

Table 2. Clinical Studies

Study No.	Title	Number of Patients Exposed and Grouped in Each Oxycodone IR Tablet Formulation Group									
		Stabilization Period Formulation Group				Treatment Period Formulation Group					
		5 mg	15 mg	30 mg	All ^a	5 mg	15 mg	30 mg	All ^a	All ^b	
XIR0596	An Open-Label, Multicenter Study to Evaluate the Safety Profile of Two Oral Formulations of Oxycodone (Immediate Release) for The Treatment of Patients with Moderate/Severe Chronic Pain	- ^c	56	48	104	- ^c	31	38	69	104	
XIR0696	An Open-Label, Multicenter, Extension Study to Evaluate the Long-Term Safety Profile of two Oral Formulations of Oxycodone (Immediate Release) for the Treatment of Patients With Moderate/Severe Chronic Pain	--	--	--	--	- ^c	19 ^d	31 ^d	(50 ^d)	- ^d	
CBI-961/962	Randomized, Double-Blind, Double-Dummy, Active-Controlled, Multi-Site Crossover Investigation Comparing the Efficacy of Oxycodone SR (Roxicodone 10 mg or 30 mg Tablets) Administered Every Twelve Hours to Oxycodone IR (Roxicodone® 5 mg Tablets) Administered Every Six Hours in Patients With Chronic Cancer Pain	63	--	--	63	43	--	--	43	63	
CBI-1252	Randomized, Double-Blind, Double-Dummy, Active-Controlled, Multi-Site Crossover Investigation Comparing the Efficacy of Oxycodone SR (Roxicodone 10 mg or 30 mg Tablets) Administered Every Twelve Hours to Oxycodone IR (Roxicodone® 5 mg Tablets) Administered Every Six Hours in Patients With Chronic Pain	- ^c	--	--	--	82	--	--	82	82	
CBI-963	A Thirty-Day, Open-Label, Multi-Center Observational Study Assessing the Safety of Oxycodone Sustained Release (Roxicodone SR 10 mg or 30 mg) Tablets Administered Every Twelve Hours (q12 Hours) in Patients Experiencing Chronic Pain	286	--	--	286	- ^d	--	--	--	286	
Clinical Phase II/III Studies Subtotal^a		349	56	48	453	125	31	38	194	535	

- ^a By definition the patients included in the totals for the "treatment period" are also included in the totals for the "stabilization period" except in Study CBI-1252, whereby patients took 5-mg oxycodone IR tablets during the treatment period only
- ^b Total number of patients exposed in each study (Note: in some studies the patients in the treatment period are a subset of the number of patients in the stabilization)
- ^c Indicates 5-mg tablets could have been used for rescue medication; Study XIR0596 5-mg tablets were used as a supplement to the schedule dose
- ^d The patients exposed to oxycodone during the extension study have been accounted for in the XIR0596 study and are not included in the subtotal

Table 3. Pharmacokinetic Studies

Study No.	Title	Number of Subjects Exposed to Oxycodone IR Tablet Formulations and Oxycodone Oral Solutions					Overall ^a
		5-mg	15-mg	30-mg	5mg/5mL	20mg/mL	
315-05	A Single-Dose, Two-Way Crossover Study to Compare the Relative Bioavailability of Oxycodone HCl 5 mg Immediate Release Tablets with Oxycodone HCl Oral Solution 5 mg/5 ml	26	--	--	26	--	26
315-07	A Single-Dose, Two-Way Crossover Study to Compare the Relative Bioavailability of Oxycodone HCl 30 mg Immediate Release Tablets with Oxycodone HCl Oral Solution 5 mg/5 ml	--	--	26 ^b	25	--	26
XIR0396	A Randomized, Open-Label, Crossover Study Comparing the Bioequivalence of Oxycodone Formulations of 6 x 5 mg Tablets, and 1 x 30 mg Tablet in Healthy volunteers	18	--	19	--	--	19
XIR0296	A Randomized, Open-Label, Crossover Study Comparing the Bioequivalence of Oxycodone Formulations of 3 x 5 mg Tablets, 1 x 15 mg Tablet, and 0.75 ml of a 20 mg/ml Oral Solution in Healthy Volunteers	25	25	--	--	26	26
XIR0196 ^c	A Single-Dose, Randomized, Double-Blind, Three-Way Crossover Study Comparing the Dose Proportionality of 5 mg, 15 mg, and 30 mg Doses of Oxycodone Administered Orally to Healthy Volunteers Under Fasting Conditions	27; 5 mg 25; 15 mg 27; 30 mg	--	--	--	--	27
Human Pharmacokinetic and Bioavailability Studies Subtotal		96	25	45	51	26	124

^a Number of subjects who received any formulation of the study drug during each study

^b Using an early formulation of the 30-mg tablet

^c All doses administered in Study XIR0196 consisted of the 5-mg tablet formulation only

SECTION 5.2 DEMOGRAPHICS

This section presents the demographic and baseline characteristics of the patients participating in the stabilization and treatment periods. The sponsor has pooled demographic data from four Phase II/III clinical studies (XIR0596, CBI-961/962, CBI-963, and CBI-1252) into one database. Demographic and baseline characteristics for

extension study XIR0696 (in Section 7.2.2.5) and the human pharmacokinetic and bioavailability studies are presented separately.

Table 4 presents the demographic and baseline characteristics by formulation group (5-, 15-, and 30-mg) for patients entered in the stabilization period.

Table 4
Demographic and Other Baseline Characteristics - Stabilization Period

Characteristic	5 mg (N=349)	15 mg (N=56)	30 mg (N=48)	Overall (N=453)
Age (years)				
N	349	56	48	453
Mean (±SD)	54 (±14)	48 (±14)	47 (±13)	52 (±14)
Range	24-94	26-79	24-80	24-94
Gender				
Male	132 (38%)	27 (48%)	35 (73%)	194 (43%)
Female	217 (62%)	29 (52%)	13 (27%)	259 (57%)
Race				
Caucasian ^a	318 (91%)	52 (93%)	45 (94%)	415 (92%)
Black	28 (8%)	3 (5%)	3 (6%)	34 (8%)
Other ^b	3 (1%)	1 (2%)	0 (0%)	4 (1%)
Weight (kg)				
N	338	55	48	441
Mean (±SD)	77 (±21)	83 (±21)	81 (±16)	78 (±21)
Range	34-163	46-124	47-127	34-163
Etiology of Pain				
Chronic malignant pain	81 (23%)	14 (25%)	9 (19%)	104 (23%)
Chronic non-malignant pain	268 (77%)	42 (75%)	39 (81%)	349 (77%)
Prior Use of Opioids				
Opioid-naïve patients	1 (<1%)	15 (27%)	5 (10%)	21 (5%)
Patients with previous opioid use	348 (99.7%)	41 (73%)	43 (90%)	432 (95%)
Rescue Medication				
Pts. who required rescue med.	272 (78%)	31 (55%)	37 (77%)	340 (75%)
Average rescue dose/day (mg)	16 mg	14 mg	26 mg	17 mg
Range	5-97 mg	5-56 mg	5-84 mg	5-97 mg
Average no. of doses/day	2 doses	2 doses	3 doses	2 doses
Range	1-6 doses	1-6 doses	1-7 doses	1-7 doses
Average TDD of Oxycodone^c				
Pts. with dosing information	349	56	48	452 ^d
Mean TDD (mg)	73 mg	79 mg	157 mg	83 mg
Median TDD (mg)	54 mg	64 mg	130 mg	60 mg
Average Range	20-680 mg	20-178 mg	60-617 mg	20-680 mg

^a Includes Hispanic; ^b Includes Native American, Asian, and Other

^c Includes scheduled doses and rescue medication

^d Patient 1801 had missing dosing information

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

Data Source: Sponsor's Tables 3.1.1 and 3.2.1

The differences in use of rescue medication are discussed in Section 7.2.1.7.

Table 5 presents the demographic and baseline characteristics by formulation group (5-, 15-, and 30-mg) for patients enrolled in the treatment period.

Table 5
Demographic and Other Baseline Characteristics - Treatment Period

Characteristic	5 mg (N=125)	15 mg (N=31)	30 mg (N=38)	Overall (N=194)
Age (years)				
N	125	31	38	194
Mean (\pm SD)	52 (\pm 14)	48 (\pm 15)	46 (\pm 13)	50 (\pm 14)
Range	26-86	26-79	24-80	24-86
Gender				
Male	52 (42%)	13 (42%)	28 (74%)	93 (48%)
Female	73 (58%)	18 (58%)	10 (26%)	101 (52%)
Race				
Caucasian ^a	115 (92%)	28 (90%)	36 (95%)	179 (92%)
Black	9 (7%)	2 (7%)	2 (5%)	13 (7%)
Other ^b	1 (1%)	1 (3%)	0 (0%)	2 (1%)
Weight (kg)				
N	122	31	38	191
Mean (\pm SD)	78 (\pm 20)	80 (\pm 19)	81 (\pm 16)	79 (\pm 19)
Range	40-159	46-124	47-127	40-159
Etiology of Pain				
Chronic Malignant Pain	44 (35%)	9 (29%)	6 (16%)	59 (30%)
Chronic Non-Malignant Pain	81 (65%)	22 (71%)	32 (84%)	135 (70%)
Prior Use of Opioids				
Opioid-naïve patients	1 (1%)	6 (19%)	2 (5%)	9 (5%)
Patients with previous opioid use	124 (99%)	25 (81%)	36 (95%)	185 (95%)
Rescue Medication				
Pts. who required rescue med.	111 (89%)	21 (68%)	25 (66%)	157 (81%)
Average rescue dose/day (mg)	20 mg	11 mg	27 mg	20 mg
Range	5-250 mg	5-28 mg	5-116 mg	5-250 mg
Average no. of doses/day	2 doses	2 doses	2 doses	2 doses
Range	1-7 doses	1-4 doses	1-6 doses	1-7 doses
Average TDD of Oxycodone ^c				
Pts. with dosing information	124	31	35	190 ^d
Mean TDD (mg)	105 mg	85 mg	151 mg	110 mg
Median TDD (mg)	67 mg	73 mg	148 mg	74 mg
Average Range	9-859 mg	30-186 mg	62-450 mg	9-859 mg

^a Includes Hispanic

^b Includes Native American, Asian, and Others

^c Includes scheduled and rescue doses

^d Dosing information was not available for four patients

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

Data Source: Sponsor's Tables 3.1.2 and 3.2.2

The demographic characteristics for the human pharmacokinetic and bioavailability studies are presented in Table 6.

Table 6.
Demographic Characteristics - Human Pharmacokinetics and Bioavailability Studies

Characteristic	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 ^b	156.3 \pm 5.77 ^b	141.4 \pm 3.94 ^b
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

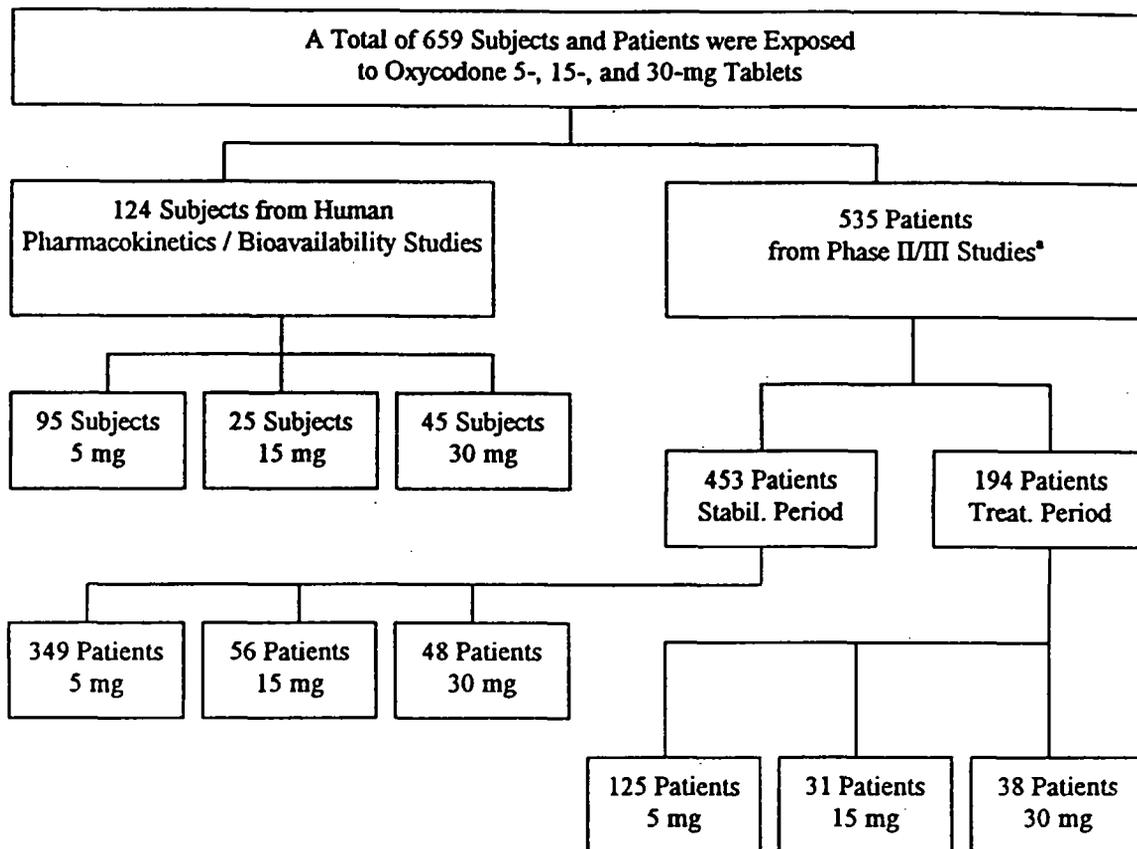
Data Source: Sponsor's Individual study reports and NDA Appendix D

SECTION 5.3 EXTENT OF EXPOSURE

Overall, a total of 659 subjects and patients (124 from the Phase I clinical studies and 535 from the Phase II/III safety trials) were exposed to 5-, 15-, and 30-mg tablet formulations and the oral solutions. Figure 1 presents the number of subjects and patients exposed to each oxycodone tablet formulation. The detailed discussions are presented in Section 8.3 of this review.

