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APPLICATION NUMBER:

21-011

MEDICAL REVIEW(S)

NDA 21-011/AZ

Sponsor: Roxane Laboratories, Inc.

Principal Investigator: N/A

Drug Name: Roxicodone tablets []([]
[] 15 and 30 mg oxycodone tablets USP)

Type of Submission: Response to AE Letter

Proposed Indication: Management of moderate to severe pain where use of an opioid analgesic is appropriate.

Reviewer: Harold Blatt, D.D.S.

Team Leader: Bob Rappaport, M.D.

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TABLE OF CONTENTS

SECTION 1.0 MATERIALS UTILIZED IN REVIEW:.....	4
SECTION 2.0 BACKGROUND:	4
SECTION 2.1 INDICATION:.....	4
SECTION 2.2 RELATED INDs AND NDAs:	4
SECTION 2.3 ADMINISTRATIVE HISTORY.....	4
SECTION 2.4 PROPOSED DIRECTIONS FOR USE:.....	6
SECTION 2.5 FOREIGN MARKETING:	8
SECTION 3.0 CHEMISTRY:	8
SECTION 4.0 ANIMAL PHARMACOLOGY/TOXICOLOGY:	9
SECTION 5.0 DESCRIPTION OF CLINICAL DATA SOURCES:.....	11
SECTION 5.1 PRIMARY SOURCE DATA:.....	11
SECTION 5.2 STUDY TYPE AND DESIGN/PATIENT ENUMERATION:	11
SECTION 5.3 DEMOGRAPHICS:.....	11
SECTION 5.4 EXTENT OF EXPOSURE:	17
SECTION 6.0 SUMMARY OF HUMAN PHARMACOKINETICS:.....	19
SECTION 7.0 EFFICACY FINDINGS.....	19
SECTION 7.1 RATIONALE FOR OXYCODONE HIGHER DOSES.....	19
SECTION 7.2 OVERVIEW OF CLINICAL STUDIES:.....	20
SECTION 7.3 SUMMARY OF STUDY PERTINENT TO EFFICACY:	20
SECTION 7.3.1 STUDY XIR0299.....	20
SECTION 8.0 SAFETY FINDINGS:.....	24
SECTION 8.1 METHODS:.....	24

SECTION 8.2 SERIOUS ADVERSE EVENTS:.....	25
SECTION 8.2.1 DEATHS:.....	26
SECTION 8.2.2 NON-FATAL SERIOUS ADVERSE EVENTS:.....	28
SECTION 8.3 ASSESSMENT OF DROPOUTS	29
SECTION 8.4 OTHER ADVERSE EVENTS:.....	30
SECTION 8.4.1 ADVERSE EVENTS BY GENDER:.....	32
SECTION 8.4.2 ADVERSE EVENTS BY AGE:.....	32
SECTION 8.4.3 ADVERSE EVENTS BY RACE:	33
SECTION 8.4.4 ADVERSE EVENTS BY ETIOLOGY OF PAIN	33
SECTION 8.4.4 POSTMARKETING EXPERIENCE:	34
SECTION 8.5 OTHER SAFETY FINDINGS:.....	37
SECTION 8.5.1 CLINICAL LABORATORY EVALUATIONS:.....	37
SECTION 8.5.2 VITAL SIGNS:.....	40
SECTION 8.5.3 SUPPORTIVE SAFETY STUDIES FROM THE LITERATURE ON SAFETY OF DOSES GREATER THAN 60MG:.....	40
SECTION 8.6 DRUG-DRUG INTERACTIONS:.....	42
SECTION 9.0 LABELING REVIEW:	43
SECTION 10.0 CONCLUSIONS:.....	43
SECTION 11.0 RECOMMENDATION.....	43

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SECTION 1.0 MATERIALS UTILIZED IN REVIEW:

Reviewer's Table 1.

Volume	Submission Date	Material
1.1	2-28-00	Index, Labeling, and Summary
1.8-1.9	2-28-00	Copies of Selected Publications
1.10	2-28-00	Integrated Summary of Efficacy
1.11-1.12	2-28-00	Integrated Summary of Safety

SECTION 2.0 BACKGROUND:**SECTION 2.1 INDICATION:**

Management of moderate to severe pain where use of an opioid analgesic is appropriate.

SECTION 2.2 RELATED INDs AND NDAs:

IND 46,618, IND 40,071, NDA 20-932

SECTION 2.3 ADMINISTRATIVE HISTORY

On September 23, 1999, the Agency issued an AE letter to the sponsor for Roxycodone IR 15 and 30 mg tablets. The Agency noted 4 clinical deficiencies and methods for correcting them. In addition, a meeting was held with the sponsor on December 15,

1999, and a teleconference on February 11, 2000. The sponsor has responded to our corrections in this submission. What follows is a brief summary of the deficiencies, corrections and sponsor's responses:

Clinical Efficacy issues

Issue No. 1 "There are no data submitted in support of the effectiveness of immediate release 15 and 30 mg oxycodone in this application. There is also no link to any product for which the FDA has made the findings of efficacy." FDA Correction No. 1 "*A bridging study or studies will be required from which the Agency can link its prior findings of efficacy for immediate release oxycodone to your product, seeking approval. Such a bridging study is generally a biopharmaceutical study demonstrating relative bioavailability to the reference listed product.*" **Issue No. 2** "There is no request for a waiver of such studies and no justification provided for the claim that clinical studies are not needed." FDA Correction No. 2 "*An adequate rationale will be required for the extension of the dosage form to 15 and 30 mg without having provided clinical studies demonstrating efficacy at higher doses.*" Sponsor's response:

- the sponsor will establish the need for higher doses of oxycodone and the rationale for the extension of the dosage form to 15- and 30-mg oxycodone tablets
- establishing a link to Percodan®, for which the FDA (through the DESI review) has made a determination of efficacy. This has been accomplished through a biopharmaceutics study (XIR0299) comparing the bioavailability of the Roxane 15-mg-IR oxycodone tablet formulation to three 5-mg Percodan® tablets
- summarizing data from the literature that support the effectiveness of oxycodone IR (including effectiveness data for oxycodone and other opioids).
- providing (in an ISE) supportive efficacy data from two uncontrolled Phase II clinical studies (XIR0596 and XIR0696) and dose-response data from one biopharmaceutics study using a cold pressor model of pain.

Clinical Safety Issues

Issue No. 3 "Clinical safety in the higher doses has not been adequately established with the database submitted. There is also no link to any product for which the FDA has made the findings of safety in higher doses. There may be adequate safety data for oxycodone 15 and 30 mg that you can bring to bear on this application. This may include data that you have developed. However, if these data are derived from studies on products other than that to which you have linked your application for purposes of establishing efficacy, an additional biopharmaceutical link must be provided." FDA Correction No. 3

"Information establishing safety at higher doses or a bridging study or studies will be required from which the Agency can link its prior, finding of safety for lower doses of oxycodone to the proposed higher doses of oxycodone. Such a bridging study will likely be a biopharmaceutical study demonstrating relative bioavailability to an approved oxycodone product. New, clinical safety data using the immediate release (IR) Oxycodone 15 and 30 mg would also be acceptable." **Issue No. 4** "The safety database as presented, correlating adverse events by tablet size rather than dose does not provide appropriate information about adverse events from which labeling can be written."

FDA Correction No. 4 *"Retabulation of all adverse events reported in clinical trials by total daily dose is required. The adverse events in the safety tables of this NDA should include only the IR formulation."* Sponsor's response:

- revising and re-submitting the Integrated Summary of Safety information by
- total daily dose (<60 mg, 60 to <120 mg, and \geq 120 mg) to provide the clinical evidence of the safety of oxycodone IR. **Note: the revised ISS only includes safety information from the immediate-release product and does not include safety information from the sustained release product.**
- comparing the safety of oxycodone to Percodan®, for which the FDA has made findings of safety, through a biopharmaceutics study (XIR0299) designed to compare the bioavailability of the Roxane 15-mg IR oxycodone tablet formulation to three 5-mg Percodan® tablets.
- additionally, supportive safety data from the literature at total daily doses greater than 60 mg will be summarized.

SECTION 2.4 PROPOSED DIRECTIONS FOR USE:

"DOSAGE AND ADMINISTRATION"

"ROXICODONE™ is intended for the management of moderate to severe pain in

patients who require treatment with an oral opioid analgesic. The dose should be individually adjusted according to severity of pain, patient response and patient size. If the pain increases in severity, — if analgesia is not adequate or tolerance occurs, a gradual increase in dosage may be required.

“Patients who have not been receiving opioid analgesics should be started on ROXICODONE™ in a dosing range of 5 to 15 mg every 4 to 6 hours as needed for pain. The dose should be titrated based upon the individual patient's response to their initial dose of ROXICODONE™. Patients with chronic pain should have their dosage given on an around the-clock basis to prevent the reoccurrence of pain rather than treating the pain after it has occurred.”

“For control of severe chronic pain, ROXICODONE™ should be administered on a regularly scheduled basis, every 4-6 hours, at the lowest dosage level that will achieve adequate analgesia.

“As with any potent opioid, it is critical to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. Although it is not possible to list every condition that is important to the selection of the initial dose of ROXICODONE™ attention should be given to: 1) the daily dose, potency, and characteristics of a pure agonist or mixed agonist/antagonist the patient has been taking previously, 2) the reliability of the relative potency estimate to calculate the dose of oxycodone needed, 3) the degree of opioid tolerance, 4) the general condition and medical status of the patient, and 5) the balance between pain control and adverse experiences.”

[Taken from sponsor's Vol. 14.1, pp. 36-37.]

In addition, there are several sections discussing specific uses as follows:

- Conversion from Fixed-Ratio Opioid/Acetaminophen, Aspirin, or Non-Steroidal Combination Drugs.
- Patients Currently on Opioid Therapy
- Maintenance of Therapy

- Cessation of Therapy

SECTION 2.5 FOREIGN MARKETING:

Oxycodone IR 15 and 30 mg has never been marketed in any country. Since the early 1980s Roxicodone HCl has been available in 5mg tablets, 5mg/5ml solution, and 20mg/ml concentrated solution (Roxicodone Intensol). In 1998, NDA 20-932 was approved for Oxycodone Sustained Release in 10 and 30 mg strengths.

SECTION 3.0 CHEMISTRY:

ROXICODONE™ (oxycodone hydrochloride tablet USP) is an opioid analgesic.¹

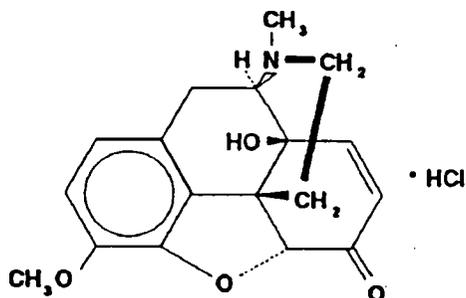
Each tablet for oral administration contains:

Oxycodone hydrochloride USP15 mg, 30 mg in a formulation that provides for immediate release of the medication.²

Oxycodone hydrochloride is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL) and is considered slightly soluble in alcohol (octanol water partition coefficient is 0.7).³

Chemically, oxycodone hydrochloride is 4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride and has the following structural formula:⁴

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MW 351.83

Each ROXICODONE™ tablet contains 15 mg or 30 mg of oxycodone hydrochloride, USP. Inactive ingredients include: microcrystalline cellulose; sodium starch glycolate; corn starch; lactose; stearic acid; D&C Yellow No. 10 (15 mg tablet); and FD&C Blue No. 2 (15 mg and 30 mg tablets).⁵

The 15 mg and 30 mg tablets contain an equivalent amount of 13.5 mg and 27.0 mg, respectively of oxycodone free base.⁶

On May 24, 2000 a teleconference was held with the sponsor. At that time the Office of New Drug Chemistry 2 requested clarification on the drug product and its impurities. Please see Chemistry review for a more complete discussion of this issue.

