noted in the label which should be amended. Refer to **Recommendations** for details.

RECOMMENDATIONS

This product is approvable from the pharmacology/toxicology perspective with the following commitments by the sponsor:

a) Labeling - Under Precautions, the following sections should be amended as follows:

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies have not been performed in animals to evaluate the carcinogenic potential of Roxicodone™ or oxycodone. The possible effects on male or female fertility have not been studied in animals.

[redacted]

guidelines.

[/S/]

Pharmacologist: Harry M. Geyer III, Ph.D.

[/S/]

Team Leader: Dou Huey Jean, Ph.D.

Sept. 14, 1999
on the revised sec
of Sept. 14, 1999

APPEARS THIS WAY
ON ORIGINAL

Review and Evaluation of Pharmacology/Toxicology Data
Division of Anesthetic, Critical Care & Addiction Drug Products
HFD-170 / Harry M. Geyer, III Ph.D.

NDA: **#21-011 original: September 30, 1998**

Information to sponsor **Yes (x)** **No ( )**

Completion Date: July 21, 1999

Sponsor: Roxane Laboratories, Inc.
Columbus, Ohio

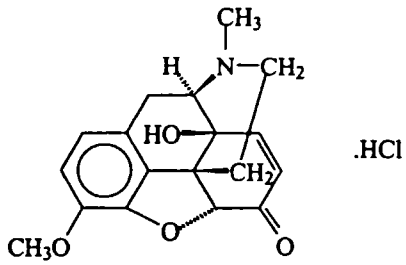
Manufacturers of Drug Substance:

[ ]

Trade Name: Roxicodone™

Drug Name: oxycodone hydrochloride - Immediate release

Chemical Name: 4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride



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Comments and Evaluation: The proposed dosages and duration has been used clinically. The deficience are noted in the label which should be amended. Refer to **Recommendations** for details.

RECOMMENDATIONS

This compound is approvable from the pharmacology/toxicology perspective.

Labeling - The data previously cited from NDA 20-553 remains proprietary and cannot be used without a right of reference. The sponsor is requested to obtain, from the public literature of oxycodone, morphine and other opiates, appropriate descriptions in the following sections; to provide information for patients and prescribing health care providers.

Carcinogenesis, Mutagenesis, Impairment of Fertility and *Pregnancy Category*

[/S/]

Pharmacologist: Harry M. Geyer III, Ph.D.

[/S/] August 19, 1999

Team Leader: Dou Hurey Jean, Ph.D.