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Figure 1. Number of Subjects and Patients Exposed to Oxycodone HCl (5-, 15-, and 30-mg Tablets)



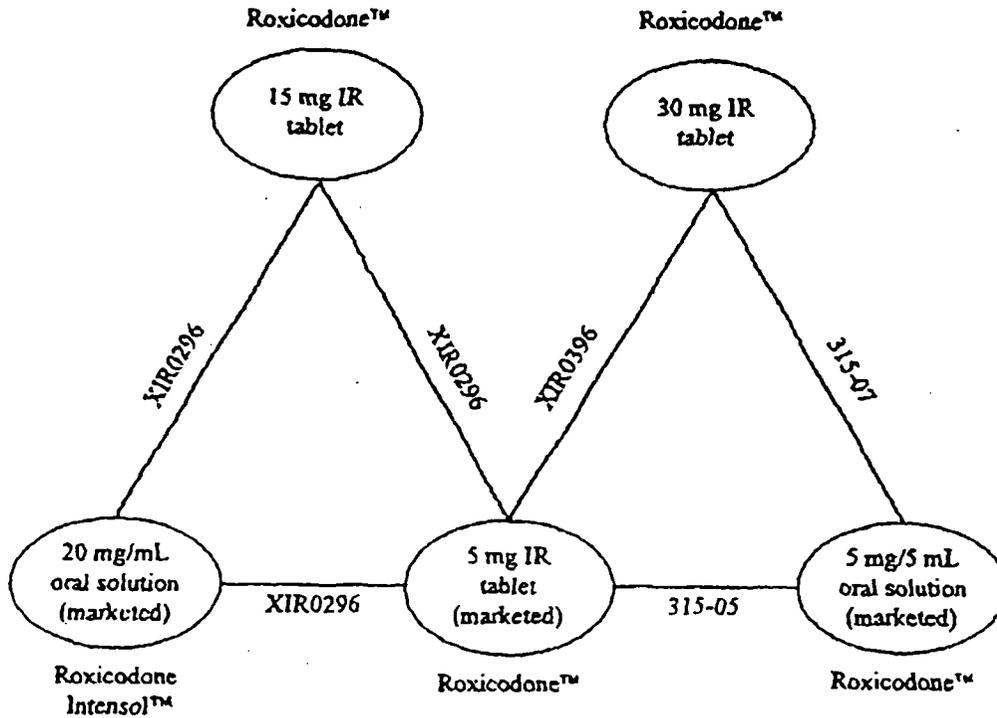
SECTION 6.0 SUMMARY OF HUMAN PHARMACOKINETICS

SECTION 6.1 SUMMARY OF PK STUDIES USING THE PROPOSED MARKET FORMULATION

The purpose of PK studies in this NDA is to correlate the PK data from the currently marketed oxycodone (tablet and solution) formulations to the to-be-marketed 15- and 30-mg oxycodone IR tablet formulations. The five phase I studies conducted in healthy volunteers consist of four single-dose bioavailability/bioequivalency studies (315—5, 315-07, XIR0296, and XIR0396) and one dose proportionality/dose response study (XIR0196).

Figure 2 shows the studies that compared the 15- and 30-mg tablet formulations to the currently marketed oxycodone formulations.

Figure 2.
Studies Comparing the Proposed with the Present Market Populations



SECTION 6.11 SUMMARY OF RESULTS OF PK STUDIES

Study Number 315-05: Relative Bioavailability

10 mg oxycodone IR (2x5-mg tablet) Vs. 10 mg oxycodone IR (5 mg/5 ml solution):

C_{max} (ng/ml)	T_{max} (hr)	AUC_{0-12h} (ngxhr/ml)	$T_{1/2}$ (hr)
19.56	1.27	130.86	4.57
20.21	1.06	135.33	4.59

Comparison of AUC indicated that the oxycodone 5-mg IR tablet was approximately 98% bioavailable to 5-mg/5 ml oral oxycodone solution following 10-mg oral dose. The average T_{max} for the tablet was 1.27 hours compared with 1.06 hours for the oral solution.

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Study Number 315-07: Relative Bioavailability

30 mg oxycodone IR (1X30-mg tablet) vs 30 mg oxycodone IR (30 ml of 5 mg/5 ml oral solution):

C_{max} (ng/ml)	T_{max} (hr)	AUC_{0-Inf} (ngxhr/ml)	$T_{1/2}$ (hr)
40.25	1.79	316.89	4.43
39.08	1.99	330.69	4.55

The 30-mg IR tablet was approximately 97% bioavailable to an equivalent dose of 5-mg/5 ml oral oxycodone solution. The average T_{max} occurred slightly earlier and the mean C_{max} was slightly higher for the tablet than for the oral solution.

Study Number XIR0396: Bioequivalence

6 x 5-mg tablets vs 1 x 30-mg tablet:

C_{max} (ng/ml)	T_{max} (hr)	AUC_{0-Inf} (ngxhr/ml)	$T_{1/2}$ (hr)
36.45	3.00	264.80	3.97
39.34	2.63	268.19	3.85

The absorption of oral oxycodone and the peak oral oxycodone were equivalent when a 30-mg dose of oxycodone using the to-be-marketed 30-mg IR tablet was compared with a 30-mg-dose of the currently marketed 5-mg IR tablet (6 x 5 mg). The elimination rate (K_e) and terminal half-life ($t_{1/2}$) of oxycodone were similar between the two formulations. The time to reach the peak concentration (T_{max}) was slightly shorter (2.63 hours) following the 1 x 30 mg dose compared with the 6 x 5 mg dose (3.00 hours).

Study Number XIR0296: Bioequivalence

3x5-mg tablets Vs. 1x15-mg tablet vs 20 mg/1 ml solution:

C_{max} (ng/ml)	T_{max} (hr)	AUC_{0-Inf} (ngxhr/ml)	$T_{1/2}$ (hr)
22.28	1.80	133.23	3.73
22.17	1.37	128.22	3.55
21.11	1.89	130.58	3.71

The absorption of oral oxycodone and the peak oral oxycodone were equivalent when a 15-mg dose of oxycodone using the to-be-marketed a 15-mg IR tablet was compared with a 15-mg-dose of the currently marketed 5-mg IR tablet (3 x 5 mg). The elimination rate (K_e) and terminal half-life ($t_{1/2}$) of oxycodone were similar between the two formulations.

Study Number XIR0196: Dose Proportionality

5 mg oxycodone IR (1x5-mg tablet) Vs. 15 mg oxycodone IR (3x5-mg tablet) Vs. 30 mg oxycodone IR (6x5-mg tablet):

C_{max} (ng/ml)	T_{max} (hr)	AUC_{0-24} (ngxhr/ml)	$T_{1/2}$ (hr)
9.68	1.28	50.67	3.16
25.55	1.72	158.75	3.57
42.85	1.89	296.79	3.56

A dose proportional increase in AUC follows single 5-mg, 15-mg, and 30-mg doses of oxycodone by using 5-mg tablets. C_{max} was proportional to dose between the 5- and 15-mg doses and between the 15- and 30-mg doses, but not between the 5-mg and 30-mg doses.

Study Number 315-04 and 315-09: Repeated Dosing

The to-be-marketed 15- and 30-mg IR tablet formulations were not used to evaluate effect of repeated dosing in these studies because of possible unacceptable side effects in opioid naïve subjects. The oxycodone 10-mg SR tablets (two different formulations) and the currently marketed 5-mg/5mL oral solution were used in healthy volunteers. Steady-state was achieved following twelve 3.33 ml doses of the 5-mg/5 ml oral IR solution (q4h) and four doses with the 10-mg SR formulation (q12h). The bioequivalence of the two formulations based on the extent of absorption (AUC) was showed.

Study Number 315-10: Food Effect

10 mg oxycodone SR^a (1x10-mg tablet), fasted Vs. 10 mg oxycodone SR^a (1x10-mg tablet), fed Vs. 10 mg oxycodone IR (5 mg/5 ml solution), fasted Vs. 10 mg oxycodone IR (5 mg/5 ml solution), fed

C_{max} (ng/ml)	T_{max} (hr)	AUC_{0-24} (ngxhr/ml)	$T_{1/2}$ (hr)
5.74	5.64	119	12.5
8.92	4.79	130	9.13
19.0	1.25	105	2.93
17.7	2.54	133	3.26

A food effect study has not been conducted using the to-be-marketed 15 or 30-mg IR tablet formulations. This NDA presents data from the 5 mg/5 ml oral solution and 10-mg oxycodone SR tablets. Food increased the extent (AUC), but not the rate (C_{max}) of oxycodone absorption from the IR solution and food increase the rate (C_{max}) but not the

extent (AUC) of oxycodone absorption from the SR tablet formulation. The clinical relevance of the enhanced extent of absorption is assumed to be low for a drug intended for chronic usage at individualized dosages, and oxycodone is recommended to be taken following a meal.

Study Number XIR0596 and XIR0196: Population-Based PK Analysis

The objectives of this analysis were 1) to describe the dose-concentration relationship for immediate-release oxycodone tablets after multiple dosing in patients, 2) to identify any sub-populations of patients with altered oxycodone PK profiles, and 3) to compare oxycodone PK parameters between patients and healthy volunteers.

A significant differences in apparent oral clearance (CL/F) between the patient and healthy volunteer populations were found, and serum creatinine was a significant predictor of apparent volume of distribution (V/F). The lack of a decrease in the random interindividual error estimates for CL/F and VF was also noticed. Given the small number of individuals (N=90, 1089 PK samples) in the studies, it is difficult to make inferences about the clinical relevance of the observations. An explanation for the significant difference in CL/F between patients and healthy volunteers is not evident from these data.

SECTION 6.2 GENERAL PHARMACOKINETICS

Absorption

Oral oxycodone is 60 to 87% bioavailable relative to a parenteral dose due to presystemic and/or first-pass metabolism. The 30-mg IR tablet was approximately 97% bioavailable to an equivalent dose of 5 mg/5 ml oral oxycodone solution. There was dose proportionality from 5 to 30 mg for the 5-mg IR tablets with respect to absorption. There is a food effect resulting in increased rate of absorption without affecting extent of absorption.

Distribution

The volume of distribution for intravenous-administered oxycodone was 2.6 L/kg. There is 45% binding to plasma protein. Distribution includes skeletal muscle, liver, intestinal tract, lungs, spleen, brain and breast milk.

Pharmacokinetics

Peak plasma concentrations were observed at 1.3-1.5 hours. The apparent elimination half-life was 3.5- 4 hours. Steady State is achieved in 18-24 hours.

Metabolism

Metabolism is extensive, mostly to noroxycodone, oxymorphone (the latter by CYP2D6) and to glucuronides. Noroxycodone, the principal metabolite, is a weak analgesic.

Elimination

Excretion is mainly by the kidney. Hence hepatic or renal impairment will be associated with increased plasma drug concentrations. Elderly patients (>65 years) have slightly reduced clearances, resulting in 25% increased plasma levels. Gender and race effects appear to be absent.

SECTION 7.0 EFFICACY FINDINGS

SECTION 7.1 OVERVIEW OF CLINICAL STUDIES

Efficacy with two well-controlled clinical trials is not a primary requirement for this NDA as the NDA is a line extension (see Administrative History Section). The sponsor currently markets products of 5-mg Roxicodone™ tablets, 5 mg/5 ml Roxicodone™ oral solution, 20 mg/ml concentrated oral solution, and Roxicodone sustained release tablets (10 mg and 30 mg). The sponsor is seeking approval for the increased dosage strengths (15- and 30-mg) of the currently marketed 5-mg IR tablets. 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. This submission is primarily a biopharmaceutical and safety submission, and it does not contain an Integrated Summary of Efficacy.

The sponsor has submitted two new open-label, clinical safety studies (XIR0596 and XIR0696) with some efficacy (pain) measurements. The study XIR0596 consisted of a 2-7 day stabilization period and a 7-day open-label treatment period. At the end of the 7-day open-label treatment period, patients were allowed to continue to take oxycodone by participating in a 1-month (4-week) extension study XIR0696. The only patients exposed to the to-be-marketed 15- and 30-mg oxycodone IR tablet formulation during the clinical studies were those patients enrolled in these two open-label studies. In these studies, patients were grouped into the 15- and 30-mg treatment groups based on the amount of medication needed to control pain and on the subsequent formulation strengths needed to comprise the dose.

Efficacy and safety data are extensively cross-referenced in NDA No. 20-932 (Roxicodone SR) since the 5-mg IR tablet formulations were used in those studies. Three studies (CBI-961/962, CBI-1252 and CBI-963) from NDA 20-932 are submitted to support efficacy claim – “the treatment of moderate-to-severe chronic pain” under this NDA. The studies, CBI-961 and CBI-962, were two double-blind, controlled pivotal trials to demonstrate efficacy of the sustained-release tablets (15- and 30-mg) as compared to the immediate release formulation of oxycodone (5 mg tablets). The two trials had the same crossover design in patients with cancer pain, but due to slow patient enrollment for both protocols, the sponsor merged the two individual protocols into one multicenter study CBI-961/962. The second pivotal trial, CBI-1252, involved patients with chronic pain (cancer or non-cancer), but with a different sample size and a change in the entry Visual Analog Scale (VAS) score from ≤ 50 mm to < 70 mm. Both the CBI-961/962 and CBI-1252 studies were multicenter crossover trials with one-week legs,

comparing pain scores and escape medication usage. Immediate-release oxycodone 5 mg tablets were used as escape medication. The study CBI-963 was a thirty-day, open-label, multicenter, observational study assessing the safety of oxycodone sustained release (Roxicodone SR 10 mg or 30 mg) tablets administered every 12 hours (q12 hours) to patients experiencing chronic pain. Dr. Monte Scheinbaum had reviewed those studies.

SECTION 7.2 SUMMARY OF STUDIES PERTINENT TO EFFICACY

SECTION 7.21 STUDY XIR0596

SECTION 7.2.1.1. Protocol Synopsis

Title:

An Open-Label, Multicenter Study to Evaluate the Safety Profile of Two Oral Formulations of Oxycodone (Immediate Release) for The Treatment of Patients with Moderate/Severe Chronic Pain

Objectives:

The primary objective of this study was to determine the safety profile of two new oral formulations (15- and 30-mg tablets) of immediate-release oxycodone hydrochloride for the treatment of patients with moderate-to-severe chronic pain. Secondary objectives were to assess the efficacy of oxycodone hydrochloride and to evaluate the correlation of oxycodone plasma concentrations with effect (Note: the PK evaluations will be the subject of a separate review).