SECTION 4.0 ANIMAL PHARMACOLOGY/TOXICOLOGY:

Oxycodone is an opioid agonist similar to morphine with both analgesic and antitussive activity. Oxycodone binds to mu opioid receptors in rats with weak affinity. Its metabolites, noroxycodone and morphine may be responsible for much of its activity.

Oxycodone had 3-6X the antinociceptive effect of morphine sulfate in the rodents and is a more potent antitussive agent than codeine. Oxycodone was more potent than morphine in causing CNS depression in rats. In mice, oxycodone and morphine increased spontaneous motor activity, caused Straub tail response, increased palpebral opening, decreased food intake, caused delayed hyperthermia, and inhibited GI motility. It can cause a morphine type of drug dependence, tolerance can develop, and it has abuse potential. Oral administration of oxycodone to beagle dogs produced effects on behavior and the cardiovascular system. A dose of 3 mg/kg caused a significant increase in systolic blood pressure accompanied by increased pulse pressure. A dose of 10 mg/kg, like morphine, produced slight sedation and a transient inhibition of respiratory movement during the sleep stage. A 30 mg/kg dose caused both significant relaxation and decreases in the awake stage, a decrease in body temperature and heart rate, but unlike morphine, no nausea or vomiting.

The sponsor submitted data on developmental and reproductive toxicity potentials of orally administered oxycodone in rats and rabbits according to standard protocols for Segment II reproductive toxicity. Results suggested that oxycodone is not a teratogen. In the rat segment II study, oxycodone was administered orally to female rats during gestation days 6-18 at doses of 1.0, 4.0, and 6.0 mg/kg/day. No teratogenic effects in the offspring were observed; however, some maternal toxicity was noted. Oxycodone-induced clinical signs (i.e., repetitive chewing, decreased motor activity, bradypnea, lacrimation and soft or liquid feces) in the high dose group (6.0 mg/kg/day) and the rate of body weight gain was reduced occurred in all treatment groups. A decrease in fetal body weight was observed in the 16.0 mg/kg/day treatment group.

In the rabbit Segment II study, oxycodone (1.0, 5.0, and 25.0 mg/kg/day) administered orally to pregnant female rabbits during critical time of gestation caused no teratogenic effects. Oxycodone at 25.0 mg/kg/day produced some maternal toxicity; and the rate of body weight gain was significantly reduced during the dosing period. [From discussion with Pharm/Tox reviewer.]

The sponsor provided protocols for mutagenicity studies for *Salmonella typhimurium* – *E. coli*/ mammalian –microsome reverse mutation mouse lymphoma forward mutation, and in vivo mouse micronucleus assays in March 2000. These protocols were received and approved by the Agency.

Pharm/Tox review for a more complete discussion of all these issues. [Vol. 1.1, p.3.]

SECTION 5.0 DESCRIPTION OF CLINICAL DATA SOURCES:

See Section 5.2

SECTION 5.1 PRIMARY SOURCE DATA:

See Section 5.2

SECTION 5.2 STUDY TYPE AND DESIGN/PATIENT ENUMERATION:

This NDA current submission contains only one new study with data not previously seen in the original NDA submission. Study XIR0299 (315-23) is a single dose, randomized, open label, two-way crossover bioequivalence study in 26 subjects that attempts to link the referenced drug Percodan to the study drug. This study was done in response to the Division's issues 1 and 3 in the Approvable Letter of September 23, 1999 (see Section 2.3) that stated a bridging study would be required demonstrating relative bioavailability to a reference listed product. [Vol. 7.7, pp. 20, 92.]

SECTION 5.3 DEMOGRAPHICS:

In this submission the sponsor has provided, in separate tables, the pooled demographic characteristics of the patients in Phase II/III studies (studies XIR0596, CBI-961/962, and CBI-963), the extension study XIR0696, and PK and bioavailability studies. The pooled data are presented in two tables. The first table is for the stabilization period and the second is for the treatment period. These data have been organized by the total daily dose (TDD).

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Table 1

Demographic and Other Baseline Characteristics - Stabilization Period

Characteristic	<60 mg (N=210)	60-120 mg (N=150)	≥120 mg (N=93)	Overall (N=453)
Age (years)				
N	210	150	93	453
Mean (±SD)	56 (± 15)	51 (± 13)	46 (± 13)	52 (± 14)
Range	24-94	24-88	24-79	24-94
Gender				
Male	68 (32%)	75 (50%)	51 (55%)	194 (43%)
Female	142 (68%)	75 (50%)	42 (45%)	259 (57%)
Race				
Caucasian ^a	189 (90%)	138 (92%)	88 (95%)	415 (92%)
Black	19 (9%)	10 (7%)	5 (5%)	34 (8%)
Other ^b	2 (1%)	2 (1%)	0 (0%)	4 (1%)
Weight (kg)				
N	204	146	91	441
Mean (±SD)	77 (± 23)	78 (± 22)	81 (± 19)	78 (± 21)
Range	34-159	40-163	37-131	34-163
Etiology of Pain				
Chronic malignant pain	40 (19%)	38 (25%)	26 (28%)	104 (23%)
Chronic non-malignant pain	170 (81%)	112 (75%)	67 (72%)	349 (77%)
Rescue Medication				
Pts. who required rescue med.	153 (73%)	112 (75%)	75 (81%)	340 (75%)
Average rescue dose/day (mg)	9 mg	16 mg	34 mg	17 mg
Range	5-25 mg	5-55 mg	5-97 mg	5-97 mg
Average no. of doses/day	1.53	1.96	2.66	1.92 doses
Range	1-4	1-5	1-7	1-7 doses

^a Includes Hispanic

^b Includes Native American, Asian, and Other

Studies pooled: XIR0596, CBI-961/962, and CBI-963

[Taken from sponsor's Table G, Vol. 1.11, p.31, Data source: Sponsor's Tables 4.1.1 and 4.2.1.]

Although not shown in the table above, the overall mean TDD taken by patients during the stabilization period was 83 mg/day (median = 60 mg/day) and the average TDD ranged from 20 to 680 mg/day. The highest overall average TDD was reported by a patient in the 5-mg treatment group and was 680 mg/day (a total of 136 5-mg tablets per day). The highest TDD on any given day was 760 mg. The mean TDD included all scheduled and rescue doses of study medication. [Sponsor's Tables D and 3.2.1 in Appendix F.]

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Table 2

Demographic and Other Baseline Characteristics - Treatment Period				
Characteristic	<60 mg (N=52)	60-<120 mg (N=85)	≥120 mg (N=54)	Overall (N=191) ^c
Age (years)				
N	52	85	54	191
Mean (±SD)	55 (± 15)	50 (± 13)	46 (± 14)	50 (± 14)
Range	32-86	26-81	24-74	24-86
Gender				
Male	21 (40%)	38 (45%)	31 (57%)	90 (47%)
Female	31 (60%)	47 (55%)	23 (43%)	101 (53%)
Race				
Caucasian ^a	47 (90%)	79 (93%)	50 (93%)	176 (92%)
Black	4 (8%)	5 (6%)	4 (7%)	13 (7%)
Other ^b	1 (2%)	1 (1%)	0 (0%)	2 (1%)
Weight (kg)				
N	51	85	52	188
Mean (±SD)	78 (± 21)	80 (± 19)	77 (± 19)	79 (± 19)
Range	43-125	47-159	40-127	40-159
Etiology of Pain				
Chronic Malignant Pain	16 (31%)	25 (29%)	18 (33%)	59 (31%)
Chronic Non-Malignant Pain	36 (69%)	60 (71%)	36 (67%)	132 (69%)
Rescue Medication				
Pts. who required rescue med.	40 (77%)	70 (82%)	47 (87%)	157 (82%)
Average rescue dose/day (mg)	8 mg	15 mg	38 mg	20 mg
Range	5-20 mg	5-35 mg	9-250 mg	5-250 mg
Average no. of doses/day	1.50 doses	1.90 doses	2.31 doses	1.92 doses
Range	1-3 doses	1-4 doses	1-7 doses	1-7 doses

^a Includes Hispanic

^b Includes Native American, Asian, and Others

^c 194 patients were exposed, but only 191 had TDD data

Studies pooled: XIR0596, CBI-961/962, and CBI-1252

[Taken from sponsor's Table H, Vol. 1.11, p.32, Data source: sponsor's Tables 4.1.2 and 4.2.2]

Although not shown in the table above, the overall average TDD taken by patients during the treatment period was 110 mg/day (median = 74 mg/day) and the range of the average

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TDD was 9-859 mg/day. The overall minimum and maximum TDD taken on a given day were 9 and 870 mg/day, respectively. The mean TDD included all scheduled and rescue doses of study medication. [Sponsor's Tables E and 3.2.2 in Appendix F.]

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Table 3 Extension Study XIR0696

Demographic and Baseline Characteristics - Study XIR0696

Characteristic	<60 mg (N=7)	60-<120 mg (N=13)	≥120 mg (N=28)	Overall (N=48 ^a)
Age (years)				
N	7	13	28	48
Mean (SD)	52 (± 11)	56 (± 15)	40 (± 11)	46 (± 14)
Range	42-68	31-79	24-67	24-79
Gender				
Male	3(43%)	5(39%)	20(71%)	28 (58%)
Female	4(57%)	8(62%)	8(29%)	20 (42%)
Race				
Caucasian ^b	6(86%)	12(92%)	28(100%)	46 (96%)
Black	0(0%)	1(8%)	0(0%)	1 (2%)
Other ^b	1(14%)	0(0%)	0(0%)	1 (2%)
Weight (kg)				
N	7	13	28	48
Mean (SD)	71 (± 16)	83 (± 18)	83 (± 17)	81 (± 17)
Range	47-94	58-109	47-132	47-132
Etiology of Pain				
Chronic Malignant Pain	3(43%)	3(23%)	1(4%)	7 (15%)
Chronic Non-Malignant Pain	4(57%)	10(77%)	27(96%)	41 (85%)

^a Includes Hispanic

^b Includes Native American, Asian, and Other

^c 50 patients were exposed to drug, but only 48 provided daily dosage information. 48 is used as the denominator in this table.

Study XIR0696

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[Taken from sponsor's Table I, Vol. 1.11, p.34, Data source: Sponsor's Tables 4.1.3 and 4.2.3]

Although not shown in this table, the overall average TDD taken by patients during the extension study was approximately 137 mg/day and ranged from 134-141 mg/day. Since Study XIR0696 measured weekly use, the daily TDD is computed based on weekly consumption of drug. The average TDD included scheduled and rescue doses of the study medication. [Sponsor's Table 6.2 in XIR0696 Study Report.]