Study Design:

This was an open-label, multi-center, observational study assessing the safety and effectiveness of 15- and 30-mg tablets of immediate-release oxycodone hydrochloride administered at regular schedule 4-6 hours intervals (approximately 4-6 doses/day) for the treatment of moderate-to-severe chronic pain. The study consisted of a 2-7 day stabilization period and a 7-day open-label treatment period. At the end of the 7-day open-label treatment period, patients could choose to participate in a 1-month (4-week) extension study (XIR0696).

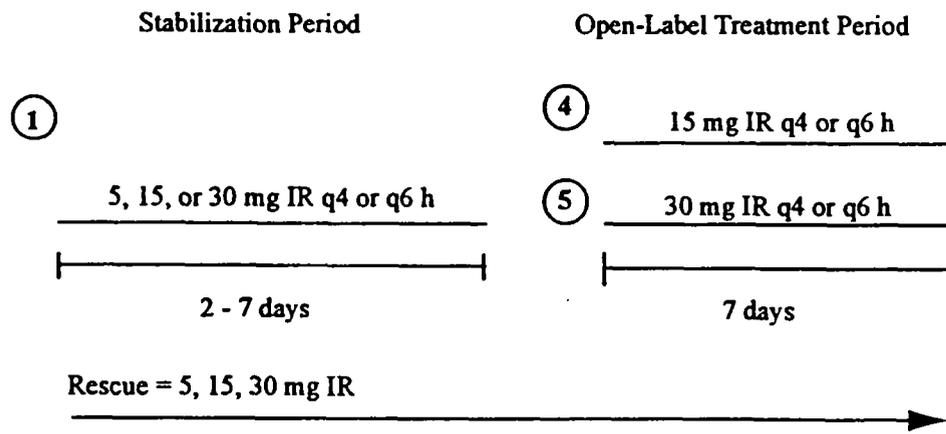
The stabilization period of this study was 2 to 7 days where patient stabilized on oxycodone hydrochloride (given on a regular schedule every 4-6 hours. A patient was considered to be stable when the total amount of oxycodone hydrochloride required every 24 hours did not change by more than 25% of the total daily dose (TDD) from the previous 24 hours. Patients were eligible for enrollment into the open-label treatment period after successful completion of the stabilization period given that they required a TDD of at least 60 mg/day. Any combination of the 5-, 15-, and 30-mg tablets could have been administered during the stabilization and the open-label treatment periods. The 5-, 15-, and 30-mg tablets were used as rescue medication for breakthrough pain.

Primary inclusion criteria included males or females, 18 to 80 years of age, inclusive; Patients who had moderate-to-severe chronic pain where the use of an opioid was

indicated; and Patients who required a TDD of at least 60 mg of oxycodone hydrochloride.

Study Schemata is provided below:

XIR0596



The circled numbers are used to identify study periods referenced and discussed in the safety section. Data from numbers 1-3 were pooled for the stabilization period summary and data from 4-9 were pooled for the treatment period summary.

Patients were not randomly assigned to treatment groups (i.e., 15- and 30-mg groups). Patients were grouped, at the analysis stage, into either the 15- or 30-mg treatment group based on the dosage form taken during the course of the study. Patients who received a dosage regimen consisting of the 15-mg oxycodone hydrochloride tablet were grouped in the 15-mg treatment group. Patients in the 15-mg formulation group may have also received 5-mg oxycodone tablets in order to titrate to the appropriate dose level. Any patient who was administered a 30-mg oxycodone tablet during either the stabilization or open-label treatment period of the study was grouped in the 30-mg treatment group. Patients in the 30-mg formulation group may have also received the 15- and/or the 5-mg tablets.

Section 7.2.1.2 Efficacy and Statistical Analysis:

Efficacy was assessed based on daily visual analogue scale (VAS) measures of pain (using a 100-mm scale where 0 mm represented “no pain” and 100 mm represented “worst pain possible”), the amount of rescue medication taken over 24 hours, and the end-of-study VAS global evaluation of pain control and satisfaction with study medication (using a 100-mm scale where 0 mm represented “poor” pain control/satisfaction and 100 mm represented “excellent” pain control/satisfaction. Safety and efficacy analyses were limited to descriptive statistics.

Section 7.2.1.3. Protocol Amendment:

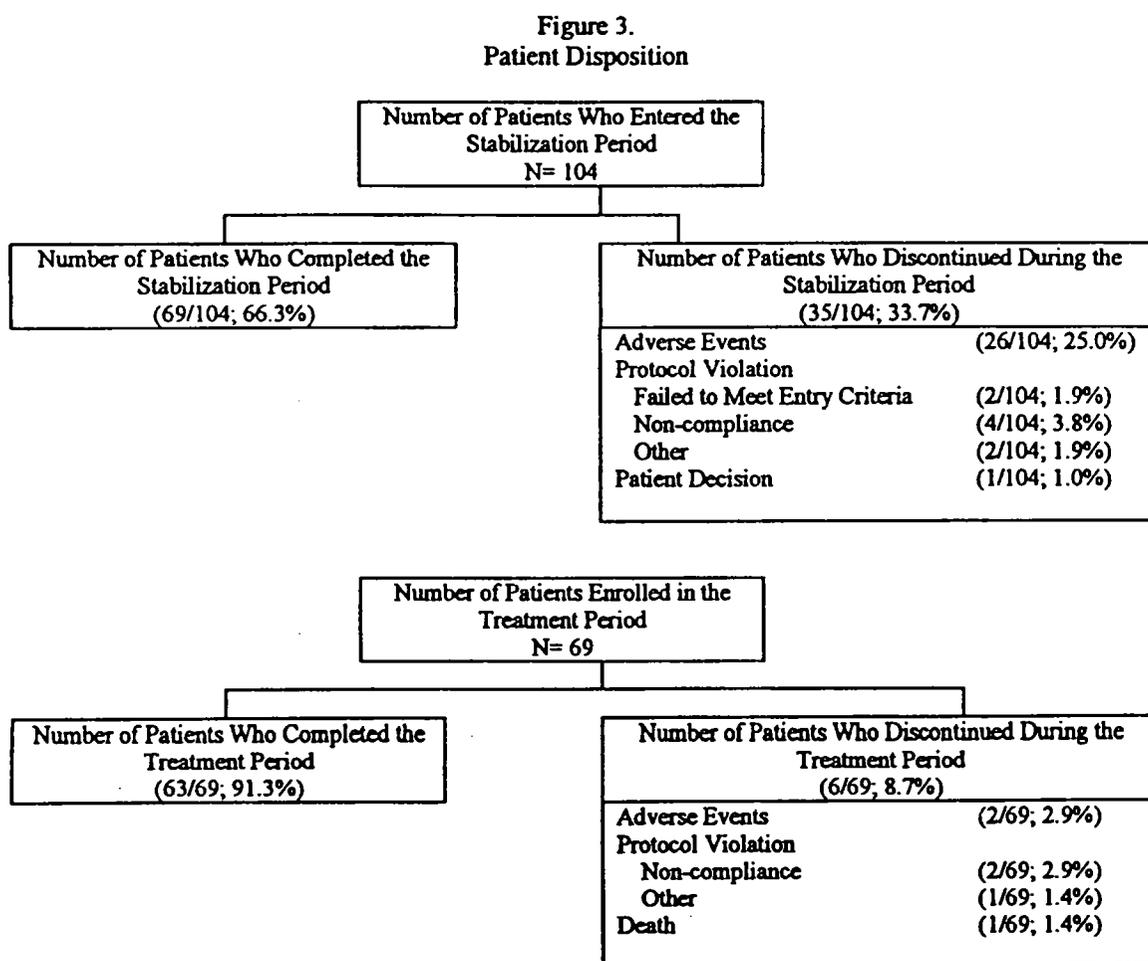
Amendment:

This amendment was dated 3/15/97. It consisted of the following features:

- 1) To eliminate the use of rescue medication taken every ~4 hours as an efficacy assessment. However, the use of rescue medication will be reported.
- 2) Descriptive statistics will be used to summarize baseline information, and delete the phrase of “baseline information for all patients entering the study after the stabilization period.”
- 3) Clarification of blood sample collection method: blood sample will be collected into tube containing EDTA rather than heparin.

Section 7.2.1.4 Conduct of Study

Patient Distribution and Disposition: Figure 3 presents a flowchart of patient disposition.



Study: Stabilization Period- XIR0596
 Treatment Period- XIR0596
 Data Source: Sponsor's Tables 1.1.1, 1.1.2, 1.2.1 and 1.2.2

A total of 108 patients were screened for eligibility into the study. Four of these patients failed screening prior to dosing and did not ingest the study medication. A total of 104

patients were entered in the stabilization period, and 69 (66%) patients completed the stabilization period. The remaining 35 patients (34%) discontinued the study prematurely. Of these, 26 patients discontinued due to adverse events, eight patients discontinued due to protocol violations, and one withdrew consent. The adverse events most frequently leading to early discontinuation were vomiting (10/26; 38%) and nausea (7/26; 27%). The type of adverse events experienced by opioid-naïve patients that lead to discontinuation were nausea, nervousness, and vomiting (Table 7).

Table 7
Discontinuations Due to Adverse Events - Stabilization Period

Adverse Event*	Patient Number	Treatment Group	Severity	Duration	Relationship	Outcome
Abnormal Vision	1410	15 mg	Moderate	17-24 hours	Probable	Resolved
Confusion	0907	15 mg	Moderate	2 days	Probable	Resolved
Hypertension	0902	30 mg	Moderate	17-24 hours	Probable	Resolved
Nausea	1108	15 mg	Moderate	7 days	Possible	Resolved
Nausea	1403	15 mg	Moderate	3-8 hours	Probable	Resolved
Nausea	1004*	15 mg	Severe	5 days	Definite	Resolved
Nausea	1602	30 mg	Severe	1-2 hours	Possible	Resolved
Nausea	1606	15 mg	Severe	6 days	Possible	Resolved
Nausea	0106*	30 mg	Severe	17-24 hours	Probable	Resolved
Nervousness	1807*	15 mg	Moderate	12 days	Definite	Resolved
Nervousness	1209	30 mg	Moderate	2 days	Probable	Resolved
Pain	0903	30 mg	Moderate	Continuing	Probable	Continuing
Pruritus	0801	15 mg	Moderate	Continuing	Possible	Continuing
Pruritus	1005	15 mg	Severe	1-2 hours	Definite	Resolved
Somnolence	0802	15 mg	Moderate	3 days	Definite	Resolved
Somnolence	0913	30 mg	Severe	3 days	Definite	Resolved
Vomiting	1101*	15 mg	Moderate	<1 hour	Possible	Resolved
Vomiting	0912	30 mg	Moderate	3-8 hours	Definite	Resolved
Vomiting	1406*	15 mg	Moderate	<1 hour	Probable	Resolved
Vomiting	0201	15 mg	Severe	9-16 hours	Definite	Resolved
Vomiting	0202	15 mg	Severe	9-16 hours	Definite	Resolved
Vomiting	1412*	15 mg	Severe	3-8 hours	Definite	Resolved
Vomiting	1829*	15 mg	Severe	17-24 hours	Definite	Resolved
Vomiting	1402	15 mg	Severe	<1 hour	Probable	Resolved
Vomiting	1404*	15 mg	Severe	<1 hour	Probable	Resolved
Vomiting	1407	15 mg	Severe	2 days	Probable	Resolved
Vomiting	1409*	15 mg	Severe	3-8 hours	Probable	Resolved

* Preferred Term from Listings 15.0, 16.0, and 17.0

* Indicates patient was opioid naïve

Source: Table 16.12.1 and Listings 8.1, 15.0, 16.0, 17.0, and 24.0

Sixty-three of the 69 patients (91%) completed the open label treatment period. Of these, 31 patients (45%) were grouped into the 15-mg tablet group and 38 patients (55%) were grouped into the 30-mg tablet group. Three patients from each treatment group discontinued the study prematurely. In the 15-mg tablet group, two patients (patients 0401 and 1405) discontinued due to adverse events (somnolence and confusion) and one patient (1801) due to protocol violation of non-compliance. In the 30-mg tablet group, one patient (1802) discontinued due to non-compliance, one (patient 0105) discontinued due to protocol violation, and one patient (0403) died.

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Section 7.2.1.5 Demographic and Other Baseline Characteristics

Table 8
Demographic and Other Baseline Characteristics – Study XIR0596

	Stabilization Period	Stabilization Period	Treatment Period	Treatment Period
Characteristic	15 mg (N=56)	30 mg (N=48)	15 mg (N=31)	30 mg (N=38)
Age (years)				
N	56	48	31	38
Mean (\pm SD)	48 (\pm 14)	47 (\pm 13)	48 (\pm 15)	46 (\pm 13)
Range	26-79	24-80	26-79	24-80
Gender				
Male	27 (48%)	35 (73%)	13 (42%)	28 (74%)
Female	29 (52%)	13 (27%)	18 (58%)	10 (26%)
Race				
Caucasian ^a	52 (93%)	45 (94%)	28 (90%)	36 (95%)
Black	3 (5%)	3 (6%)	2 (7%)	2 (5%)
Other ^b	1 (2%)	0 (0%)	1 (3%)	0 (0%)
Weight (kg)				
N	55	48	31	38
Mean (\pm SD)	83 (\pm 21)	81 (\pm 16)	80 (\pm 19)	81 (\pm 16)
Range	46-124	47-127	46-124	47-127
Etiology of Pain				
Chronic malignant pain	14 (25%)	9 (19%)	9 (29%)	6 (16%)
Chronic non-malignant pain	42 (75%)	39 (81%)	22 (71%)	32 (84%)
Average TDD of Oxycodone ^c				
Pts. with dosing information	56	48	31	35
Mean TDD (mg)	79 mg	157 mg	85 mg	151 mg
Median TDD (mg)	64 mg	130 mg	73 mg	148 mg
Average Range	20-178 mg	60-617 mg	30-186 mg	62-450 mg
Prior Use of Opioids				
Opioid-naïve patients	15 (27%)	5 (10%)	6 (19%)	2 (5%)
Patients with previous opioid use	41 (73%)	43 (90%)	25 (81%)	36 (95%)

^a Includes Hispanic

^b Includes Native American, Asian, and Other

^c Includes scheduled doses and rescue medication

Data Source: Sponsor's Tables 3.1.1 and 3.2.1

Of the patients enrolled in the stabilization period, 62 patients (62/104; 60%) were male and 42 (42/104; 40%) were female. The majority of patients were Caucasian (93%), and the average age of patients enrolled in the stabilization period was 48 years (range: 24-80). Forty-one of the 69 patients (59%) enrolled in the open-label treatment period were male and 28 (41%) of the patients were female. The majority of patients were Caucasian

(64/69; 93%), and the average age of patients enrolled in the open-label treatment period was 47 years.

Section 7.2.1.6 Sponsor's Efficacy Results:

There was little change in the daily pain intensity as measured by VAS scores. The average scores remained below 36 mm on a 100 mm scale where 0 represents no pain. The average pain control rating was 74.9 and the average satisfaction with the medication rating was 80.6 on a scale of 0-100 (where 100=Excellent). The mean VAS pain control rating score out of 100 for the 15-mg tablet group was 69.4 (median =80) and for the 30-mg group, it was 80.1 (Median=87). The number of patients requiring rescue medication for breakthrough pain decreased slightly over the course of the study. The dose level of rescue medication and the number of doses of rescue medication required varied slightly over the course of the study.

Section 7.2.1.7 Reviewer's Efficacy Discussion

This was an open-label study, and efficacy was not primary outcome. The mean VAS assessment scores for Days 0 through 8 (Table 9) are summarized by oxycodone formulation.

Table 9. Mean VAS Assessment Score (mm) During the Open-Label Treatment Period

Time point		Formulation	
		Oxycodone IR 15 mg	Oxycodone IR 30 mg
Day 0	N	31	37
	Mean	28.1	24.8
	S.D.	20.9	24.3
Day 1	N	31	35
	Mean	34.5	29.0
	S.D.	24.0	26.6
Day 2	N	31	35
	Mean	33.7	33.6
	S.D.	25.6	26.5
Day 3	N	33	35
	Mean	34.1	34.2
	S.D.	24.1	30.9
Day 4	N	30	35
	Mean	29.5	33.9
	S.D.	23.9	28.3
Day 5	N	30	35
	Mean	35.0	35.3
	S.D.	28.1	27.3
Day 6	N	29	35
	Mean	31.1	32.1
	S.D.	26.0	26.4
Day 7	N	29	32
	Mean	30.3	33.8
	S.D.	29.6	31.0
Day 8	N	20	22
	Mean	30.3	26.2
	S.D.	30.1	24.4

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These mean VAS scores were similar to the baseline mean VAS scores recorded at the end of stabilization (Day 0), which indicated continued pain relief. No inferential statistical tests were conducted, because the study was not randomized.

There were increased uses of rescue medication in the 30-mg group compared to the 15-mg group during the stabilization period while the use of rescue medication between the two groups was similar during the treatment period (Table 10). The 30-mg group contained patients with a high average daily dose of morphine. In addition, patients received a combination of 5, 15 and 30 mg tablets. The results indicate that those patients may have some difficulties in dose titration and product conversions (from other opioids to oxycodone hydrochloride) compared to the 15-mg group. Once patients are stabilized on oxycodone hydrochloride, it appears that the need for rescue medication is similar (in rate) between the two groups.

Table 10
Comparison of Rescue Medication Uses

	Stabilization Period	Stabilization Period	Treatment Period	Treatment Period
Rescue Medication	15 mg (N=56)	30 mg (N=48)	15 mg (N=31)	30 mg (N=38)
Pts. who required rescue med.	31 (55%)	37 (77%)	21 (68%)	25 (66%)
Average rescue dose/day (mg)	14 mg	26 mg	11 mg	27 mg
Range	5-56 mg	5-84 mg	5-28 mg	5-116 mg
Average no. of doses/day	2 doses	3 doses	2 doses	2 doses
Range	1-6 doses	1-7 doses	1-4 doses	1-6 doses

SECTION 7.2.2 STUDY XIR0696

SECTION 7.2.2.1. Protocol Synopsis

Title: An Open-Label, Multicenter, Extension Study to Evaluate the Long-Term Safety Profile of two Oral Formulations of Oxycodone (Immediate Release) for the Treatment of Patients With Moderate/Severe Chronic Pain.

Objectives: The objective of this study was to generate long-term safety information for two oral formulations (15- and 30-mg tablets) of IR oxycodone hydrochloride for the treatment of patients with moderate to severe chronic pain.

Study Design:

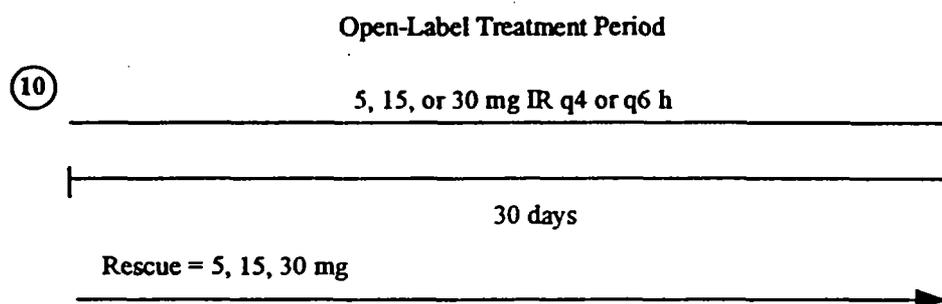
This was a 4-week (1 month), open-label, multicenter, extension study of Protocol XIR0596 to assess the safety of 15- and 30-mg tablets of oxycodone hydrochloride administered at regular schedule 4-6 hours intervals (approximately 4-6 doses/day; TDD range: 60-480 mg) for the treatment of moderate-to-severe chronic pain. Patients from

Protocol XIR0596 entered the extension study within 14 days of having completed the XIR0596 study, were allowed to continue to taking their respective doses of oxycodone hydrochloride for an additional 4 weeks. Dosage titration during the extension study was permitted.

Primary inclusion criteria included males or females, 18 to 80 years of age, inclusive; Patients who had moderate-to-severe chronic pain where the use of an opioid was indicated; and Patients had completed the 7-day MIR0596 study and had continued need for pain control as well as an acceptable safety profile.

Study Schemata is provided below:

XIR0696



The circled numbers are used to identify study periods referenced and discussed in the safety section. Data from numbers 1-3 were pooled for the stabilization period summary and data from 4-9 were pooled for the treatment period summary.

Section 7.2.2.2 Efficacy and Statistical Analysis:

Efficacy was assessed based on weekly visual analogue scale (VAS) measures of pain, the use of rescue medication taken each week, and the end-of-study VAS global evaluation. These assessments were based on weekly responses to the questions "How much pain did you have this week?", the end-of-study VAS global VAS assessment of pain control ("How well did this medication control your pain?") and patient satisfaction with study medication ("How satisfied were you with this medication?"). Weekly assessments of pain and end-of-study global assessments were made using a 100-mm visual analogue scale.

Patients who required a dosage regimen consisting of only the 15-mg tablet formulation or the 15-mg formulation in combination with 5-mg tablets were grouped in the 15-mg tablet formulation group. Patients who required a dosage regimen consisting of the 30-mg tablet formulation, alone or in combination with 5-mg tablets and/or 15-mg tablets, were grouped in the 30-mg tablet formulation group. Safety and efficacy analyses were limited to descriptive statistics.

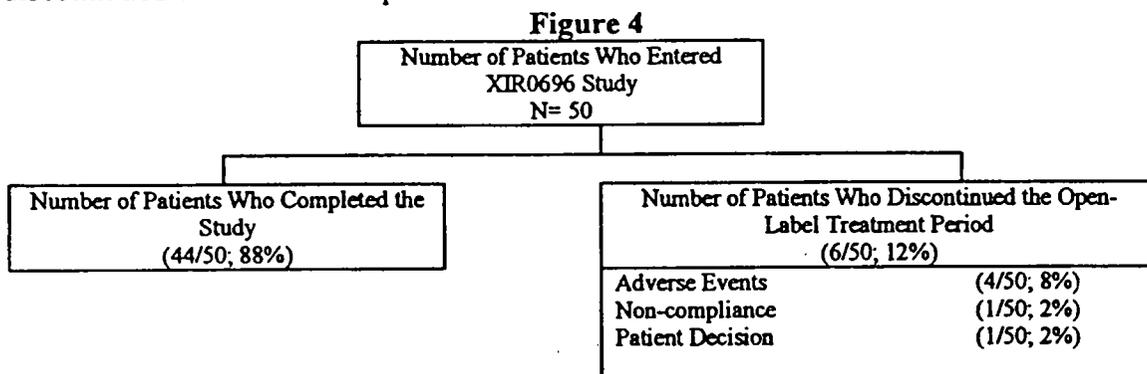
Section 7.2.2.3. Protocol Amendment:

This amendment was dated 4/4/97. It consists of changes of numbers of safety assessments including physical examinations, vital sign measurements, and clinical laboratory evaluations, and it indicates that safety will be assessed based on adverse experiences reporting. Incidence of adverse events will be summarized using descriptive statistics.

Section 7.2.2.4 Conduct of Study

Patient Distribution and Disposition

A total of 50 patients were enrolled (19 and 31 patients in the 15- and 30-mg formulation groups, respectively) from a total of 10 investigational sites. Forty-four (44) of these patients completed the study (Figure 4). In the 15-mg tablet group two patients discontinued prematurely due to an adverse event (pneumonia and gastrointestinal carcinoma) and one patient withdrew consent. In the 30-mg tablet group two patients discontinued due to an adverse event (cerebrovascular accident and rash) and one patient discontinued due to non-compliance.



Data Source: Sponsor's End-of-Text Tables 1.1., 1.2, and 5.6

Discontinuations Due to Adverse Events

Patient Number	Treatment Group	Adverse Event ^a	Severity	Duration	Relationship	Outcome
0402	30 mg	Cerebrovascular accident (SAE)	Mild	Continuing	Not Related	Continuing
1501	15 mg	Gastrointestinal carcinoma (AE)	Severe	Continued until patient's death	Not Related	Patient died due to aspiration pneumonia
0905*	15 mg	Pneumonia (SAE)	Severe	4 days	Not Related	Resolved
1604	30 mg	Rash (AE)	Moderate	5 days	Possible	Resolved

^a Preferred Term from Listings 11.0, 12.0, and 13.0

* Indicates patient was opioid naive prior to the XIR0596 study. (Source: Listing 8.1 of XIR0596)

Source: End-of-text Tables 6.11.1a, 6.11.1b, 2.12, Listings 11.0, 12.0, 13.0, 18.0.

Section 7.2.2.5 The demographic and baseline characteristics of the patients enrolled in extension study XIR0696 (Table 11).

**Table 11.
Demographic and Baseline Characteristics - Study XIR0696**

Characteristic	15 mg (N=19)	30 mg (N=31)	Overall (N=50)
Age (years)			
N	19	31	50
Mean (SD)	50 (±15)	44 (±13)	50 (±14)
Range	26-79	24-69	24-79
Gender			
Male	6 (32%)	23 (74%)	29 (58%)
Female	13 (68%)	8 (26%)	21 (42%)
Race			
Caucasian ^a	17 (90%)	30 (97%)	47 (94%)
Black	1 (5%)	1 (3%)	2 (4%)
Other ^b	1 (5%)	0 (0%)	1 (2%)
Weight (kg)			
N	19	31	50
Mean (SD)	78 (±18)	83 (±17)	81 (±17)
Range	48-109	47-133	47-133
Etiology of Pain			
Chronic Malignant Pain	6 (32%)	2 (7%)	8 (16%)
Chronic Non-Malignant Pain	13 (68%)	29 (94%)	42 (84%)

^a Includes Hispanic

^b Includes Native American, Asian, and Other

Study XIR0696

Data Source: Sponsor's Individual study report

The average age of patients enrolled in extension study XIR0696 was 50 years (range: 24-79 years) and was slightly lower for patients grouped in the 30-mg group (44 years) than for patients grouped in the 15-mg group (50 years). Fifty-eight percent (29/50) of the patients were male and 42% (21/50) of the patients were female. The majority of the patients were Caucasian (94%; 47/50) and were being treated for chronic non-malignant pain (84%; 42/50).

The overall average total daily dose (TDD) taken by patients during the extension study was approximately 137 mg/day and ranged from 134-141 mg/day. The average total daily dose of patients grouped in the 30-mg formulation group was higher (172 mg/day) than those patients grouped in the 15-mg formulation group (83 mg/day). The average total daily dose included scheduled and rescue doses of the study medication.

Section 7.2.2.6 Sponsor's Efficacy Results:

Overall mean duration of exposure to study drug was 28.5 days. There was little change in the weekly pain intensity as measured by VAS scores. The average scores remained below 36 mm on a 100 mm scale where 0 represents no pain. A majority of patients rated global evaluation of pain control and the satisfaction rating at 80 or better (where 100=Excellent).

The average dose level of rescue medication taken for breakthrough pain increased (Week 1 – baseline = 137.0 mg; Week 4 = 172.4 mg) as did the average number of doses of rescue medication taken for breakthrough pain increased (Week 1 – baseline = 12.4 doses; Week 4 = 14.4 doses) during the course of the study.

Section 7.2.2.7 Reviewer's Efficacy Discussion

This was an open-label study, and efficacy was not primary outcome. The mean VAS assessment scores for Week 1 through 4 are summarized by oxycodone formulation in Table 12. These mean VAS scores in the follow-ups were similar to the baseline mean VAS scores recorded at Week 1, which indicated continued pain relief. The increased use of rescue medication is expected because of development of tolerance. No inferential statistical tests were conducted since the study was not randomized.

Table 12. Summary of Weekly Pain Intensity Rating Scores (VAS)

Time point		Formulation	
		Oxycodone IR 15 mg	Oxycodone IR 30 mg
Week 1	N	19	30
	Mean	36.5	34.9
	S.D.	32.1	25.2
Week 2	N	17	30
	Mean	30.8	36.2
	S.D.	26.7	27.7
Week 3	N	17	30
	Mean	31.8	38.3
	S.D.	29.7	30.1
Week 4	N	16	28
	Mean	32.4	34.8
	S.D.	33.7	28.6

SECTION 7.2.3 OTHER SUPPORTING CLINICAL TRIALS

SECTION 7.2.3.1 STUDY CBI-961/962

The to-be-marketed 15- and 30-mg tablets were not used in this study. However, the 5-mg IR tablet formulation with similar dosage ranges was used (in Study CBI-961/962, 1252 and 963), which provides some supporting evidence on efficacy based on bioequivalence data reviewed in Section 6.11. Studies CBI-1252 and CBI-963 are

reviewed below for the same reason. Patients were treated based on the amount of medication needed to control pain. The formulation strengths, including 5 mg tablets, were used to comprise the dose. Dr. Monte Scheinbaum had reviewed the study. A summary of his review is provided below.