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Table 4 PK and Bioavailability Studies

Demographic Characteristics - Human Pharmacokinetics and Bioavailability Studies

Characteristics	315-05 (N=26)	315-07 (N=26)	XIR0296 (N=27)	XIR0396 (N=20)	XIR0196 (N=28)
Age (years)					
Mean (\pm SD)	33 \pm 10	32 \pm 10.98	29 \pm 1	29 \pm 2	26 \pm 1
Range	19-51	19-53	20-45	19-45	19-37
Gender					
Male	26 (100%)	26 (100%)	15 (55.6%)	10 (50%)	10 (35.7%)
Female	0	0	12 (44.4%)	10 (50%)	18 (64.3%)
Race					
White	25 (92%)	24 (92%)	21 (78%)	13 (65%)	24 (86%)
Black	0	0	2 (7%)	2 (10%)	1 (4%)
Hispanic	1 (4%)	2 (8%)	4 (15%)	4 (20%)	3 (11%)
Asian	0	0	0	1 (5%)	0
Weight (lb.)					
Mean (\pm SD)	174.5 \pm 24.90	176.9 \pm 21.38	152.2 \pm 4.05*	156.3 \pm 5.77*	141.4 \pm 3.94*
Range	125.0 - 217.0	132 - 216	118.5 - 191.5	102.5 - 199.5	100.5 - 183.5

Studies pooled: 315-05, 315-07, XIR0296, XIR0396, and XIR0196

[Taken from sponsor's Table J, Vol. 1.11, p.35, Data source: Sponsor's individual study reports and Appendix D.]

The mean age of subjects in the PK studies ranged from 26 to 33 years with an overall range of 19 to 53 years. Studies 315-05 and 315-07 enrolled only male subjects. The number of male and female subjects were similar for studies XIR0296 and XIR0396, but XIR0196 enrolled a larger number of female (18/28; 64%) subjects than male (10/28; 36%) subjects. The majority (24/28; 86%) of subjects were Caucasian. The average weight among patients in the two studies that only enrolled male subjects (315-05 and 315-07) was slightly higher than the three studies that enrolled both male and female subjects (XIR0196, XIR0296, and XIR0396). [Vol. 1.11, p.35.]

SECTION 5.4 EXTENT OF EXPOSURE:

A total of 662 subjects and patients were exposed to 5, 15, and 30 mg tablets and the oral solutions (124 from Phase I trials and 538 from Phase II/III trials).

[Vol. 1.11, pp. 11, 15-16, 18, 21]

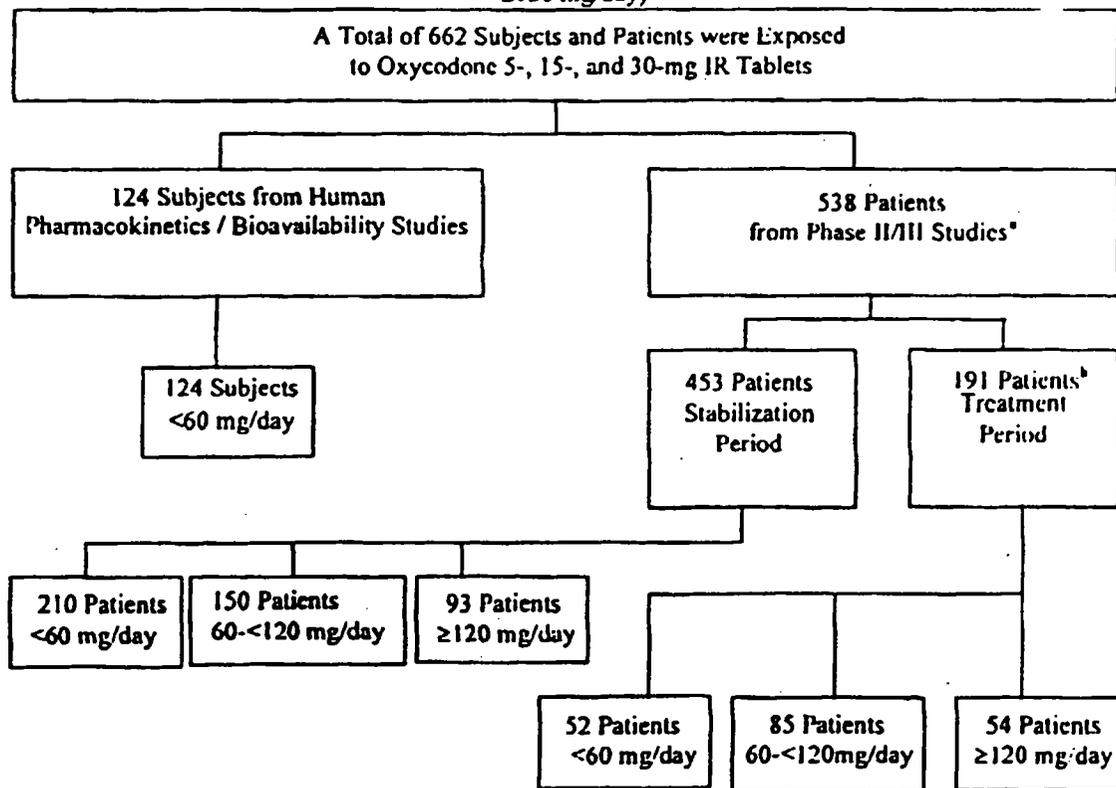
On the following page is a chart representing the number of patients exposed to different TDDs:

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Chart A

Number of Subjects and Patients Exposed to Oxycodone HCl (<60 mg/day, 60 to <120 mg/day, and ≥120 mg/day)



* The number of patients in the stabilization period and the treatment period can not be added to determine the total number of patients exposed during the Phase II/III studies, since patients exposed during the treatment period of studies XIR0596 and CBI-961/962 are a subset of the patients exposed during the stabilization period.
 † 194 patients were actually exposed to Oxycodone IR, but only 191 provided complete TDD records.

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[Taken from sponsor's Figure B, Vol. 1.11, p.14.]

SECTION 6.0 SUMMARY OF HUMAN PHARMACOKINETICS:

See SECTION 7.2.1 of this review.

SECTION 7.0 EFFICACY FINDINGS

SECTION 7.1 RATIONALE FOR OXYCODONE HIGHER DOSES

The sponsor notes that the literature provides documentation of both the need for and documented use of oxycodone in higher doses. As far as documented need is concerned, the sponsor gives the following information from the literature: In controlled studies in cancer patients, total daily doses (TDD) of oral morphine needed to control moderate-to-severe pain averaged 100 mg - 300 mg, though an individual's TDD could exceed 1000 mg.

The sponsor makes the argument that oxycodone in higher dose forms would be useful in opioid rotation, or switching a patient from one strong opioid to another if there is inadequate pain relief or intolerable side effects. Although a 1:1 oral morphine to oral oxycodone conversion ratio is suggested in various guidelines for patients on stable doses, titration may still be necessary. Since oxycodone is a pure opioid agonist (i.e., no ceiling effect), physicians are able to titrate doses without dose limiting side effects as a patient's disease state progresses.

A problem with the current 5mg immediate-release (IR) tablet is that it would require a many tablets to provide the higher doses needed after titration. For example, in a study in cancer patients, after titration, the TDD of oxycodone IR required to relieve moderate-to-severe pain averaged 127 mg/day with the upper range at 640 mg/day. The availability of higher dosage strengths would decrease the number of tablets taken at each dose administration making dose titration easier, and would increase convenience for patients and caregivers.

With regard to documented use of oxycodone, the sponsor makes the following observations: While the overall opioid class has experienced moderate growth (non-injectable morphine had a 2-fold increase in prescriptions), oxycodone has experienced a 220-fold increase in single-entity prescriptions. With this increase in prescriptions is a trend towards higher doses. Today, the oxycodone market exceeds the morphine market by over 1.8 million prescriptions a year. The sponsor feels this indicates that physicians rely more on oxycodone for pain management. Today, the average dose and duration of oxycodone are 64 mg/day and 22 days, respectively compared to 34 mg/day and 15 days, respectively in 1991. By comparison, today's average dose and duration of morphine are 144mg/day and 20 days, respectively, in contrast to 1991 when the average dose and duration were 112mg/day and 22 days, respectively. However, it is more difficult to determine high strength oxycodone use compared to morphine based on the limitations of the database and the available dosage strengths. The sponsor feels that the use of higher doses of oxycodone has been underestimated and could actually exceed the prescriptions written.

[Vol. 1.7, pp. 14-18.]

SECTION 7.2 OVERVIEW OF CLINICAL STUDIES:

In response to the two clinical efficacy issues raised in the AE letter of September 23, 1999 (see Section 2.3), the sponsor has provided a bioequivalence Study (XIR0299) to provide a link between 3x5 mg of Percodan (the established drug) and 15 mg IR of oxycodone and provided a rationale for the extension to higher doses of 15 and 30 mg of oxycodone as well as a summary of supportive literature data and ISE supportive data from 2 uncontrolled Phase II studies and dose response data from a Biopharm study. The previous medical officer in his review for the original submission has already reviewed these 3 supportive studies and will not be re-reviewed at this time. The Biopharm reviewer will provide an in-depth review of Study XIR 0299 but this reviewer will review Study XIR0299 for safety and the sponsor's rationale for extension to the higher doses.

SECTION 7.3 SUMMARY OF STUDY PERTINENT TO EFFICACY:

See SECTION 7.3.1

SECTION 7.3.1 STUDY XIR0299

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Protocol Synopsis: This is a single dose, randomized, open label, two way crossover study to assess the bioavailability of oxycodone HCl IR 15 mg tablet (Treatment A) compared to a 3 tablet dose of oxycodone/aspirin (Treatment B) in 26 healthy male and female volunteers (13/13). The average age was 37 and ranged from 18-55. The Biopharm reviewer agreed with the sponsor's conclusion that the two treatments were bioequivalent with respect to oxycodone. For a more complete discussion and analysis of the results of this study, please see Biopharm review. A summary of PK results are listed in the Table below:

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Table 5

Study No.	No. of Subjects	Route	Dose (mg)	Dose Form	AUC ₍₀₋₄₎ (ng*h/mL)	AUC _(0-INF) (ng*h/mL)	C _{max} (ng/mL)	T _{max} (h)	k _e (1/h)	t _{1/2}
XIR0299	26*	Oral	A) 1x15mg oxycodone HCl IR	Tablet	146.1± 33.02	148.9± 35.55	22.08± 6.43	1.49±0 .975	0.184±0 .0305	3.86± 0.615
			B) 1x 4.50 oxycodone HCl/0.38mg oxycodone terephthalate/325mg aspirin (Percodan® Tablets)		144.3± 33.40	148.1± 33.28	20.93± 4.74	1.64± 1.51	0.189± 0.0310	3.76± 0.588

*Subjects 3, 5, 6, and 19 were excluded from Treatment A because of vomiting. subjects 22 and 26 were excluded from Treatment B, and subjects 23 and 24 were excluded from Treatments A and B.

[Vol. 1.6, pp. 1-2.]

After analysis of the data, the Biopharm reviewer concluded that the 90% confidence intervals for the parameters of AUC_t, AUC_{INF}, and C_{max} were all within the bioequivalency criteria of 80-125% and therefore the 15mg oxycodone IR tablet was bioequivalent to 3 tablets of Percodan® (reference drug) for oxycodone. For a more complete discussion of Study XIR0299, please see Biopharm review.