Section 7.2.3.1.1 Protocol Synopsis

Title: Randomized, Double-Blind, Double-Dummy, Active-Controlled, Multi-Site Crossover Investigation Comparing the Efficacy of Oxycodone SR (Roxicodone 10 mg or 30 mg Tablets) Administered Every Twelve Hours to Oxycodone IR (Roxicodone® 5 mg Tablets) Administered Every Six Hours in Patients With Chronic Cancer Pain.

Objective: The primary aim of this study was to assess the ability of oxycodone SR tablets administered every 12 hours (q 12 hours) versus oxycodone IR tablets administered every 6 hours (q 6 hours) to control pain in patients with chronic pain of cancer origin. Secondary objectives were to compare population pharmacokinetics and safety for the two formulations.

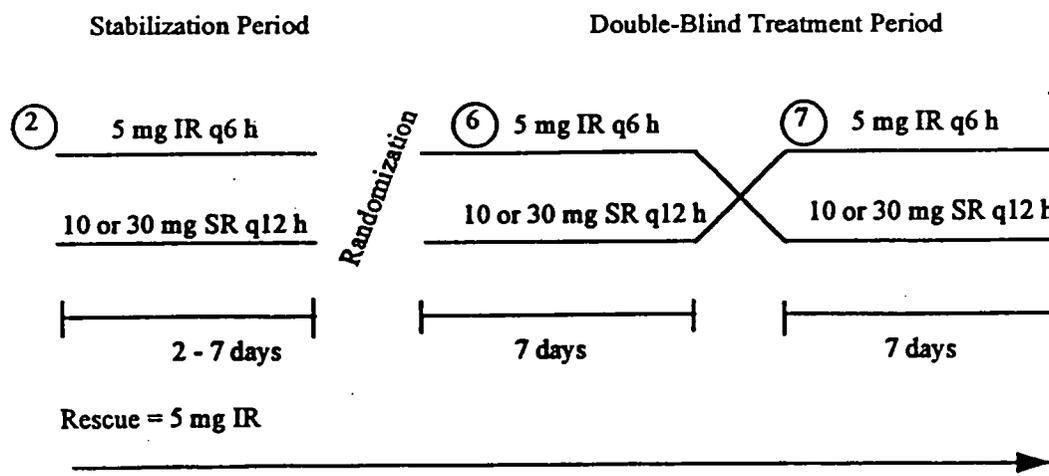
Population: Patients with pain intensity VAS assessment score ≤ 50 mm (0 = no pain, 100 = worst pain possible) for over the 24 hours prior to randomization were eligible for the study.

Study Design:

This was a randomized, double-blind, double-dummy, active-controlled, multi-center two-period crossover (one-week legs) investigation. The study was divided into a Stabilization Period of five days and a Double-blind Treatment Period lasting two weeks.

Study Schemata

CBI-961/962



The circled numbers are used to identify study periods referenced and discussed in the safety section. Data from numbers 1-3 were pooled for the stabilization period summary and data from 4-9 were pooled for the treatment period summary.

Patients completed each day VAS (100-mm) assessment measuring pain intensity “right now”, immediately prior to their 6:00 am, 12:00 noon, and 6:00 p.m. doses. The primary efficacy variables were the VAS scores as recorded on Day 6 of each 7-day double-blind treatment.

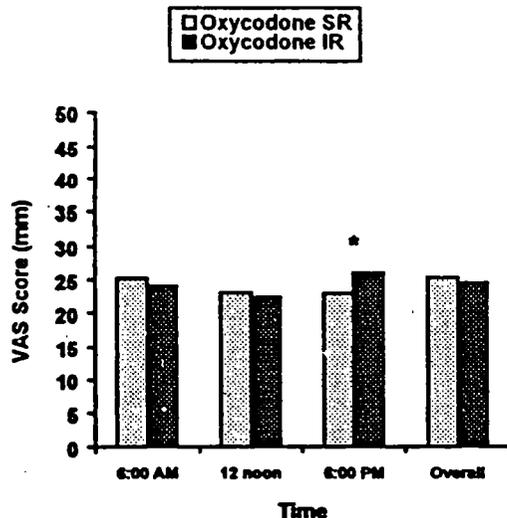
A calculated sample size of 34 patients for this cross-over study, 17 in each of the two treatment sequences, provided 90% power to ensure that the average difference in VAS pain relief between formulations was no more than 8 mm based on a 100-mm scale.

Results:

A total of 69 patients entered, and 50 of these patients (72.5%) completed the stabilization period. Forty-nine of these 50 patients were randomized to receive one of two treatment sequences during the double-blind treatment period: 24 patients received SR/IR and 25 patients received the IR/SR sequence. One patient withdrew consent prior to randomization. There were 47 of the 49 (95.9%) randomized patients who actually took study medication during this phase of the study. There were thirty-seven (78.7%) patients who completed this phase of the study; five patients withdrew due to AE’s (3 IR, 2SR), three withdrew due to inadequate therapeutic response (1 IR, 2 SR), and two withdrew consent (1 IR, 1 SR).

There were no significant differences between treatments for the overall day 6 means and at the 6 am and 12 noon time points (Figure 5). There was a significant difference ($p=0.049$) favoring SR (22.94 vs. 26.00 mm) at 6 pm. However, this difference may not be clinically meaningful based on the sponsor’s defined meaningful difference of 8 mm.

Figure 5: Mean VAS Score (mm) on Day 6



* $p < 0.05$

The numbers and percentages of patients (intent-to-treat population) experiencing breakthrough pain were not significantly different for either formulation for Days 1-3, Days 4-6, and Days 1-6.

Conclusion

The efficacy of the sustained release formulation (10 mg or 30 mg Tablets) given q12h appeared no different than that seen with oxycodone IR (5 mg tablets) administered every 6 hours in this study of cancer patients with chronic pain.

SECTION 7.2.3.2 STUDY CBI-1252

The to-be-marketed 15- and 30-mg tablets were not used in this study. Patients were treated based on the amount of medication needed to control pain. The formulation strengths, including 5 mg tablets, were used to comprise the dose. Dr. Monte Scheinbaum had reviewed the study. A summary of his review is provided below.

Title: Randomized, Double-Blind, Double-Dummy, Active-Controlled, Multi-Site Crossover Investigation Comparing the Efficacy of Oxycodone SR (Roxicodone 10 mg or 30 mg Tablets) Administered Every Twelve Hours to Oxycodone IR (Roxicodone® 5 mg Tablets) Administered Every Six Hours in Patients With Chronic Pain.

Objective: The primary aim of this study was to compare the efficacy of oxycodone SR tablets administered every 12 hours (q 12 hours) versus oxycodone IR tablets administered every 6 hours (q 6 hours) for controlling chronic pain of cancer or non-malignant origin.

Population:

Patients with chronic pain of pain intensity VAS assessment score < 70 mm (0 = no pain, 100 = worst pain possible), who were currently being treated with at least 20 mg daily of oral oxycodone, but required no more than two breakthrough doses of analgesic during the prior 24 hours, were eligible for randomization.

Study Design:

This was a multicenter, randomized, double-blind, double-dummy, active-controlled, two-period crossover trial, comparing the efficacy of oxycodone SR administered q 12 hours to oxycodone IR administered q 6 hours in patients with chronic pain of cancer or non-cancer origin. The study was divided into a Stabilization Period of five days and a Double-blind Treatment Period lasting two weeks.

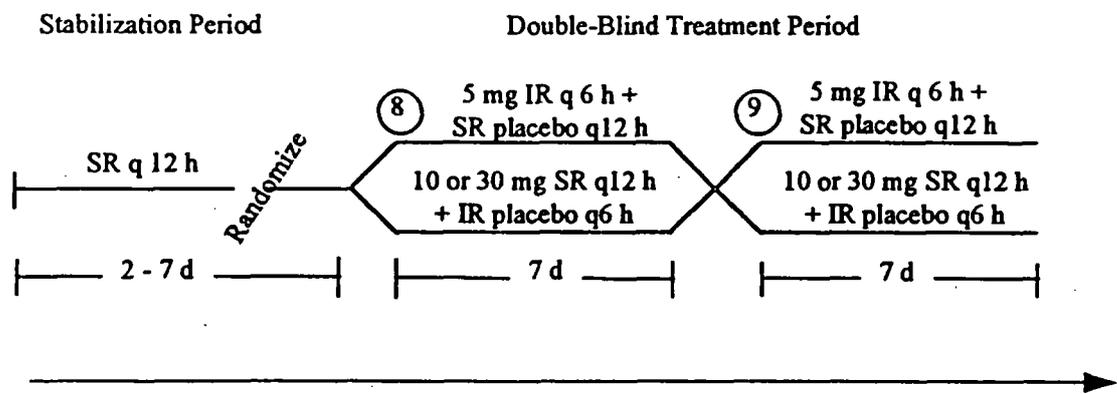
Patients completed a VAS assessment measuring pain intensity “right now,” immediately prior to their double-blind 6:00 am, 12:00 noon, and 6:00 pm doses. The scores recorded on Day 6 of each 7-day double-blind treatment, were the primary efficacy variables for the study.

An “intent-to-treat” analysis of efficacy was performed, including all patients who were randomized, received at least one dose of double-blind study drug and recorded at least

one VAS score or used rescue medication. One treatment was considered more effective if there was >10 mm less VAS pain or at least 10 mg less escape medication use on Day 6 (or its alternate) with no opposing exacerbation of the other parameter.

Study Schemata

CBI-1252



The circled numbers are used to identify study periods referenced and discussed in the safety section. Data from numbers 1-3 were pooled for the stabilization period summary and data from 4-9 were pooled for the treatment period summary.

Results:

A total of 114 patients entered and 87 of these patients (76.3%) completed the stabilization period; 86 of these 87 patients were randomized to receive one of two treatment sequences during the double-blind treatment period. Forty-two patients were randomized to receive SR/IR and 44 to the IR/SR sequence. One patient on SR withdrew due to protocol violation, one on IR was lost to follow-up, and two (one on each treatment) withdrew consent.

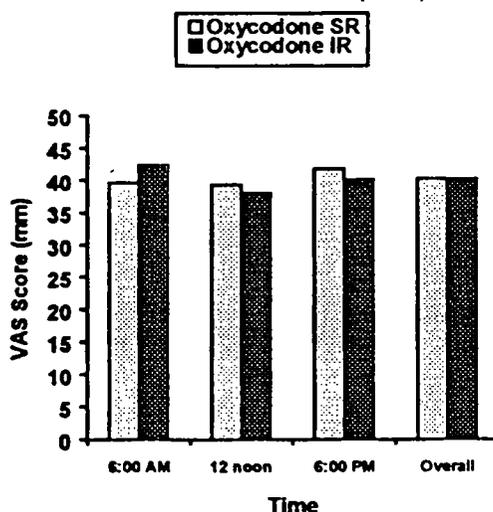
There were no statistically significant differences between sequence groups in demographic and baseline characteristics.

The mean VAS scores during SR treatment ranged from 39.48 mm to 41.94 mm at specified time points, with the overall mean score on Day 6 of 40.35 mm. During IR treatment, the mean VAS scores on Day 6 ranged from 38.08 mm to 42.43 mm, with an overall mean score of 40.33 mm. These mean VAS scores were consistent with the mean VAS score recorded at the end of stabilization (41.1 mm), which indicated continued pain relief. The mean changes from baseline for VAS scores on Day 6 were not statistically different between the SR and the IR formulations.

The overall total daily dose of rescue medication was approximately 14 mg per day for patients who took either formulation of oxycodone. For Days 1 through 6, the majority of patients (76/79; 96%) required at least one dose of rescue medication while on each formulation of oxycodone. The McNemar's chi-square test shows no statistically

significant association between drug formulation and the need for at least one dose of rescue medication (Figure 6).

Figure 6. Mean VAS Score (mm) on Day 6



Conclusion:

The primary efficacy variable, VAS pain intensity for Day 6, had similar mean values for both formulations. The efficacy of the sustained release formulation given q12h appeared no different than that seen with oxycodone IR administered every 6 hours in this study of patients with chronic pain.

SECTION 7.2.3.3 STUDY CBI-963

The to-be-marketed 15- and 30-mg tablets were not used in this study. Patients were treated based on the amount of medication needed to control pain. The formulation strengths, including 5 mg tablets, were used to comprise the dose. Dr. Monte Scheinbaum had reviewed the study. A summary of his review is provided below.

Title: A Thirty-Day, Open-Label, Multi-Center Observational Study Assessing the Safety of Oxycodone Sustained Release (Roxicodone SR 10 mg or 30 mg) Tablets Administered Every Twelve Hours (q12 Hours) in Patients Experiencing Chronic Pain.

Objectives: To evaluate the safety profiles of oxycodone SR tablet.

Population: Eligible patients had a diagnosis of chronic pain of malignant or non-malignant origin requiring continued treatment with opioid analgesics. They were to have pain intensity VAS score ≤ 50 mm (0 mm = no pain and 100 mm = the worst possible pain) and require no more than two breakthrough doses of analgesic during the

previous 24-hours prior to entry into the SR Treatment Period. Patients were to require a total daily dose (TDD) of at least 20 mg of oral oxycodone IR.

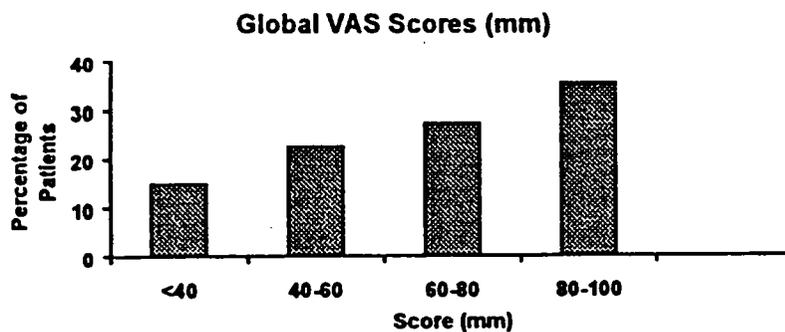
Study Design: This was a 30-day, open-label, multi-center, observational study assessing the safety and effectiveness of oxycodone SR tablets administered q 12 hours in patients with chronic pain. Patients underwent a 2-7 day stabilization period with oxycodone IR. When eligible patients required no more than 2 doses of breakthrough pain medication in a 24-hour period and, on a verbal scale of 0 to 10, pain intensity was rated ≤ 5 , and 100-mm VAS assessment was ≤ 50 mm for pain intensity over the prior 24-hour dosing period, they entered into the 30-day SR Treatment Period of the study.

Results:

A total of 292 patients entered the IR Stabilization Period, and 238 patients (81.5%) completed this phase of the study. Two hundred thirty-three patients entered the SR Treatment Period, and 188 patients (80.7%) completed this phase of the study. Of the 45 patients who discontinued prior to completion of the SR Treatment Period, eight had inadequate therapeutic response, twenty-one had adverse experiences, and the remainder were discontinued for other reasons. The patient population of the SR Treatment Period was predominantly female (63.5%) and white (93.6%), with a mean age of 52.8 years. Most of the patients (218/233, 93.6%) suffered from chronic pain that was unrelated to cancer and all of them had taken other opioid medication prior to this study.

Global VAS scores for “intent-to-treat” patients (0 mm = poor pain control; 100 mm = excellent pain control) indicated that patients rated oxycodone SR as generally effective (mean score: 65.9 mm) in controlling their pain over the 30-day SR Treatment Period. Global VAS scores for completers and for patients grouped on the basis of cancer vs. non-cancer pain were generally similar (Figure 7).

Figure 7. Global Pain Control VAS Scores (CBI-963)



Patients who entered the SR Treatment Period, regardless of whether they completed the study, took an average daily dose of 71.1 mg of oxycodone SR. They required an average of 8 to 13 mg of rescue medication per day taken in one or two doses per day, on average. Rescue medication was needed for at least half of the duration of the time periods

examined. The majority of patients (158/233, 67.8%) did not require an adjustment of their oxycodone SR TDD over the course of the study.

Conclusion

This was an open-label study intended primarily to provide evidence of repeated-dose safety over a 30 day period. However, the efficacy results of this nonpivotal trial are in accord with those of the double-blind, controlled trials.

SECTION 8.0 SAFETY FINDINGS

The primary focus of this review is to present the safety profiles of the 15-mg and 30-mg oxycodone IR tablet formulations. In addition, the safety profiles of the 15-mg and 30-mg oxycodone IR tablet formulations are compared with the safety profile of the currently marketed 5-mg oxycodone IR tablet formulation following drug administration at comparable dosage levels.

SECTION 8.1 METHODS

The safety data from 10 completed studies (five Phase I and five Phase II/III studies) conducted with 5-, 15-, or 30-mg oxycodone IR tablets are evaluated. The five Phase I human pharmacokinetic and bioavailability studies (315-05, 315-07, XIR0396, XIR0296, and XIR0196) were conducted in healthy volunteers. These studies provide safety information following acute dosing with oxycodone IR in healthy (opioid-naive) volunteers. Two primary open-label safety trials (XIR0596 and XIR0696) were conducted primarily to evaluate safety of the to-be-marketed 15- and 30-mg tablets. Three additional trials (CBI-961/962, CBI-963, and CBI-1252) were conducted to evaluate the safety and efficacy of Roxane's oxycodone sustained-release (SR) tablet formulations (NDA 20-932). However, since the 5-mg immediate-release tablet formulation was also used in these studies, relevant safety information from exposure to the 5-mg IR formulation is included in this review.

The sponsor has pooled safety data from four Phase II/III clinical studies (XIR0596, CBI-961/962, CBI-963, and CBI-1252) into one database and the data are presented by stabilization period and treatment period. Each study consisted of a 2-7 day stabilization period and at least a 7-day treatment period. There was no a Stabilization Period in study XIR0696. Because the XIR0696 study is an extension of the XIR0596 study and provides extended exposure data from the same patients presented in the XIR0596 study, these data were not included as additional patients in the pooled ISS analysis. All relevant safety data collected during this study are presented separately. Safety data from five human pharmacokinetic and bioavailability studies have been also pooled in a separate data base and provide supportive safety information pertaining to acute oxycodone exposure in an opioid-naive, healthy-volunteer population.

Patients who only needed the 15-mg tablet (i.e., did not need 30 mg or more at each dose administration) to make up a scheduled dose were grouped into the 15-mg tablet group. Likewise, patients who needed the 30-mg tablet (i.e., needed 30 mg or more at each dose administration) were grouped into the 30-mg tablet group. Patients grouped in the 30-mg tablet group may have also received the 15-mg tablet (i.e., a patient who received a 30-mg tablet at any point during the study and then changed to a dosage regimen that did not consist of the 30-mg tablet was grouped into the 30-mg group). However, patients grouped in the 15-mg tablet group did not receive the 30-mg tablet. Patients in either group may have also received the 5-mg tablet as part of the scheduled dose or as rescue medication.

Statistical comparisons of the data were not performed due to the nature of the pooled data which came from portions of the clinical trials conducted for the sustained-release NDA and from the immediate-release trials conducted for this NDA. It would be difficult to interpret the results of the statistical analysis due to the imbalance in sample sizes between the 5-mg group and the 15- and 30-mg groups, such analyses may result in spurious interpretation.

The sponsor used the COSTART classification system for coding the actual AE's as written on the CRF to the preferred terms.

This review of safety of oxycodone 15- and 30-mg tablets in the exposed population focuses on the information provided by the sponsor in the Integrated Summary of Safety and study summaries for the above noted trials. In addition, narrative summaries of deaths, serious adverse events and discontinuations were reviewed. Finally, many of the original tabular summaries were examined in their entirety.

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SECTION 8.1 SERIOUS ADVERSE EVENTS:

The number of subjects and patients who died, or experienced serious adverse event(s), is summarized in Table 13:

Table 13.
Number (%) of Patients who Died, Had Serious Adverse Experiences, and Had Adverse Experiences Resulting in Discontinuation

Category	Oxycodone IR Formulation Group				
	5-mg IR Tablet	15-mg IR Tablet	30-mg IR Tablet	5 mg/5 ml Oral Solution	All Treatments
Deaths					
Human PK and BA Studies	0/96 (0%)	0/25 (0%)	0/45 (0%)	0/51 (0%)	0/124 (0%)
Clinical Safety Studies					
Stabilization Period	1/349 (<1%)	0/56 (0%)	0/48 (0%)	N/A	1/453 (<1%)
Treatment Period	0/125 (0%)	0/31 (0%)	1/38 (3%)	N/A	1/194 (1%)
Extension Study (XIR0696)	N/A	1/19 (5%)	0/31 (0%)	N/A	1/50 (2%)
Total	1	1	1	0	3
Serious Adverse Events					
Human PK and BA Studies	0/96 (0%)	0/25 (0%)	0/45 (0%)	0/51 (0%)	0/124 (0%)
Clinical Safety Studies					
Stabilization Period	3/349 (1%)	0/56 (0%)	0/48 (0%)	N/A	3/453 (1%)
Treatment Period	2/125 (2%)	1/31 (3%)	1/38 (3%)	N/A	4/194 (2%)
Extension Study (XIR0696)	N/A	2/19 (11%)	1/31 (3%)	N/A	3/50 (6%)
Total	5	3	2	0	10

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

Data Source: Sponsor's Tables 6.1.1, 6.1.2, 6.2.1, 6.2.2, 6.3.1, 6.3.2 and individual study reports

SECTION 8.2.1 DEATHS:

Overall, there were three deaths (Table 14), and two occurred in the studies on the to-be-marketed 15- and 30-mg tablets: one during the treatment period (Study XIR0596; Patient 0403), one during the extension study (Study XIR0696; Patient 1501). One death occurred during the stabilization period (Study 961/962; Patient 0002; 5-mg tablet group). All three patients died from complications associated with their underlying disease. Patient 0403 (Study XIR0596) died from heart failure, due to 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. Patient 0002 (Study CBI-961/962) died from breast cancer during the stabilization period. None of these deaths was considered by the investigators to be related to the study medication. The reviewer agrees (the same statement applies to in all safety review sections unless the reviewer specifies).

Table 14
All 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
CBI-961/962 Stabilization	02/0002	46	Female	5 mg	60 mg/day	Breast carcinoma	5 days	Not related

SECTION 8.2.2 NON-FATAL SERIOUS ADVERSE EVENTS:

A total of 5 patients experienced serious adverse events in the studies on the to-be-marketed 15- and 30-mg tablets (Table 15). Two patients experienced serious adverse events during the treatment period (Study XIR0596; Patients 0403 and 1405), and three patients experienced serious adverse events during the extension study (Study XIR0696; Patients 0402, 0905, and 1501). Of those SAE's reported, one (patient 1405) was judged by the investigators to be related or possibly related to study drug.

Table 15
Serious Adverse Events Reported During the Clinical Studies (XIR0596/0696)

Study No. Period.	Site No. /Patient No.	Age (yr.)	Gender	IR Tablet Group	Average TDD (mg/day)	COSTART Term and SAE Classification	Relation to Study Drug
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
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
XIR0696 Extension	04/0402	64	Male	30 mg	180 mg	Cerebrovascular accident (stroke) resulting in prolonged hospitalization	Not related

Five patients experienced serious adverse events in the studies on the 5-mg tablets (Table 16). Three patients experienced serious adverse events during the stabilization period (Study CBI-961/962; Patients 0002, 0011, and 0006), and two patients experienced serious adverse events during the treatment period (Study CBI-961/962; Patients 0015 and 0001). No patients experienced serious adverse events during the human pharmacokinetic and bioavailability studies.

Table 16
Serious Adverse Events Reported During the Clinical Studies

Study No. Period.	Site No. /Patient No.	Age (yr.)	Gender	IR Tablet Group	Average TDD (mg/day)	COSTART Term and SAE Classification	Relation to Study Drug
CBI-961/962 Stabilization	02/0002	46	Female	5 mg	60 mg/day	Breast carcinoma resulting in death	Not related
						Sepsis due to cat bite resulting in hospitalization	Not related
CBI-961/962 Stabilization	02/0011	59	Female	5 mg	120 mg/day	Sepsis resulting in hospitalization	Not related
CBI-961/962 Stabilization	09/0006	54	Male	5 mg	60 mg/day	Worsening of GI carcinoma; and	Unlikely
						Confusion resulting in prolonged hospitalization	Possibly
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

SECTION 8.3 ASSESSMENT OF DROPOUTS

SECTION 8.3.1 OXICODONE HCL EXPOSURE

Table 17 and 18 summarize the duration of exposure by average total daily dose for 15 and 30-mg formulation groups during the stabilization and treatment period. The average TDD was calculated using all available dosing information (i.e., scheduled + rescue doses) during the study period. The total medication taken during the week was divided by the number of days of study participation.

The maximum duration of exposure during the XIR0596 study, including exposure during the stabilization period and treatment period, was 22 days. The overall maximum duration of exposure of patients who continuously dosed with oxycodone from the beginning of the stabilization period in XIR0596 to the end of the treatment period in XIR0596 was 56 days.

A total of 56 patients were in the 15-mg oxycodone IR tablet group during the stabilization period (Table 17). Patients averaged a TDD between 60 and 120 mg/day and accounted for 61% (34/56) of the patients. Twenty-three percent (13/56) of patients averaged a TDD that was less than 60 mg/day and 16% (9/56) averaged a TDD greater than 30 mg/day.

Forty-eight patients were in the 30-mg treatment group during the stabilization period. Patients in this group average a TDD that was 60 mg/day or higher. Forty-two percent (20/48) of the patients averaged a TDD between 60 and 120 mg/day and 58% (28/48) averaged a TDD over 120 mg/day.

Table 17 – (Study: XIR0596)
Duration of Exposure by Average Total Daily Dose for Each Formulation - *Stabilization Period*

Therapy Duration (days)	Number (%) of Patients Exposed			
	Average Total Daily Dose (mg/day) of Oxycodone IR*			
	<60 n (%)	60-120 n (%)	>120 n (%)	Total n (%)
15 mg (N=56)				
≤ 7	4	13	1	18 (32%)
>7-14	7	20	8	35 (63%)
>14	2	1	0	3 (5%)
Overall	13 (23%)	34 (61%)	9 (16%)	56 (100%)
30 mg (N=48)				
≤ 7	0	6	5	11 (23%)
>7-14	0	12	20	32 (67%)
>14	0	2	3	5 (10%)
Overall	0 (0%)	20 (42%)	28 (58%)	48 (100%)
Total (N=104)	13 (13%)	54 (52%)	37 (35%)	104 (100%)

* Each patient's average TDD (including rescue medication) was calculated based on the number of days of dosing. Denominator used to calculate the percent is 56 patients for the 15 mg group, and 48 patients for the 30 mg group. Total indicates the total number of patients exposed to each therapy duration for each formulation group. Overall indicates the overall number of patients averaging a TDD in each TDD category for each formulation group. Study: XIR0596

Source: the sponsor's Table 2.1

A total of 31 patients were exposed to and grouped in the 15-mg oxycodone IR tablet formulation group during the treatment period (Table 18). The majority of patients (84%; 26/31) were exposed to oxycodone for 8 to 14 days. The average TDD administered to patients in the 15-mg formulation group was generally between 60 and 120 mg/day. Thirty-two percent (10/31) of the patients averaged a TDD <60 mg/day and 19% (6/31) of the patients had an average TDD that was greater than 120 mg/day.

A total of 38 patients (35 had recorded dosing information; 3 patients had missing drug information) were exposed to and grouped in the 30-mg oxycodone IR tablet formulation group during the treatment period. The majority of patients (71%; 27/38) were exposed to the study medication for 8 to 14 days. The average TDD administered to patients in the 30-mg formulation group was generally greater than 120 mg/day.