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SECTION 8.0 SAFETY FINDINGS:

In response to the two safety issues raised in the AE Letter of September 23, 1999 (see Section 2.3), the sponsor has provided a comparison of the safety of oxycodone to Percodan in the Biopharmaceutics Study XIR0299, a revised and retabulated ISS by total daily dose (TDD) that only contains safety information on the immediate release formulation, and a summary of supportive literature safety data on doses greater than 60mg.

SECTION 8.1 METHODS:

Study XIR0299 is a single dose, randomized, open label, two-way crossover study that was designed to show a bioequivalent link between 3 Percodan 5mg tablets and one 15mg oxycodone IR tablet. There were no serious or severe adverse events (AEs) and no subject discontinued due to AEs. Twenty subjects (20/26, 76.9%) reported a total of 93 AEs. The events with the highest incidence were those generally associated with opioid use and included lightheadedness (12/26, 46.2%), nausea (10/26, 38.5%), and vomiting (9/26, 34.6%). Seventeen subjects (17/25, 68.0%) reported 59 AEs after receiving the 15-mg oxycodone IR tablet, while 16 subjects (16/26, 61.5%) reported 34 AEs after receiving the three-tablet dose of Percodan®. Nearly all (91/93, 97.8%) AEs were considered to have a possible, probable, or almost certain relationship to treatment, but 92/93 or 98.9% were considered mild and all resolved by study exit (NDA Amendment Section 6.8.1).

Please see Addendum 1 to this review for a Summary Table of AEs for PK Study XIR 0299.

In support of XIR0299, the sponsor also conducted 2 in vitro dissolution studies. Technical Report No. 0966-028 compares the dissolution profiles of Roxicodone IR and Percodan®. The sponsor concluded that the results indicate Percodan® and Roxicodone™ 15- and 30-mg tablets meet an appropriate in vitro bioequivalence standard and therefore the availability of oxycodone in Roxicodone™ and Percodan® are equivalent. [Vol. 1.7, p.92.]

According to the sponsor, the revised and reformatted ISS has been submitted to address Issue #4 in the AE Letter of September 23, 1999. That is, by presenting the AEs by Total Daily Dose (TDD) and by utilizing data on the IR formulation only. The sponsor also states that the primary focus of the ISS is to show the safety profiles of the

15 and 30mg IR-tablets as they relate to TDD. The sponsor has pooled this safety data from 10 completed studies. Five studies were Phase I PK and bioavailability studies (315-05, 315-07, XIR0396, XIR0296, and XIR0196) and were done on healthy, opioid naïve volunteers following acute dosing. Five studies were Phase II/III studies. Two of these Phase II/III studies were open label safety trials. XIR0596 was a 7-day trial in patients with moderate to severe pain and XIR0696 was a 30 day extension trial. Because XIR0696 is an extension study with the same exposure data as XIR0596, these data are not included as additional patients in the ISS. Trials CBI-961/962, CBI-963, and CBI-1252 were Phase II/III studies that contained data on IR and SR formulations. Only data from the 5mg IR formulation were included in this new, revised ISS.

SECTION 8.2 SERIOUS ADVERSE EVENTS:

The number of subjects and patients who died, or experienced serious adverse events (SAEs) resulting in discontinuation is summarized below:

Table 6

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Number (%) of Patients who Died, had Serious Adverse Events, or had Adverse Events Resulting in Discontinuation

Category	Oxycodone TDD Group			All Treatments
	<60 mg/day	60- <120 mg/day	≥120 mg/day	
Deaths				
Human PK and BA Studies	0/124 (0%)	N/A	N/A	0/124 (0%)
Clinical Safety Studies				
Stabilization Period	0/210 (0%)	0/150 (0%)	0/93 (0%)	0/453 (0%)
Treatment Period	1/52 (2%)	0/85 (0%)	0/54 (0%)	1/191 (<1%)
Extension Study (XIR0696)	1/7 (14%)	0/13 (0%)	0/28 (0%)	1/48 (2%)
Total	2	0	0	2
Serious Adverse Events				
Human PK and BA Studies	0/124 (0%)	N/A	N/A	0/124 (0%)
Clinical Safety Studies				
Stabilization Period	0/210 (0%)	2/150 (1%)	0/93 (0%)	2/453 (<1%)
Treatment Period	3/52 (6%)	1/85 (1%)	0/54 (0%)	4/191 (2%)
Extension Study (XIR0696)	1/7 (14%)	1/13 (8%)	0/28 (0%)	2/48 (4%)
Total	4	4	0	8
Adverse Events Resulting in Discontinuation				
Human PK and BA Studies	6/124 (5%)	N/A	N/A	6/124 (5%)
Clinical Safety Studies				
Stabilization Period	13/210 (6%)	28/150 (19%)	8/93 (9%)	49/453 (11%)
Treatment Period	2/52 (4%)	1/85 (1%)	2/54 (4%)	5/191 (3%)
Extension Study (XIR0696)	1/7 (14%)	1/13 (8%)	1/28 (4%)	3/48 (6%)
Total	22	30	11	63

Note: The percentage of patients are not reported in the totals because of the overlap in exposure (i.e., the patients enrolled in the treatment periods of studies XIR0596 and CBI-961/962 were also exposed to the study medication during the stabilization periods)

Studies Pooled: Pharmacokinetic Studies- 315-05, 315-07, XIR0396, XIR0296, XIR0196 and Clinical Safety Studies- XIR0596, XIR0696, CBI-961/962, CBI-1252, CBI-963

[Taken from sponsor's Table AA, Vol. 1.11, p.77; data source sponsor's Tables 7.1.1, 7.1.2, 7.2.1, 7.2.2, 7.3.1, 7.3.2]

SECTION 8.2.1 DEATHS:

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Table 7

Patient Deaths Reported During the Clinical Studies								
Study No. Period.	Site No. /Patient No.	Age (yr.)	Gender	Tablet Group	Average TDD (mg/day)	COSTART Term	Exposure (days)	Relation to Study Drug
XIR0596 Treatment	04/0403	80	Male	30 mg	52 mg/day	Heart failure	15 days	Unlikely
XIR0696 Extension	15/1501	54	Male	15 mg	60 mg/day	Aspiration pneumonia	26 days	Not related

[Taken from sponsor's Table BB, Vol. 1.11, p.78; data source sponsor's Table 7.3.2]

There were a total of three deaths. One death was not reported in the data and is described as follows: Patient 9612020002, a 46-year-old female patient who entered Study CBI 961/962 stabilization period on 3/16/96 left the stabilization period on 3/20/96. On 3/18/96, during the stabilization period, the patient experienced confusion, which was reported as an AE and also sepsis, apparently subsequent to a cat bite. The investigator recorded this event as an SAE not related to drug. This AE and SAE are recorded in this ISS. On 3/19/96, the patient experienced two AEs: leukopenia and hypercalcemia. These events are also recorded in this ISS. On 3/20/96, the patient completed the stabilization period of the study, as noted above. On 3/21/96, the patient experienced an SAE related to breast cancer. She died on 3/26/96. The sponsor notes that since the onset of the SAE leading to death was after completion of the stabilization period and prior to the treatment period, this patient did not die while enrolled in the study and her death was removed from the tables in the revised ISS. The two reported deaths included in the ISS were as follows: One occurred during the treatment period (Study XIR0596; Patient 0403), and one occurred during the extension study (Study XIR0696; Patient 1501). All patients died from complications associated with their underlying disease. Patient 0403 (Study XIR0596) died from heart failure, because of progression of lung cancer, during the treatment period. Patient 1501 (Study XIR0696) discontinued the study after discovery that this patient's gastrointestinal carcinoma had metastasized, the patient died later the same day from pneumonia caused by aspiration. None of these deaths was considered by the investigators to be related to the study medication. [Vol. 1.11, p.78].

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SECTION 8.2.2 NON-FATAL SERIOUS ADVERSE EVENTS:

Table 8

Serious Adverse Events Reported During the Clinical Studies

Study No. / Patient No.	Site No. / Patient No.	Age (yr.)	Gender	IR Tablet Group	Average TDD (mg/day)	COSTART Term and SAE Classification	Relation to Study Drug
961/962 Stabilization	02/0002	46	Female	5 mg	60 mg/day	Sepsis due to cat bite resulting in hospitalization	Not related
961/962 Stabilization	09/0006	54	Male	5 mg	60 mg/day	Worsening of GI carcinoma; and Confusion resulting in prolonged hospitalization	Unlikely Possibly
XIR0596 Treatment	04/0403	80	Male	30 mg	52 mg/day	Heart failure resulting in death	Unlikely
XIR0596 Treatment	14/1405	41	Female	15 mg	55 mg/day	Confusion and personality disorder, the signs and symptoms of an overdose	Related
CBI-961/962 Treatment	02/0015	70	Female	5 mg	73 mg/day	Sepsis resulting in hospitalization	Not related
CBI-961/962 Treatment	11/0001	75	Female	5 mg	55 mg/day	Pathological fracture resulting in hospitalization	Not related
XIR0696 Extension	09/0905	57	Female	15 mg	60 mg/day	Pneumonia resulting in prolonged hospitalization	Not related
XIR0696 Extension	15/1501	54	Male	15 mg	60 mg/day	Aspiration pneumonia resulting in prolonged hospitalization and death	Not related

[Table was taken from sponsor's Table CC, Vol. 1.11, p.79; Data source sponsor's table 7.3.2.]

A total of eight patients had SAEs including the three deaths mentioned above. Two patients during the stabilization period (Study CBI-961/962; Patients 0002 and 0006), four patients during the treatment period (Study XIR0596; Patients 0403 and 1405 and Study CBI-961/962; Patients 0015 and 0001), and two patients during the extension study XIR0696; (Patients 0905 and 1501). No patients experienced SAEs during the PK and bioavailability studies. [Vol. 1.11, p. 79.]

SECTION 8.3 ASSESSMENT OF DROPOUTS

Overall, 61 patients were discontinued or dropped out because of AEs. A total of 54 patients withdrew during the clinical safety studies, three patients withdrew during extension study XIR0696, and six patients withdrew from the PK and bioavailability studies (refer to Table 1) but no SAEs were reported.

The majority (49/54; 91%) of patients who were withdrawn because of AEs in the clinical studies discontinued during the stabilization period. [Vol. 1.11, p.80.]

Please see Addendum 1 for a Summary Table of Discontinuations:

SECTION 8.4 OTHER ADVERSE EVENTS:

A total of 538 patients were exposed to the IR formulation including 5, 10 and 15 mg formulations and were grouped in 3 dosage groups. Those who received <60 mg/day TDD (237 patients), those who received 60-<120mg/day TDD (197 patients), and those who received >120mg/day TDD (104 patients). 453 patients were in the stabilization phase and 194 were in the treatment phase (only 191 actually provided complete dosing information).

During the stabilization phase, the highest incidence of AEs occurred in the digestive system (35%; 157/453), followed by the nervous system (29%; 132/453), body as a whole (27%; 123/453), and skin and appendages (16%; 72/453). In general, the types of AEs experienced were similar to the AE profile expected for opioids. Patients who took >120 mg/day generally showed higher incidences for body as a whole, digestive, respiratory, and skin and appendage systems, than those patients who took smaller dosages. The incidence of nausea increases with dose level (13%; 28/210, 24%; 36/150, 30%; 28/93) as did vomiting (7%; 14/210, 16%; 23/150, 16%; 15/93), constipation (9%; 19/210, 12%; 18/150, 13%; 12/93), dry mouth (3%; 6/210, 3%; 5/150, 7%; 6/93) and insomnia (3%; 6/210, 6%; 9/150, 8%; 7/93). The incidence of headache decreased as the dose level increased (14%; 29/210, 13%; 14/150, 11%; 10/93). The percentage of AEs reported in the cardiovascular, hemic and lymphatic, metabolic and nutritional, musculoskeletal, nervous, special senses, and urogenital systems remained constant or decreased as the dose level increased. [Vol. 1.11, pp.45-46.]