**Table 18. (Study: XIR0596)
Duration of Exposure by Average Total Daily Dose for Each Formulation - Treatment Period**

Therapy Duration (days)	Number (%) of Patients Exposed			
	Average Total Daily Dose (mg/day) of Oxycodone IR ^a			
	<60 n (%)	60-120 n (%)	>120 n (%)	Total n (%)
15 mg (N=31)				
≤ 7	3	1	1	5 (16%)
>7-14	7	14	5	26 (84%)
>14	0	0	0	0 (0%)
Overall	10 (32%)	15 (48%)	6 (19%)	31 (100%)
30 mg (N=38)				
≤ 7	0	3	4	7 (18%)
>7-14	0	8	19	27 (71%)
>14	1	0	0	1 (3%)
Overall	1 (3%)	11 (29%)	23 (61%)	35 (92%)^b
Total (N=69)	11 (16%)	26 (38%)	29 (42%)	66 (96%)^b

^a Each patient's average TDD (including rescue medication) was calculated based on the number of days of dosing

^b Three patients were missing dosing information; therefore, the total for the 30-mg group is 35 instead of 38 and is 66 instead of 69 for the overall total.

Denominator used to calculate the percent is 31 patients for the 15 mg group, and 38 patients for the 30 mg group

Total indicates the total number of patients exposed to each therapy duration for each formulation group

Overall indicates the overall number of patients averaging a TDD in each TDD category for each formulation group

Study: XIR0596

Source: The sponsor's Table 2.2.

Patients in Study XIR0696 were exposed to oxycodone IR during the stabilization and treatment periods of the XIR0596 study prior to entry into the 4-week extension study. Table 19 presents the duration of exposure reported during the extension study only.

A total of 50 patients (19 in the 15-mg formulation group and 31 in the 30-mg group) were enrolled and exposed to the oxycodone IR during the extension study (XIR0696). Overall, the most patients (37/50; 74%) were exposed to the study medication for more than 28 days during the extension study. The estimated average daily dose was approximately 172 mg/day in the 30-mg group compared with 83 mg/day in the 15-mg group.

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**Table 19.
Long Term Exposure - Extension Study XIR0696**

Duration (days)*	Number (%) of Patients Exposed		
	Oxycodone IR Formulation		
	15 mg (N= 19)	30 mg (N= 31)	Overall (N= 50)
1-14	2 (11%)	1 (3%)	3 (6%)
>14-28	6 (32%)	4 (13%)	10 (20%)
>28 (Max = 39 days)	11 (58%)	26 (84%)	37 (74%)
Total	19 (100%)	31 (100%)	50 (100%)

* Does not include patients' prior exposure to oxycodone IR during the XIR0596 study

Denominator used to calculate the percent is 19 patients for the 15 mg group, and 31 patients for the 30 mg group

Total indicates the total number of patients exposed to each formulation group

Overall indicates the overall number of patients in each duration of exposure category

Study included: XIR0696

Source: Sponsor's Table 6.1 of individual study report

Patients who exposed to 5-mg tablet formulation are presented in Table 20.

**Table 20. Duration of Exposure by Average Total Daily Dose for 5-mg
Formulation -**

Therapy Duration (days)	Number (%) of Patients Exposed			
	Average Total Daily Dose (mg/day) of Oxycodone IR ^a			
	<60 n (%)	60-120 n (%)	>120 n (%)	Total n (%)
5 mg (N=349) - Stabilization Period				
≤ 7	141 (40%)	73 (21%)	28 (8%)	242 (69%)
>7-14	52 (15%)	33 (10%)	17 (5%)	102 (29%)
>14	3 (1%)	1 (<1%)	0 (0%)	4 (1%)
Overall	196 (56%)	107 (31%)	45 (13%)	348 (99%)^b
5 mg (N=125) - Treatment Period				
≤ 7	21 (17%)	33 (26%)	14 (11%)	68 (54%)
>7-14	20 (16%)	26 (21%)	11 (9%)	57 (46%)
>14	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Overall	41 (33%)	59 (47%)	25 (20%)	125 (100%)

^a Each patient's average TDD (including rescue medication) was calculated based on the number of days of dosing

^b Patient 1801 was missing dosing information; therefore, the total for the 5-mg groups is 348 instead of 349 and the overall total is 452 instead of 453.

Denominator used to calculate the percent is 349 patients for the 5-mg group. Total indicates the total number of patients exposed to each therapy duration for each formulation group

Overall indicates the overall number of patients averaging a TDD in each TDD category for each formulation group

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

Source: Sponsor's Table 2.1

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SECTION 8.3.2. Patient Disposition

Patient accounting for the studies on the to-be-marketed 15- and 30-mg tablets has been presented in Section 7.2.1.4 and 7.2.2.4. The Table 21 compares patient discontinuation across different IR formulations.

**Table 21.
Number (%) of Patients who Had Adverse Experiences Resulting in Discontinuation**

Category	Oxycodone IR Formulation Group				
	5-mg IR Tablet	15-mg IR Tablet	30-mg IR Tablet	5 mg/5 ml Oral Solution	All Treatments
Adverse Experiences Resulting in Discontinuation					
Human PK and BA Studies	1/96 (1%)	1/25 (4%)	3/45 (7%)	1/26 (4%)*	6/124 (5%)
Clinical Safety Studies					
Stabilization Period	30/349 (9%)	21/56 (38%)	5/48 (10%)	N/A	56/453 (12%)
Treatment Period	6/125 (5%)	2/31 (6%)	1/38 (3%)	N/A	9/194 (5%)
Extension Study (XIR0696)	N/A	2/19 (11%)	2/31 (6%)	N/A	4/50 (8%)
Total	37	26	11	1	75

* 10 mg/ml oral solution

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

Data Source: Sponsor's Tables 6.1.1, 6.1.2, 6.2.1, 6.2.2, 6.3.1, 6.3.2, individual study reports and Appendix B & C.

Overall, 75 patients were discontinued due to adverse events. A total of 65 patients withdrew during the clinical safety studies, four patients withdrew during extension study XIR0696, and six patients withdrew from the human pharmacokinetic and bioavailability studies.

The majority (56/65; 86%) of patients who were withdrawn due to adverse events in the clinical studies discontinued during the stabilization period. Particularly, it appears that patients in the 15-mg formulation had a much higher discontinued rate (38%) than other formulations (9-10%). The more common adverse events that lead to withdrawal consisted of nausea, vomiting, dizziness, confusion, and pruritus. Most of these adverse events (51 of 75, 68%) were considered to be drug-related side effects. Two drug-related adverse events (confusion/disorientation) were considered serious with the 5- and 15-mg formulations.

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SECTION 8.4 OTHER ADVERSE EVENTS:

SECTION 8.4.1 ADVERSE EVENTS OVERALL:

Table 22 summarizes the number of patients who experienced adverse events by study period and formulation group (Study XIR0596 and XIR0696). Overall, over 70% of the patients experienced at least one adverse event during the stabilization period.

Approximately 60% of the patients experienced at least one adverse event related to the study medication. During the treatment period, 50-60% of the patients experienced at least one adverse event. Approximately 40% of the patients experienced at least one adverse event related to the study medication.

Sixty-six (33/50) percent of the patients in Study XIR0696 experienced adverse events, 36% (18/50) of whom experienced adverse events which were considered to be drug-related.

Table 22 (Study XIR0596 and XIR0696)
Summary of Adverse Experiences -

Adverse Event Category	Number (%) of Patients	
	15 mg Group	30 mg Group
Stabilization Period: Study XIR0596	(N=56)	(N=48)
With One or More Adverse Events	42 (75%)	34 (71%)
With Drug-Related Adverse Events	35 (63%)	29 (60%)
Treatment Period: Study XIR0596	(N=31)	(N=28)
With One or More Adverse Events	19 (61%)	19 (50%)
With Drug-Related Adverse Events	14 (45%)	14 (37%)
Study XIR0696 (4 week extension):	(N=19)	(N=31)
With One or More Adverse Events	15 (79%)	18 (58%)
With Drug-Related Adverse Events	6 (32%)	12 (39%)

Data Source: the sponsor's Table 4.1.1, 4.1.2, and 6.5.1

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Table 23 compares the overall AE experience across the three IR formulations.

Table 23.
Summary of Adverse Experiences

Adverse Event Category	Number (%) of Patients			
	5 mg	15 mg	30 mg	Overall
<u>Stabilization Period</u>	(N=349)	(N=56)	(N=48)	(N=453)
With One or More Adverse Events	199 (57%)	42 (75%)	34 (71%)	275 (61%)
With Drug-Related Adverse Events	148 (42%)	35 (63%)	29 (60%)	212 (47%)
<u>Treatment Period</u>	(N=125)	(N=31)	(N=38)	(N=194)
With One or More Adverse Events	64 (52%)	19 (61%)	19 (50%)	102 (53%)
With Drug-Related Adverse Events	38 (30%)	14 (45%)	14 (37%)	66 (34%)

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

Data Source: Sponsor's Table 4.1.1 and Table 4.1.2

The incidence of adverse events during the stabilization period was similar between the 15- and 30-mg treatment groups and accounted for 75% and 71% of the patients, respectively which was higher than that seen in the 5-mg group (57%). The 15-mg group reported the highest incidence (61%) of adverse events for the treatment period. This group also had the highest incidence of drug-related adverse events and accounted for 45% of the patients in the 15-mg group. The increased incidence of adverse events reported by patients in the 15-mg group might be a result of the influence of small sample size and the number of opioid-naïve patients (19%) enrolled in this group, compared with 5% (2/38) of the patients in the 30-mg group, and one patient (0.3%) in the 5-mg treatment group.

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THE ADVERSE EXPERIENCES (≥3%)

THE TABLE 24 PRESENTS ADVERSE EXPERIENCES IN THE STUDY XIR0596.

Table 24.

Incidence of Adverse Events ≥3% by Body System – Study XIR0596

	Number (%) of Patients			
	Stabilization Period	Stabilization Period	Treatment Period	Treatment Period
Body System	15 mg	30 mg	15 mg	30 mg
COSTART Term^a	(N=56)	(N=48)	(N=31)	(N=38)
Mean TDD	79 mg	157 mg	85 mg	151 mg
Median TDD	64 mg	130 mg	73 mg	148 mg
Body as a Whole	15 (27%)	12 (25%)	11 (36%)	4 (11%)
Asthenia	1 (2%)	0 (0%)	1 (3%)	1 (3%)
Headache	9 (16%)	6 (13%)	2 (7%)	2 (5%)
Pain	2 (4%)	4 (8%)	2 (7%)	1 (3%)
Cardiovascular System	1 (2%)	2 (4%)	0 (0%)	1 (3%)
Digestive System	29 (52%)	24 (50%)	10 (32%)	9 (24%)
Constipation	9 (16%)	12 (25%)	4 (13%)	6 (16%)
Nausea	18 (32%)	14 (29%)	5 (16%)	2 (5%)
Vomiting	14 (25%)	9 (19%)	3 (10%)	1 (3%)
Nausea and Vomiting	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hemic and Lymphatic System	0 (0%)	0 (0%)	1 (3%)	0 (0%)
Metabolic and Nutritional System	1 (2%)	1 (2%)	0 (0%)	1 (3%)
Musculoskeletal System	2 (4%)	1 (2%)	0 (0%)	0 (0%)
Nervous System	22 (39%)	15 (31%)	5 (16%)	8 (21%)
Dizziness	11 (20%)	4 (8%)	2 (7%)	1 (3%)
Dry Mouth	0 (0%)	3 (6%)	0 (0%)	1 (3%)
Insomnia	3 (5%)	3 (6%)	2 (7%)	2 (5%)
Somnolence	7 (13%)	4 (8%)	1 (3%)	1 (3%)
Respiratory System	3 (5%)	8 (17%)	4 (13%)	2 (5%)
Skin and Appendages	11 (20%)	11 (23%)	4 (13%)	3 (8%)
Pruritus	7 (13%)	9 (19%)	2 (7%)	2 (5%)
Sweating	4 (7%)	2 (4%)	1 (3%)	0 (0%)
Special Senses	2 (4%)	0 (0%)	1 (3%)	0 (0%)
Urogenital System	2 (4%)	1 (2%)	0 (0%)	0 (0%)

^a The adverse event COSTART term is included if the overall incidence is ≥3%

Study: XIR0596

Data Source: sponsor's Tables 3.2.1 and 4.2.1

Stabilization Period

Overall, the highest incidence of adverse events occurred in the digestive system (50-52%), followed by the nervous system (31-39%), body as a whole (25-27%), and skin and appendages (20-23%). In general, the type of adverse events experienced were similar among the two formulation groups.

The incidence of constipation, nausea, and vomiting was similar among patients in the 15- and 30-mg treatment group. The incidence of dizziness and somnolence was higher among patients in the 15-mg treatment group compared with the 30-mg treatment group. The increased incidence of adverse events reported by patients in the 15-mg group may be a result of the influence of small sample size and the number of opioid-naive patients enrolled in this group. The most common drug-related adverse events occurring during the stabilization period consisted of nausea (29-32%), vomiting (19-25%), constipation (16-25%), and pruritus (13-19%). The drug-related adverse events seen in this study were typical of a drug with opioid agonist properties.

Treatment Period

The overall incidence of adverse events occurring in the digestive system was slightly higher in the 15-mg group compared with the 30-mg formulation group. The incidence of adverse events occurring in the body as a whole for patients grouped in the 15-mg group (36%; 11/31) was higher than the incidence occurring in either the 30-mg (11%; 4/38) formulation group.

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Adverse Events in Study XIR0696 (4 Week Extension Study)

Table 25 presents a summary of the number of patients who experienced adverse events during the 4-week study.

Table 25.
Incidence of Adverse Events by Body System and COSTART Term (An AE ≥ 10%)
Study XIR0696

Body System COSTART Term ^a	Number (%) of Patients		
	15-mg Group (N=19)	30-mg Group (N=31)	Overall (N=50)
Body as a Whole	7 (37%)	4 (13%)	11 (22%)
Headache	2 (11%)	2 (7%)	4 (8%)
Pain	2 (11%)	1 (3%)	3 (6%)
Cardiovascular System	0 (0%)	1 (3%)	1 (2%)
Digestive System	8 (42%)	9 (29%)	17 (34%)
Constipation	2 (11%)	7 (23%)	9 (18%)
Nausea	3 (16%)	1 (3%)	4 (8%)
Hemic and Lymphatic System	0 (0%)	0 (0%)	0 (0%)
Metabolic and Nutritional System	0 (0%)	1 (3%)	1 (2%)
Nervous System	4 (21%)	2 (7%)	6 (12%)
Insomnia	2 (11%)	1 (3%)	3 (6%)
Respiratory System	4 (21%)	2 (7%)	6 (12%)
Skin and Appendages	1 (5%)	6 (19%)	7 (14%)
Special Senses	0 (0%)	0 (0%)	0 (0%)
Urogenital System	3 (16%)	0 (0%)	3 (6%)

^a The individual adverse event COSTART term is included if the incidence is ≥10% for any study

Study Presented: XIR0696

Data Source: The sponsor's Table 4.6.0, 6.5.2, and 6.5.3

Since the Study XIR0696 was an extension of the Study XIR0596, the incidence of adverse events from the Study XIR0596 (consisting of a 2-7 day stabilization period and a 7-day treatment period) was compared to the XIR0696 extension study (Table 26).