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Incidence of AEs by Body System and COSTART Term: Stabilization Period

	<60mg (N=210) (Incidence %)	60-<120mg (N=150) (Incidence %)	>120mg (N=93) (Incidence %)	Overall N=453 (Incidence %)
Digestive System	56/210(26.7%)	60/150(40%)	41/93(44.1%)	157/453(34.7%)
Nervous System	53/210(25.2%)	50/150(33.3%)	29/93(31.2%)	132/453(29.1%)
Body as a Whole	57/210(27.1%)	37/150(24.7%)	29/93(31.2%)	123/453(27.2%)
Skin and Appendages	32/210(15.2%)	22/150(14.7%)	18/93(19.4%)	72/453(15.9%)

[Based on Sponsor's Table 5.2.1, Vol. 1.11, p.256.]

During the treatment phase the highest incidence of AEs occurred in the digestive system (20%; 39/191), then body as a whole (14%; 27/191), and nervous system (13%; 24/191). The incidence of AEs in all remaining body systems was below 10%. Again the type of AEs experienced was similar to those expected for opiates.

The incidence of AEs occurring in the digestive system was lower in the >120-mg/day group (15%; 8/54) than in either the <60-mg/day group (27%; 14/52) or the 60 to <120-mg/day group (20%; 17/85). In the incidence of nausea, the > 120-mg/day group had the lowest incidence of the three groups (2%; 1/54). The incidence of constipation was lower in the 60 to <120-mg/day group (2%; 2/85) than in the <60-mg/day group (8%; 4/52) or the >120-mg/day group (7%; 4/54). The highest incidence of vomiting was seen in the <60-mg/day group (10%; 5/52). [Vol.1.11, pp.50-51.]

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Incidence of AEs by Body System and COSTART TERM: Treatment Period

	>60mg (N=52) (Incidence %)	60-<120mg (N=85) ((Incidence %)	>120mg (N=54) (Incidence %)	Overall (N=191) (Incidence %)
Digestive System	14/52(26.9%)	17/85(20%)	8/54(14.8%)	39/191(20.4%)
Nausea	4/52(7.7%)	10/85(11.8%)	1/54(1.9%)	15/191(7.9%)
Constipation	4/52(7.7%)	2/85(2.4%)	4/54(7.4%)	10/191(5.2%)
Vomiting	5/52(9.6%)	6/85(7.1%)	2/54(3.7%)	13/191(6.8%)
Body as a whole	7/191(13.5%)	19/191(22.4%)	1(1.9%)	27(14.1%)
Nervous System	6/191(11.5%)	12/191(14.1%)	6/191(11.1%)	24/191(12.6%)

[Based on sponsor Table 5.2.2, Vol. 1.11, p. 260.]

It appears to this reviewer that in both the stabilization and treatment phases of the pooled safety data, that the study drug presents a profile similar to those of other opiates of this type with the most common being nausea, vomiting, constipation, etc.

SECTION 8.4.1 ADVERSE EVENTS BY GENDER:

The overall incidence of AEs reported by male and female patients during the stabilization period was similar. Sixty-two percent (121/194) of the male patients experienced AEs compared to 59% (152/259) of the female patients. The incidence of AEs for females was slightly higher during the treatment period compared to males. During the treatment period, 52% (53/101) of the female patients and 36% (32/90) of the male patients experienced AEs. [Vol. 1.11, p.97.]

SECTION 8.4.2 ADVERSE EVENTS BY AGE:

Of the 538 patients in clinical studies of oxycodone IR, 21% (112/538) were 65 and over. while 7% (39/538) were 75 and over. The sponsor felt that even though there were no

overall differences in safety between elderly and younger patients, either in the clinical studies or other reported clinical experiences, greater sensitivity of some older individuals cannot be ruled out.

Generally, the incidence of AEs during the stabilization period was slightly higher for patients under 65 years (62%) than those 65 years or older (54%). Dizziness had a higher incidence in patients ≥ 65 years of age compared to patients < 65 years of age (16% vs. 7%) during the stabilization period. During the treatment period, 59% (23/39) of the patients 65 years or older reported AEs during the treatment period compared to 41% (62/152) of the patients who were under the age of 65 years. Dizziness had a higher incidence in patients > 65 years of age compared to patients < 65 years of age (8% vs. 3%) during the treatment period.

[Vol. 1.11, p.96.]

Section 8.4.2.1 Adverse Events in Children:

There was no data on children below 18 years. The sponsor feels that there are no specific increased risks expected if the dosing is weight adjusted. [Vol. 1.11, p90.]

SECTION 8.4.3 ADVERSE EVENTS BY RACE:

The majority (92% for both treatment periods) of the 453 patients who received oxycodone IR during the stabilization period and of the 191 patients who received oxycodone IR during the treatment period were Caucasian, which made it hard to detect racial differences. However, the incidence of constipation and vomiting was higher for Black patients during both the stabilization and treatment periods. [Vol. 1.11, p.97.]

SECTION 8.4.4 ADVERSE EVENTS BY ETIOLOGY OF PAIN

Of the 453 patients who received oxycodone IR during the stabilization period, most (77%) had non malignant chronic pain. Overall, the incidence of drug-related AEs was slightly higher in chronic malignant pain patients (65%) than in chronic non-malignant pain patients (59%).

Of the 191 patients who received oxycodone-IR during the treatment period, most (69%) had non malignant chronic pain. Overall, the incidence of AEs was higher for patients who had chronic malignant pain (53%) than patients who had chronic non-malignant pain (41%). [Vol. 1.11, p.97.]

SECTION 8.4.4 POSTMARKETING EXPERIENCE:

The following 15 AEs have been reported with Roxicodone™ 5 mg Tablets, Roxicodone™ Oral Solution (5mg/5mL), and Roxicodone Intensol™ (20 mg/mL) over nine years of experience:

“October 11, 1991: Report from patient on Roxicodone Intensol™ that one of three bottles dispensed did not provide the same analgesia as the other two bottles. The bottle reported with decreased efficacy was of a different lot than the other two bottles dispensed. No other effects were noted from the Roxicodone.

“October 16, 1991: Report from a patient describing psychological reactions to Halcion, in combination with Roxicodone™ and other medications. Report forwarded to Roxane by Upjohn Pharmaceuticals. No information provided on dosing of Roxicodone.

“August, 1994: Report of loss of potency of a single lot by a patient who had been taking Roxicodone™ tablets for a month in duration. Reported better pain relief with previous prescription filled. Reported by Pharmacist dispensing medication to the patient.

“April 24, 1996: Verbal reporting of an adverse event (of unknown character and duration). Attempts were made in writing and verbally to obtain further information, but could not gain cooperation of reporting party.

“February 19, 1997: Report of a death of a six-year-old female child. RoxicodoneTM was not prescribed for the child and the dose administered to the child was unknown. Child was also taking Ritalin 5-mg tablets (5 per day) and Imipramine 25-mg tablets 3 at bedtime). No follow-up data was submitted concerning cause of death or other contributing factors, including actual dose of RoxicodoneTM administered to the child. This was part of a pending police investigation into the death of the child.

“April 15, 1998: Series of three patients reported by one institution in which the Roxicodone 5-mg tablet was given and reported as not being effective. Reported by physician's office prescribing product for postoperative pain (orthopedic surgery) All three patients were to receive 5 to 10 mg every 2 hours as needed for pain. All three patients were given other medications for pain, but no follow up of efficacy of alternative medications was received. Assay and dissolution tests performed at Roxane on returned material indicated that the product was within release specifications.

“May 15, 1998: Patient's mother reported that her son experienced back spasms after being treated for headaches with Roxicodone, Roxicet and Percocet, Reported dose of Roxicodone was 5 mg QID. Patient was subsequently placed on Oxycontin 20 mg q 12 h, Valium 5 mg bid, Prozac 40 mg qd and an unspecified amount of Trilafon. All information provided by mother. Permission was not given to contact physician. No further follow up obtained.

“May 19, 1998: Patient reported heart palpitations after being prescribed Roxicodone 5 mg bid for pain from herniated disk. No apparent history of cardiovascular problems, but reported that cardiologist stated she had a “slightly leaky valve and extra heartbeats.” Permission denied to contact physician to investigate further. Patient now taking meperidine for pain (dose not given). Roxicodone apparently prescribed from 10/97 until 3/98.

“May 28, 1998: Received report from an attorney that a 13-year-old male patient with cerebral palsy was prescribed one teaspoon of Roxicodone Oral solution (5mg/5ml, administered at home by parents), every 6 hours for pain from a fractured leg. The patient died within 14 hours of initiation of therapy (two doses reported as being administered).

No further details were released except that the family did not receive adequate counseling from the physician or pharmacist, No names of patient or physician were provided for follow up. Concomitant medications were not reported as well.

"June 23, 1998: Pharmacist reported from the patient that the Roxicodone 5 mg tablets started dissolving in his mouth, and that within 45 minutes he feels "like he is going to die." Dose of product was not provided, as well as no information on patient medical history, or concomitant medications. Patient would not return drug for testing. No additional information available.

"January 15, 1999: Report from a 55-year-old male suffering severe back and neck pain secondary to an auto accident and a fall down a flight of stairs. Taking approximately 100 mg/day of RoxicodoneTM 5 mg tablets for two years. He experienced arthritic pain, severe fatigue, lowered testosterone levels, and gynecomastia. Dose was gradually lowered to approximately 10-15 mg/day and symptoms, with the exception of fatigue, resolved.

"January 25, 1999: A physician called to inquire about information on panic attacks or anxiety associated with RoxicodoneTM and dose relationship. Medwatch form forwarded to acquire additional information. No response received.

"February 3, 1999: Seventy-four-year-old IDD, diabetic male. Underwent hip replacement surgery and received Ambien (10 mg) and RoxicodoneTM (10 mg hr/pm) for insomnia and pain. Patient noticed a dramatic drop in glucose levels; medications were discontinued and glucose levels returned to normal.

"August 6, 1999: Forty-eight-year-old male receiving RoxicodoneTM (10 mg q 4 hrs) complained of extreme dry mouth and no pain relief. A sample of product was returned for analysis. Sample assayed within product specifications at ~~labeled~~ labeled amount of Roxicodone HCl. Results of dissolution testing also met specifications.

"January 17, 2000: Forty-six-year-old female receiving 10-15 mg RoxicodoneTM q 3-4 hrs complained that she did not receive the same degree of pain relief obtained with Percocet. She added acetaminophen to her dosing regimen, but still complained of

ineffective pain relief. Unused product will be returned for assay and patient will be notified of the results." [Vol. 1.11, pp.98-100.]

SECTION 8.5 OTHER SAFETY FINDINGS:

SECTION 8.5.1 CLINICAL LABORATORY EVALUATIONS:

Clinically relevant laboratory values were based on investigators' assessments and the following criteria as provided by PPD medical experts (at the analysis stage) to further evaluate the renal function, hepatic function, and hematologic function of patients enrolled in this study:

HGB	≤ 10 g/dL
HCT	$< 25\%$
RBC	$< 2.5 \times 10^6/\text{mm}^3$
Platelet	$< 100 \times 10^3/\text{mm}^3$
Bilirubin	> 1.8 mg/dl
ALT	male: > 86 IU/L; female: ≥ 68 IU/L
AST	male: > 72 IU/L; female: ≥ 68 IU/L
BUN	> 36 mg/dL
Creatinine	> 2 mg/dL

Based on these criteria, 11 clinically relevant abnormal values at baseline were reported (3 ALT, 2 AST, 1 BUN, 1 HCT, 1 HGB, 2 Platelet, 1 RBC), and 11 clinically relevant abnormal values were reported at the final visit (4 ALT, 3 AST, 3 HGB, 1 Platelet).

Table 9, on the following page, presents the mean baseline, final visit, and the change from baseline for the parameters selected. [Vol. 1.11, p.81.]

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Table 9

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Blood Chemistry and Hematology Values at Baseline and the Final Visit to Evaluate Renal, Hepatic, and Hematology Function – Study XIR0596

Laboratory Test	N ^a	Mean (±SD) Baseline	Mean (±SD) Final Visit	Change (±SD) [Final ^b -Baseline]
Blood Chemistry				
ALT (IU/L) Overall	67	26.70 (±27.20)	27.93 (±28.32)	1.22 (±10.43)
<60 mg	11	21.55 (±13.27)	25.55 (±22.52)	4.00 (±12.51)
60 to <120 mg	25	26.00 (±23.60)	26.96 (±23.95)	0.96 (±8.62)
≥120 mg	31	29.10 (±33.27)	29.55 (±33.62)	0.45 (±11.15)
AST (IU/L) Overall	67	24.70 (±15.35)	26.78 (±18.98)	2.07 (±9.32)
<60 mg	11	21.64 (±7.42)	25.73 (±13.43)	4.09 (±7.18)
60 to <120 mg	25	26.52 (±18.35)	26.84 (±19.22)	0.32 (±10.22)
≥120 mg	31	24.32 (±14.97)	27.10 (±20.88)	2.77 (±9.26)
BUN (mg/dL) Overall	68	14.54 (±6.50)	13.71 (±5.96)	-0.83 (±4.75)
<60 mg	11	16.09 (±7.92)	13.64 (±6.62)	-2.45 (±7.05)
60 to <120 mg	25	15.68 (±6.91)	14.48 (±6.49)	-1.20 (±4.74)
≥120 mg	32	13.11 (±5.49)	13.11 (±5.39)	0.01 (±3.67)
Creatinine (mg/dL) Overall	68	0.90 (±0.23)	0.94 (±0.21)	0.04 (±0.13)
<60 mg	11	0.97 (±0.29)	0.97 (±0.22)	0.00 (±0.15)
60 to <120 mg	25	0.88 (±0.23)	0.93 (±0.22)	0.05 (±0.12)
≥120 mg	32	0.88 (±0.20)	0.93 (±0.21)	0.05 (±0.12)
Total Bilirubin (mg/dL) Overall	67	0.53 (±0.18)	0.51 (±0.18)	-0.03 (±0.14)
<60 mg	11	0.54 (±0.13)	0.61 (±0.13)	0.07 (±0.10)
60 to <120 mg	25	0.56 (±0.19)	0.56 (±0.20)	0.00 (±0.14)
≥120 mg	31	0.51 (±0.20)	0.43 (±0.15)	-0.08 (±0.13)
Hematology				
Hematocrit (%) Overall	67	41.97 (±5.18)	41.28 (±4.91)	-0.69 (±3.78)
<60 mg	10	39.75 (±8.04)	38.88 (±6.92)	-0.87 (±3.09)
60 to <120 mg	25	41.90 (±4.41)	41.86 (±4.98)	-0.04 (±4.89)
≥120 mg	32	42.72 (±4.60)	41.57 (±4.00)	-1.14 (±2.92)
Hemoglobin (g/dL) Overall	67	14.17 (±1.89)	13.87 (±1.76)	-0.30 (±1.15)
<60 mg	10	13.60 (±2.87)	13.20 (±2.47)	-0.40 (±1.18)
60 to <120 mg	25	14.13 (±1.55)	14.00 (±1.61)	-0.13 (±1.50)
≥120 mg	32	14.39 (±1.77)	13.98 (±1.62)	-0.40 (±0.79)
Platelet (x10³/mm³) Overall	65	255.46 (±96.39)	260.92 (±94.69)	5.46 (±69.20)
<60 mg	9	241.78 (±122.32)	204.44 (±68.34)	-37.33 (±131.10)
60 to <120 mg	24	257.71 (±92.69)	265.21 (±85.22)	7.50 (±39.62)
≥120 mg	32	257.63 (±94.24)	273.60 (±103.98)	15.97 (±60.32)
RBC (x10⁶/mm³) Overall	67	4.59 (±0.66)	4.49 (±0.59)	-0.10 (±0.39)
<60 mg	10	4.32 (±0.92)	4.22 (±0.77)	-0.10 (±0.36)
60 to <120 mg	25	4.56 (±0.59)	4.52 (±0.62)	-0.04 (±0.50)
≥120 mg	32	4.69 (±0.61)	4.55 (±0.50)	-0.14 (±0.29)

^a Includes the number of patients who had baseline and final visit laboratory results

^b Final visit for patients who completed the study or the time of withdrawal for patients who discontinued the study

Studies Pooled: Study XIR0596 only

[Taken from sponsor's Table DD, Vol. 1.11, p.82, Data source Table 8.1.1]

In the PK and bioavailability studies there were no clinically relevant changes in hematology, chemistry, or urinalysis test results. [Vol. 1.11, p.83.]

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SECTION 8.5.2 VITAL SIGNS:

Overall during the stabilization periods of the pooled studies, one patient experienced hypertension (60 to <120 mg/day group) which was considered related to the study medication. Five patients experienced tachycardia (3 patients in the <60 mg/day group and 1 patient each in the 60 to <120 mg/day and the >120 mg/day groups). Of these, four were considered by the investigator to be related to the study medication.

During the treatment period, of the pooled studies, one patient in the <60 mg/day group experienced hypotension that was considered by the investigator not to be related to the study medication. One patient in the 60 to <120 mg/day group experienced tachycardia which was considered by the investigator to be related to the study medication.

There did not appear to be any clinically relevant vital sign changes during Study XIR0596, the extension study (XIR0696), or the PK and bioavailability studies that would suggest an abnormality. [Vol. 1.11, pp. 83-84.]

SECTION 8.5.3 SUPPORTIVE SAFETY STUDIES FROM THE LITERATURE ON SAFETY OF DOSES GREATER THAN 60MG:

The sponsor included five studies from the literature as supportive of the safety of oxycodone in doses greater than 60mg. These included the following:

Glare and Walsh in an open label, repeated dose study of oxycodone solution in 24 patients with chronic cancer pain found that the median stable dose of oxycodone in this study was 20 mg (range, 15-60 mg) every 4 hours. At 5 or 6 doses per day, the lowest TDD was 75 mg and the highest TDD was 360 mg. The most common side effects were sedation (n=20), constipation (n=13), and nausea/vomiting (n=8). Dose limiting side effects occurred in 3 patients and included sedation, nausea, and respiratory depression. Each of these patients improved with dose reduction or withdrawal.

Kalso and Vainio (1990) in a double blind, multiple-dose, randomized, two way crossover study examined single-entity morphine and oxycodone solutions in the treatment of severe cancer pain in 20 safety evaluable (9M/11F) patients. The mean TDD of oral morphine utilized in this study was 204 mg (range, 72-360 mg) and the mean TDD of oral oxycodone was 150 mg (range, 57-302 mg). The most frequent side effects for both drugs were common to opioids and included sedation, nausea, and constipation. Oral morphine caused significantly more nausea than oral oxycodone. Hallucinations were also seen with morphine. Excessive perspiration was slightly more common with IV oxycodone than with morphine. There were no other significant differences in the side effects.

Kaplan et al (1998) in a double blind, multi-center, randomized, repeated dose, parallel group study of 160 safety evaluable patients compared oxycodone IR tablets and oxycodone controlled-release (CR) tablets in the treatment of moderate-to-severe chronic cancer pain. The TDD of oxycodone IR averaged 127 mg (range, 40-640 mg) and the TDD of oxycodone CR averaged 114 mg (range, 20-400 mg). Six patients in the CR group discontinued due to AEs and 10 patients in the IR group discontinued due to AEs, with GI complaints the most common reason for discontinuation. The AEs generally seen in opioids included nausea, somnolence, constipation, and vomiting.

Heiskanen and Kalso (1997) in a 21 day, randomized titration followed by a double blind, randomized, two way crossover study compared oxycodone CR tablets and morphine CR tablets in 45 cancer patients with chronic pain (5). At the end of titration, the mean TDD of oxycodone was 123 mg and the mean TDD of morphine was 180 mg. The most commonly reported AEs were constipation, sedation, and nausea during both treatments. The total number of AEs were similar with each drug, though vomiting (10/27) was significantly more common with morphine and constipation (18/27) was significantly more common with oxycodone.

Bruera et al (1998) in a double blind, randomized, two-way crossover study in 23 safety evaluable patients compared oxycodone CR tablets and morphine CR tablets in the treatment of cancer pain (6). The mean dose of oxycodone was 46.5 ± 57 mg every 12 hours (TDD~90 mg) and the mean dose of morphine was 72.6 ± 102 mg every 12 hours (TDD~145 mg). Three patients discontinued due to AEs while receiving morphine, and two patients discontinued due to AEs while receiving oxycodone. There were no significant differences in sedation or nausea between oxycodone and morphine. There were no significant differences in mean severity of elicited AEs or in the frequency of reporting unelicited AEs. [Vol. 1.7, pp.94-99.]

SECTION 8.6 DRUG-DRUG INTERACTIONS:

There were no specific studies in this clinical development program of drug-drug interaction with oxycodone; however, the sponsor has provided following information based on the literature:

“Opioid analgesics, including oxycodone IR, may enhance the neuromuscular-blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. Oxycodone is metabolized in part to oxymorphone via CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs and anti-depressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction.

“Interactions with Alcohol and Drugs of Abuse

“Oxycodone may be expected to have addictive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system (CNS) depression.

“Oxycodone IR is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

“Oxycodone IR, like all opioid analgesics, should be started at one third to one half of the usual dosage in patients who are concurrently receiving other CNS depressants, including sedatives or hypnotics, general anesthetics, phenothiazines, centrally-acting anti-emetics, tranquilizers, and alcohol, because respiratory depression, hypotension, and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

“Interactions with Mixed Agonist/Antagonist Opioid Analgesics

“Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, and

buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.”

[Vol. 1.11, pp.90-91.]

SECTION 9.0 LABELING REVIEW:

See Appendix “A”

SECTION 10.0 CONCLUSIONS:

This submission is essentially a Biopharm and safety submission and is based on the concerns expressed in the Approvable letter of September 23, 1999. The sponsor has shown bioequivalency for oxycodone with the marketed product and adequate safety in the target population. The sponsor has provided a rationale for the higher doses of oxycodone based on documented need and use. The sponsor has also provided a reformatted ISS. The rate and type of AEs appear to be similar those that occur with other drugs of this class. It is the opinion of this reviewer that oxycodone HCl (15mg and 30 mg tablets) appears to be reasonably safe when used as recommended.

SECTION 11.0 RECOMMENDATION

Based on the data submitted, NDA 21-011 is recommended for approval with appropriate labeling.

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Harold Blatt, D.D.S.

Clinical Reviewer

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NDA 21-011/AZ

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Addendum to the review.

Please note that the following two tables were inadvertently left out of the original review and are appended here as an addendum:

1. This Summary Table for AEs in the PK Study XIR0299 belongs in Section 8.1 METHODS of the review under the first paragraph of the section.

<u>Summary Table for AEs in PK Study XIR0299</u>	Group A – 15mg Oxycodone IR	Group B – 3 Percodan Tablets
Lightheadedness	8/25(32%)	4/26(15%)
Nausea	8/25(32%)	4/26(15%)
Vomiting	7/25(28%)	5/26(19%)
Itching	4/25(16%)	5/26(19%)
Headache	4/25(16%)	2/26(8%)
Pale	3/25(12%)	0/26(0%)
Dizzy	2/25(9%)	4/26(15%)
Tired	2/25(9%)	1/26(4%)
Diaphoresis	1/25(4%)	1/26(4%)
Feels Cold	2/25(9%)	2/26(8%)
Feels Hot	1/25(4%)	1/26(4%)
Visual Disturbances	1/25(4%)	0/26(0%)
Photosensitivity	1/25(4%)	0/26(0%)
Euphoria	1/25(4%)	0/26(0%)
Hiccups	1/25(4%)	0/26(0%)
Numbness in Extremities	1/25(4%)	0/26(0%)

All subjects randomized to Treatment A were given a single oral dose of one 15 mg Oxycodone Hydrochloride tablet taken with 240 mL of water.

All subjects randomized to Treatment B were given a single oral dose of three Percodan tablets taken with 240 mL of water.

2. This Summary Table of Discontinuations belongs in Section 8.3 ASSESSMENT OF DROPOUTS of the review after the second paragraph of the section.

NDA 20-1011 Summary Table of Discontinuations

	Average Daily Dose (Incidence %)	Number (Incidence %)
Vomiting	11/29 had 60-<120mg (38%) 4/11 had >120mg (36%) 5/15 had <60mg (33%)	20/61(33%)
Nausea	10/29 had 60-<120mg (34%) 3/11 had >120mg (27%) 2/15 had <60mg (13%)	15/61(25%)
Confusion	3/29 had 60-<120mg (10%) 2/11 had >120mg (18%) 2/15 had <60mg (13%)	7/61(11%)
Pruritis	2/29 had 60-120mg (7%) 3/15 has <60mg (20%)	5/61(8%)
Dizziness	1/29 had 60<120mg (3%) 1/11 had >120mg (9%) 2/15 had <60mg (13%)	4/61((7%)
Somnolence	3/29 had 60-<120mg (10%) 1/11 had >120mg (9%)	4/61(7%)
Rash	1/29 had 60-<120mg (3%)	2/61(3%)

	1/11 had >120mg (9%)	
Nervousness	1/11 had >120mg (9%) 1/15 had <60mg (7%)	2/61(3%)
Gastrointestinal Carcinoma	1/29 had 60-<120mg (3%) 1/15 had <60mg (7%)	2/61(3%)
Chills	1/29 had 60-<120mg (3%)	1/61(2%)
Hypertension	1/29 had 60-<120mg (3%)	1/61(2%)
Tachycardia	1/15 had <60mg (7%)	1/61(2%)
Pneumonia	1/29 had 60-<120mg (3%)	1/61(2%)
Pathological Fracture	1/15 had <60mg (7%)	1/61(2%)
Constipation	1/15 had <60mg (7%A)	1/61(2%)
Insomnia	1/11 had 60-<120mg (9%)	1/61(2%)
Abnormal Vision	1/11 had 60-<120mg (9%)	1/61(2%)
Urinary Frequency	1/11 had 60-<120mg (9%)	1/61(2%)
Vasodilatation	1/11 had 60-<120mg (9%)	1/61(2%)
Hyperesthesia	1/15 had <60mg (7%)	1/61(2%)
Hypercalcemia	1/29 had 60-<120mg (3%)	1/61(2%)
Leukopenia	1/29 had 60-<120mg (3%)	1/61(2%)
Accidental Injury	1/29 had 60-<120mg (3%)	1/61(2%)
Back Pain	1/15 had <60mg (7%)	1/61(2%)
Bone Pain	1/29 had 60-<120mg (3%)	1/61(2%)
Asthenia	1/11 had >120mg (9%)	1/61(2%)
Migraine	1/29 had 60-<120mg (3%)	1/61(2%)

[/S/]

Harold Blatt, D.D.S.

Clinical Reviewer

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FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857

Tel: (301) 827-7410

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA Number: 21-011

Sponsor: Roxane Laboratories

Drug Name

Generic Name: Oxycodone Hydrochloride (Immediate Release)

Trade Name: Roxicodone

Drug Categorization

Pharmacological Class: Opioid Analgesic

Proposed Indication: Moderate to Severe Pain

NDA Classification: 3 S

Dosage Forms: 15 and 30 mg tablets

Route: Oral

Reviewer Information

Clinical Reviewer: Chang Q. Lee, MD, M.S.H.A., Dr.PH [

/S/

8/26/99

Peer Medical reviewer: Bob Rappaport, MD, Deputy Division Director]

Original Receipt Date: September 30, 1998

Completion Date: August 26, 1999

TABLE OF CONTENTS

SECTION 1.0 MATERIALS UTILIZED IN REVIEW.....	4
SECTION 2.0 BACGROIND.....	4
SECTION 2.1 INDICATION:.....	4
SECTION 2.2 RELATED IND'S AND NDA'S:.....	4
SECTION 2.3 ADMINISRRATIVE HISTORY:.....	4
SECTION 2.4 PROPOSED DIRECTIONS FOR USE:.....	6
SECTION 2.5 FOREIGN MARKETING:.....	7
SECTION 3.0 CHEMISTRY.....	7
SECTION 4.0 ANIMAL PHARMACOLOGYITTOXICOLOGY.....	8
SECTION 5.0 DESRIPTON OF CLINICAL DATA SOURCES.....	9
SECTION 5.1 STUDYTYPE AND DESIGNIPATIENT ENUMERATION.....	11
SECTION 5.2 DEMOGRAPHICS:.....	11
SECTION 5.3 EXTENT OF EXPOSURE:.....	14
SECTION 6.0 SUMMARY OF HUMAN PHARMACOKINETICS.....	15
SECTION 6.1 SUMMARY OF PK STUDIES:.....	16
SECTION 6.2 GENERAL PHARMACOKINETICS:.....	19
SECTION 7.0 EFFICACY FINDINGS:.....	20
SECTION 7.1 OVERVIEW OF CLINICAL STUDIES:.....	20
SECTION 7.2 SUMMARY OF STUDIES PERTINENT TO EFFICACY:.....	21
SECTION 7.2.1 STUDY XIR0596.....	21
Section 7.2.1.1 Protocol Synopsis:.....	21
Section 7.2.1.2 Statistical Analysis:.....	22
Section 7.2.1.3 Protocol Amendments:.....	22
Section 7.2.1.4 Conduct of Study:.....	23
Section 7.2.1.5 Demographic and Other Baseline Characteristics.....	25
Section 7.2.1.6 Sponsor's Efficacy Results:.....	25
Section 7.2.1.7 Reviewer's Efficacy Discussion:.....	25
SECTION 7.2.2 STUDY XIR0696.....	27
Section 7.2.2.1 Protocol Synopsis:.....	27
Section 7.2.2.2 Statistical Analysis:.....	28
Section 7.2.2.3 Protocol Amendments:.....	29
Section 7.2.2.4 Conduct of Study:.....	29
Section 7.2.2.5 Demographic and Baseline Characteristics.....	30
Section 7.2.2.6 Sponsor's Efficacy Results:.....	31
Section 7.2.2.7 Reviewer's Efficacy Discussion:.....	31
SECTION 7.2.3 OTHER SUPPORTING CLINICAL TRIALS.....	31
Section 7.2.3.1 Study CBI-961-/962.....	31
Section 7.2.3.2 Study CBI-1252.....	34
Section 7.2.3.3 Study CBI-963.....	36
SECTION 8.0 SAFITY FINDINGS.....	38
SECTION 8.1 METHODS:.....	38
SECTION 8.2 SERIOUS ADVERSE EVENTS:.....	40

SECTION 8.2.1	DEATHS:.....	40
SECTION 8.2.2	NON-FATAL SERIOUS ADVERSE EVENTS:.....	41
SECTION 8.3	ASSESSMENT OF DROPOUTS.....	42
SECTION 8.3.1	ROXICODONE EXPOSURE:.....	42
SECTION 8.3.2	PATIENT DISPOSITION - ADVERSE EVENTS:.....	45
SECTION 8.4	OTHER ADVERSE EVENTS:.....	46
SECTION 8.4.1	ADVERSE EVENTS OVERALL:.....	46
SECTION 8.4.2	ADVERSE EVENTS BY GENDER:.....	58
SECTION 8.4.3	ADVERSE EVENTS BY AGE:.....	59
SECTION 8.4.4	ADVERSE EVENTS BY RACE:.....	59
SECTION 8.4.5	ADVERSE EVENTS BY ETIOLOGY OF PAIN.....	60
SECTION 8.4.6	ADVERSE EVENTS IN PATIENTS WITH HEPATIC INSUFFICIENCY, RENAL INSUFFICIENCY, OR RELATED PREGNANCY NURSING, LABOR AND DELIVERY.....	60
SECTION 8.5	OTHER SAFETY FINDINGS:.....	61
SECTION 8.5.1	CLINICAL LABORATORY EVALUATIONS:.....	61
SECTION 8.5.2	VITAL SIGNS:.....	62
SECTION 8.6	DOSE RESPONSE ADVERSE EXPERIENCE INFORMATION...	63
SECTION 8.7	DRUG-RELATED EFFECTS OF CONCERN.....	63
SECTION 8.8	DRUG-DRUG INTERACTIONS:.....	65
SECTION 8.9	ADVERSE EFFECTS IN LONG TERM USE:.....	66
SECTION 8.10	POST-MARKETING REPORTS:.....	66
SECTION 9.0	COMMENTS AND CONCLUSIONS.....	67
SECTION 9.1	SUMMARY AND COMMENTS.....	67
SECTION 9.2	CONCLUSIONS.....	68
SECTION 10.0	RECOMMENDATIONS.....	68

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SECTION 1.0 MATERIAL UTILIZED IN REVIEW

NDA Hard Copy of Clinical Data: 49 Volumes

<u>Volume</u>	<u>Contents</u>
1	Draft labeling, clinical data summary, risk/benefit
27-29	clinical pharmacology studies
30-39	Study CBI-961/962
40-49	Study CBI-1252
50-53	Study XIR0596
54-56	Study XIR0696
57-67	Study CBI-963
68	Published Clinical Pharmacology Studies
69	Published Efficacy Studies
70-71	Published Safety Studies
72-74	Integrated Summary of Safety

Electronic Data: 3 diskettes: safety data for studies XIR0596 and XIR0696, MS Word Text for the Integrated Summary of Safety and Labeling.

SECTION 2.0 BACKGROUND

SECTION 2.1 INDICATION:

The proposed indication for Roxicodone™ is:

“ROXICODONE is indicated for the management of moderate-to-severe pain where the use of an opioid analgesic is appropriate.”

SECTION 2.2 RELATED IND'S AND NDA'S:

The related IND is 46,618 and the related NDA is 20,932.

SECTION 2.3 ADMINISTRATIVE HISTORY:

Roxane Laboratories, Inc (Roxane) currently markets Roxicodone as a 5-mg tablet and as a 5-mg/5 ml oral solution, and as a 20 mg/ml concentrated oral solution. These products have been marketed in the United States since the early 1980's as "grandfather" pre-1938 drug products. The FDA approved the company's Oxycodone sustained release tablets (10 mg and 30 mg) in 1998 (NDA 20,932).

Roxane opened the IND 46,618 in November 1994 for the development of a 15 mg and 30 mg IR tablet for the relief of moderate to severe pain. These strengths mimic those available for morphine sulfate immediate release tablets.

The FDA held a meeting with Roxane on March 7, 1996 to discuss the development plan for the IR tablets. During the meeting, Roxane indicated that the company did not wish to seek exclusivity for the 15- and 30-mg IR tablets as it would need to follow traditional requirements (2 well-controlled clinical trials). At that time, it was agreed that what Roxane needs to show is: bioequivalency to marketed products, dose strength equivalence, dose proportionality, and safety in the target population. Efficacy, while not a primary requirement, should be considered as well. Additional studies may be required based on the proposed labeling. For example, are there comparisons between Roxane product(s) and approved drug products?

The FDA sent Roxane ten questions on September 10, 1997 as a follow-up to the March 1996 meeting. Roxane responded the questions on February 19, 1998. The ten questions and some related responses were provided below:

1. Please identify the formulation you wish to market.
2. Have you done any pharmacokinetic studies with your to-be-marketed formulation?
3. Please identify the formulations used in the bioavailability and dose proportionality studies.
 - *Response: The dose proportionality study used the previously "approved" 5-mg tablet formulation in a three-way crossover design comparing 1 x 5 mg tablet, 3 x 5 mg tablets, and 6 x 5 mg tablets. The relative bioavailability studies compared the 15 mg and 30 mg tablet formulations to previously marketed formulations.*
4. What are the indications that the sponsor is seeking for the drug product?
 - *Response: Roxane is seeking approval for the treatment of moderate to severe pain (in patients who require treatment with an oral opioid analgesic).*
5. Will the sponsor make clinical efficacy and safety claims based on the solution or on the market? If it is on the solution, then the to-be-marketed formulation needs to be better tied to the solution.
 - *Response: Clinical efficacy and safety claims will be based on drug class labeling and the results from Phase I and Phase II/III clinical studies. Claims will be based on the tablet formulations. However, the pharmacokinetic performance of the tablets and solutions will be linked by Phase I studies.*
6. What are the sponsor's plans for conducting efficacy trials and clinical studies?
 - *Response: Roxane has conducted two clinical trials in patients with moderate/severe chronic pain using the 15 and 30 mg tablet formulation. Study XIR0596 was an open-label, multi-center, 7-day study. This study was primarily conducted to evaluate safety; however, efficacy and population pharmacokinetic assessments were also evaluated. The XIR0696 study is a 4-week (1-month) extension of the XIR0596 study. This study was conducted to primarily evaluate safety, with a secondary efficacy assessment.*
7. Please identify the batch numbers of drug product used for all clinical, pharmacokinetic and preclinical studies.
8. We would like the sponsor to describe in detail their proposed clinical study.

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9. We would like to see preclinical data for the mutagenicity and pregnancy categories of the package insert.
10. Does the sponsor plan to submit a 505(b)2 application?
- *Response: Roxane will not file a 505(b)2 application, but will file an NDA. No preclinical studies were conducted. Therefore, nonclinical pharmacology, ADME (absorption, distribution, metabolism, and excretion), and toxicology will be supported by literature references and NDA 20,553. However, clinical data from Phase I and II/III studies sponsored by Roxane will be submitted as support for marketing approval. Appropriate clinical safety and efficacy information derived from the literature will also be provided.*

On May 1, 1998, a pre-NDA meeting was held to review the proposed NDA submission for format and presentation of data. Roxane indicated in the meeting that the NDA would not contain an Integrated Summary of Efficacy, rather than each study report would contain the efficacy from that study.

Roxane submitted the NDA on September 30, 1998. This NDA extensively cross-references NDA #20,932 (Roxicodone SR). The new information resident in this NDA include CMC, two biopharmaceutical studies (XIR-0396 and CBI-315-07), and two clinical safety studies (XIR-0596 and XIR0696) with an attendant pharmacokinetic summation.

Roxane is requesting three years exclusivity for Roxicodone 15 and 30 mg tablets although the sponsor indicated that the company did not wish to seek the exclusivity during the 7 March 1996 meeting.

SECTION 2.4 PROPOSED DIRECTIONS FOR USE:

“The dose must be individually adjusted according to severity of pain, patient response and patient size. If the pain increases in severity, analgesia is not adequate or tolerance occurs, a gradual increase in dosage may be required.”

“Patients who have not been receiving opioid analgesics should be started on ROXICODONE in a dosing range of 5 to 15mg every 4 to 6 hours as needed for pain. The dose should be titrated based upon the individual patient's response to their initial dose of ROXICODONE.”

“For control of severe chronic pain, ROXICODONE should be administered on a regularly scheduled basis, every 4-6 hours, at the lowest dosage level that will achieve adequate analgesia.”

“Although it is not possible to list every condition that is important to the selection of the initial dose of ROXICODONE, attention should be given to: 1) the daily dose, potency, and characteristics of a pure agonist or mixed agonist/antagonist the patient has been taking previously, 2) the reliability of the relative potency estimate to calculate the dose

of oxycodone needed, 3) the degree of opioid tolerance, 4) the general condition and medical status of the patient, and 5) the balance between pain control and adverse experiences.”

In addition, there are several sections discussing specific uses. They are:

- Conversion From Fixed-Ratio Opioid/Acetaminophen, Aspirin, or Nonsteroidal Combination Drugs
- Patients Currently on Opioid Therapy
- Maintenance of Therapy
- Cessation of Therapy

SECTION 2.5 FOREIGN MARKETING:

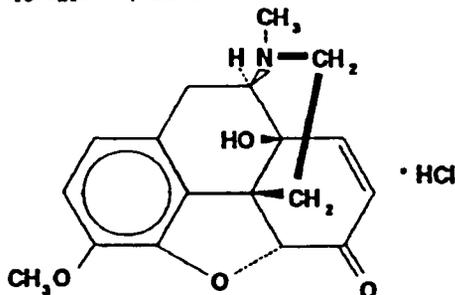
OXYCODONE IR in 15 mg and 30 mg has not been marketed in any country. Oxycodone HCl is marketed for the management of pain by Roxane, as Roxicodone. It is currently available as a 5-mg tablet and as a 5-mg/5 ml oral solution, and as a 20 mg/ml concentrated oral solution. These products have been marketed in the United States since the early 1980's as “grandfather” pre-1938 drug products. The FDA approved the company's Oxycodone sustained release tablets (10 mg and 30 mg) in 1998 (NDA 20,932).

SECTION 3.0 CHEMISTRY

Compound Name: Oxycodone hydrochloride

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

The structural formula is: $C_{18}H_{21}NO_4 \cdot HCl$



The molecular formula is $C_{18}H_{21}NO_4 \cdot HCl$ and the molecular weight is 351.83. Oxycodone hydrochloride is a white, odorless crystalline powder derived from the opium

alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 ml) and is considered slightly soluble in alcohol (octanol water partition coefficient 0.7).

Oxycodone hydrochloride is stable for a period of _____ based analyses on a _____ basis in a stability program (DMF No. _____). Samples from _____ lot per year were selected and stored at _____ The samples are tested initially, _____ No indications of instability have been detected (DMF No. _____).

Each ROXICODONE tablet contains 15 mg or 30 mg of oxycodone hydrochloride, USP. Inactive ingredients include: microcrystalline cellulose; sodium starch glycolate; corn starch; lactose; stearic acid; D&C Yellow No. 10 (15 mg tablet); and FD&C Blue No. 2 (15 mg and 30 mg tablets). The formulation provides for immediate release of the medication.

SECTION 4.0 Animal Pharmacology

The sponsor has summarized the literature on toxicology data for oxycodone hydrochloride in Section 3.5. The following is a condensation of that summary.

Oxycodone is an opioid agonist with pharmacological properties similar to morphine. It has both analgesic and antitussive activity. Oxycodone binds to mu opioid receptors in rats with weak affinity. Its metabolites, noroxycodone and morphine, are active opioid analgesics, and may be responsible for much of its activity. Oxycodone had three to six times the antinociceptive effect of morphine sulfate in rodent analgesic model testing. Oxycodone is a more potent antitussive agent than codeine. Oxycodone was more potent than morphine in causing CNS depressant effects in rats. In mice, oxycodone and morphine increased spontaneous motor activity, caused Straub tail response, increased palpebral opening, decreased food intake, caused delayed hyperthermia, and inhibited gastrointestinal motility. Oxycodone suppressed abstinence in a dose-related manner in dogs. It can cause a morphine type of drug dependence. Tolerance can develop, and it has abuse potential. Oral administration of oxycodone to beagle dogs produced effects on behavior and the cardiovascular system. A dose of 3 mg/kg caused a significant increase in systolic blood pressure accompanied by increased pulse pressure. A dose of 10 mg/kg, like morphine, produced slight sedation and a transient inhibition of respiratory movement during the sleep stage. A 30 mg/kg dose caused much relaxation and significant decreases in the awake stage, a decrease in body temperature and a decrease in heart rate, but unlike morphine, no nausea or vomiting. Carcinogenicity, mutagenicity and effect on fertility studies have not been carried out.

SECTION 5.0**DESCRIPTION OF CLINICAL DATA SOURCES****SECTION 5.1****STUDY TYPE AND DESIGN/PATIENT ENUMERATION:**

The clinical development program for this NDA contains data from a total of 13 studies: 8 phase I studies and 5 phase II/III studies (Table 1-3). Three phase I studies were conducted with the SR tablet formulation, but data on the multiple-dose PK and food effect PK of oxycodone IR are provided. These three studies do not provide safety data for oxycodone IR tablet exposure and number of subjects are therefore not included in the following table.

Table 1. Summary of All Studies Submitted to this NDA

Table 1

Type of Study	Number of Studies	Number of Subjects/Patients Exposed to Each Formulation Group			Overall
		Oxycodone IR 5-mg tablets	Oxycodone IR 15-mg tablets	Oxycodone IR 30-mg tablets	
Human Pharmacokinetics and Bioavailability Studies ^a	5	96	25	45	124
Phase II/III Safety Studies					
Stabilization Period ^b	3	349	56	48	453
Treatment Period ^c	3	125	31	38	194
Study XIR0696 ^d	1	0	19	31	50

^a Studies pooled: 315-05, 315-07, XIR0396, XIR0296, and XIR0196

^b Studies pooled: XIR0596, CBI-961/962, and CBI-963

^c Studies pooled: XIR0596, CBI-961/962, and CBI-1252

^d Patients in XIR0696 are a subset of the XIR0596 study

Source: the sponsor's Tables 1.1.1, and 1.1.2 and individual study reports

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