In general, the overall incidence of adverse events in the XIR0596 study (i.e., including the stabilization and treatment periods) was higher than the incidence seen in the 4-week extension study (XIR0696). The incidences in the treatment period of XIR0596 were comparable to that of the XIR0696 study, with the incidence of vomiting having the largest difference (6%). The largest differences in the incidence of adverse events were seen in the nervous system, digestive system, respiratory system, and body as a whole, all of which were notably higher overall in the XIR0596 study. The incidence of headache, constipation, nausea, vomiting, dizziness, somnolence, and pruritus all decreased notably and in some cases (vomiting and dizziness) were not reported during the extension study.

The incidence of adverse events in the digestive system, respiratory system, skin and appendages, and urogenital system which were higher in the XIR0696 study than in the treatment period of Study XIR0596. Specifically, the events within these systems that were higher in the XIR0696 extension study were constipation, rhinitis, and sweating.

Three of the most common adverse events (vomiting, confusion, and dizziness) reported in the XIR0596 study were not reported during the 4-week extension study (Study XIR0696), indicating that if patients experience vomiting, confusion, and dizziness they usually occurred early (within approximately the first 7 days) in the treatment period.

Table 26.
Comparison of the Incidence of Adverse Events by Body System and COSTART Term (≥3%) -
Study XIR0596 and Study XIR0696

Body System COSTART Term ^a	Number (%) of Patients		
	Overall XIR0596 ^b (N=104)	Treatment XIR0596 (N=69)	Overall XIR0696 (N=50)
Body as a Whole	32 (31%)	15 (22%)	11 (22%)
Accidental Injury	3 (3%)	2 (3%)	3 (6%)
Asthenia	2 (2%)	2 (3%)	1 (2%)
Headache	15 (14%)	4 (6%)	4 (8%)
Pain	7 (7%)	3 (4%)	3 (6%)
Cardiovascular System	4 (4%)	1 (1%)	1 (2%)
Digestive System	60 (58%)	19 (28%)	17 (34%)
Anorexia	3 (3%)	3 (4%)	2 (4%)
Constipation	26 (25%)	10 (15%)	9 (18%)
Diarrhea	3 (3%)	1 (1%)	1 (2%)
Dry Mouth ^c	3 (3%)	1 (1%)	0 (0%)
Nausea	35 (34%)	7 (10%)	4 (8%)
Vomiting	25 (24%)	4 (6%)	0 (0%)
Hemic and Lymphatic System	1 (1%)	1 (1%)	0 (0%)
Metabolic and Nutritional System	3 (3%)	1 (1%)	1 (2%)
Nervous System	41 (39%)	13 (19%)	6 (12%)
Confusion	5 (5%)	2 (3%)	0 (0%)
Dizziness	18 (17%)	3 (4%)	0 (0%)
Insomnia	7 (7%)	4 (6%)	3 (6%)
Somnolence	12 (12%)	2 (3%)	1 (2%)
Respiratory System	14 (14%)	6 (9%)	6 (12%)
Rhinitis	3 (3%)	1 (1%)	2 (4%)
Skin and Appendages	25 (24%)	7 (10%)	7 (14%)
Pruritus	17 (16%)	4 (6%)	3 (6%)
Rash	3 (3%)	2 (3%)	2 (4%)
Sweating	7 (7%)	1 (1%)	2 (4%)
Special Senses	3 (3%)	1 (1%)	0 (0%)
Urogenital System	3 (3%)	0 (0%)	3 (6%)

^a The adverse event COSTART term is included if the incidence is ≥3% for any study

^b Includes the stabilization and treatment periods of Study XIR0596

^c Dry mouth is reported within the digestive system in the XIR0596 report, but is included within the nervous system within the ISS tables

Studies Presented: XIR0596 and XIR0696

Data Source: Sponsor's Table 4.6.0 and Table 6.6.1 of Study XIR0596

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Comparisons of Adverse experiences across the 5-, 15, and 30-mg Formulations
Stabilization Period

Table 27.
Incidence of Adverse Events (≥3%) by Body System - Stabilization Period

Body System COSTART Term ^a	Number (%) of Patients			
	5 mg (N=349)	15 mg (N=56)	30 mg (N=48)	Overall (N=453)
Mean TDD	73 mg	79 mg	157 mg	83 mg
Median TDD	54 mg	64 mg	130 mg	60 mg
Body as a Whole	96 (28%)	15 (27%)	12 (25%)	123 (27%)
Asthenia	19 (5%)	1 (2%)	0 (0%)	20 (4%)
Headache	43 (12%)	9 (16%)	6 (13%)	58 (13%)
Pain	13 (4%)	2 (4%)	4 (8%)	19 (4%)
Cardiovascular System	9 (3%)	1 (2%)	2 (4%)	12 (3%)
Digestive System	105 (30%)	29 (52%)	24 (50%)	158 (35%)
Constipation	29 (8%)	9 (16%)	12 (25%)	50 (11%)
Nausea	60 (17%)	18 (32%)	14 (29%)	92 (20%)
Vomiting	30 (9%)	14 (25%)	9 (19%)	53 (12%)
Hemic and Lymphatic System	3 (1%)	0 (0%)	0 (0%)	3 (1%)
Metabolic and Nutritional System	13 (4%)	1 (2%)	1 (2%)	15 (3%)
Musculoskeletal System	16 (5%)	2 (4%)	1 (2%)	19 (4%)
Nervous System	95 (27%)	22 (39%)	15 (31%)	132 (29%)
Dizziness	25 (7%)	11 (20%)	4 (8%)	40 (9%)
Dry Mouth	14 (4%)	0 (0%)	3 (6%)	17 (4%)
Insomnia	16 (5%)	3 (5%)	3 (6%)	22 (5%)
Somnolence	32 (9%)	7 (13%)	4 (8%)	43 (10%)
Respiratory System	15 (4%)	3 (5%)	8 (17%)	26 (6%)
Skin and Appendages	51 (15%)	11 (20%)	11 (23%)	73 (16%)
Pruritus	36 (10%)	7 (13%)	9 (19%)	52 (12%)
Sweating	15 (4%)	4 (7%)	2 (4%)	21 (5%)
Special Senses	13 (4%)	2 (4%)	0 (0%)	15 (3%)
Urogenital System	12 (3%)	2 (4%)	1 (2%)	15 (3%)

^a The adverse event COSTART term is included if the overall incidence is ≥3%

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

Data Source: Sponsor's Tables 3.2.1 and 4.2.1

The overall incidence of adverse events in the digestive system for patients grouped in the 15- (52%; 29/56) and 30-mg (50%; 24/48) formulation groups was higher than for those patients grouped in the 5-mg (30%; 105/349) treatment group. The incidence of constipation, nausea, and vomiting was also higher among patients in the 15- and 30-mg treatment group compared with the 5-mg treatment group. The incidence of dizziness and somnolence was higher among patients in the 15-mg treatment group compared with

the 5-mg treatment group. The incidence of these same events among patients in the 30-mg treatment group was similar to that seen in the 5-mg treatment group.

TREATMENT PERIOD

Table 28.
Incidence of Adverse Events ($\geq 3\%$) by Body System - Treatment Period

Number (%) of Patients				
Body System COSTART Term ^a	5 mg (N=125)	15 mg (N=31)	30 mg (N=38)	Overall (N=194)
Mean TDD	105 mg	85 mg	151 mg	110 mg
Median TDD	67 mg	73 mg	148 mg	74 mg
Body as a Whole	22 (18%)	11 (36%)	4 (11%)	37 (19%)
Asthenia	4 (3%)	1 (3%)	1 (3%)	6 (3%)
Headache	7 (6%)	2 (7%)	2 (5%)	11 (6%)
Cardiovascular System	5 (4%)	0 (0%)	1 (3%)	6 (3%)
Digestive System	26 (21%)	10 (32%)	9 (24%)	45 (23%)
Constipation	5 (4%)	4 (13%)	6 (16%)	15 (8%)
Dyspepsia	5 (4%)	0 (0%)	0 (0%)	5 (3%)
Nausea	9 (7%)	5 (16%)	2 (5%)	16 (8%)
Vomiting	9 (7%)	3 (10%)	1 (3%)	13 (7%)
Hemic and Lymphatic System	1 (1%)	1 (3%)	0 (0%)	2 (1%)
Metabolic and Nutritional System	4 (3%)	0 (0%)	1 (3%)	5 (3%)
Musculoskeletal System	7 (6%)	0 (0%)	0 (0%)	7 (4%)
Nervous System	16 (13%)	5 (16%)	8 (21%)	29 (15%)
Dizziness	4 (3%)	2 (7%)	1 (3%)	7 (4%)
Insomnia	4 (3%)	2 (7%)	2 (5%)	8 (4%)
Somnolence	4 (3%)	1 (3%)	1 (3%)	6 (3%)
Respiratory System	6 (5%)	4 (13%)	2 (5%)	12 (6%)
Skin and Appendages	8 (6%)	4 (13%)	3 (8%)	15 (8%)
Pruritus	6 (5%)	2 (7%)	2 (5%)	10 (5%)
Special Senses	0 (0%)	1 (3%)	0 (0%)	1 (1%)
Urogenital System	1 (1%)	0 (0%)	0 (0%)	1 (1%)

^a The adverse event COSTART term is included if the overall incidence is $\geq 3\%$

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

Data Source: Sponsor's Tables 3.2.2 and 4.2.2

The highest incidence of adverse events (Table 28) occurred in the digestive system (23%; 45/194), followed by body as a whole (19%; 37/194), and the nervous system (15%; 29/194). The incidence of adverse events occurring in the body as a whole for patients grouped in the 15-mg group (36%; 11/31) was higher than the incidence occurring in either the 30-mg (11%; 4/38) or 5-mg (18%; 22/125) formulation group. The incidence of constipation was higher among patients grouped in the 15-mg (13%; 4/31)

and 30-mg (16%; 6/38) formulation groups compared with the incidence in the 5-mg formulation group (4%; 5/125). Patients in the 15-mg formulation group reported the highest incidences of nausea and vomiting.

Adverse Experiences ($\geq 3\%$) of the volunteers in the PK studies

The adverse events experienced during these studies are those commonly associated with opioid administration (Table 29). The adverse events with the highest incidence reported by healthy volunteers were dizziness (75%; 93/124), nausea (56%; 70/124), pruritus (40%; 50/124), somnolence (37%; 46/124), vomiting (37%; 46/124), headache (32%; 40/124), asthenia (23%; 28/124), vasodilation (18%; 22/124), fatigue (17%; 21/124), hiccup (13%; 16/124), and euphoria (13%; 16/124).

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Table 29.
Incidence of Adverse Events (≥3%) by Body System
Human Pharmacokinetic and Bioavailability Studies

Body System COSTART Term	Number (%) of Subjects						Total No. of Events (N=936)
	Oxycodone IR Formulations						
	5 mg (N=96)	15 mg (N=25)	30 mg (N=45)	5 mg/5 ml (N=51)	20 mg/ml (N=26)	Overall (N=124)	
Body as a Whole							
Fatigue	14 (15%)	7 (28%)	3 (7%)	0 (0%)	4 (15%)	21 (17%)	30
Asthenia	5 (5%)	1 (4%)	11 (24%)	15 (29%)	0 (0%)	28 (23%)	34
Headache	15 (16%)	0 (0%)	14 (31%)	11 (22%)	2 (8%)	40 (32%)	60
Temperature Changes	4 (4%)	0 (0%)	2 (4%)	0 (0%)	0 (0%)	5 (4%)	6
Cardiovascular System							
Vasodilation	14 (15%)	1 (4%)	6 (13%)	2 (4%)	2 (8%)	22 (18%)	29
Digestive System							
Dyspepsia	3 (3%)	1 (4%)	3 (7%)	0 (0%)	0 (0%)	7 (6%)	8
Hiccup	7 (7%)	5 (20%)	4 (9%)	0 (0%)	2 (8%)	16 (13%)	20
Dry Mouth	2 (2%)	1 (4%)	5 (11%)	4 (8%)	0 (0%)	10 (8%)	12
Vomiting	21 (22%)	9 (36%)	9 (20%)	11 (22%)	5 (19%)	46 (37%)	111
Nausea	25 (26%)	13 (52%)	14 (31%)	12 (24%)	6 (23%)	70 (56%)	133
Nervous System*							
Dizziness	28 (29%)	15 (60%)	23 (51%)	31 (61%)	11 (42%)	93 (75%)	202
Somnolence	19 (20%)	3 (12%)	14 (31%)	13 (25%)	5 (19%)	46 (37%)	62
Euphoria	9 (9%)	2 (8%)	0 (0%)	4 (8%)	1 (4%)	16 (13%)	17
Paraesthesia	6 (6%)	0 (0%)	0 (0%)	2 (4%)	1 (4%)	7 (6%)	7
Tremor	4 (4%)	1 (4%)	4 (9%)	1 (2%)	0 (0%)	8 (6%)	11
Nervousness	4 (4%)	0 (0%)	1 (2%)	0 (0%)	1 (4%)	6 (5%)	7
Confusion	2 (2%)	0 (0%)	0 (0%)	2 (4%)	0 (0%)	4 (3%)	5
Skin and Appendages							
Pruritus	21 (22%)	8 (32%)	18 (40%)	16 (31%)	8 (31%)	50 (40%)	103
Sweat	0 (0%)	0 (0%)	6 (13%)	3 (6%)	0 (0%)	7 (6%)	9
Increased Sweat	2 (2%)	0 (0%)	4 (9%)	0 (0%)	0 (0%)	6 (5%)	6

* Nervous system and psychiatric and nervous system disorders are combined into the Nervous System

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

Data Source: Sponsor's Appendix D and individual study reports

Incidence of Drug-Related Adverse Events

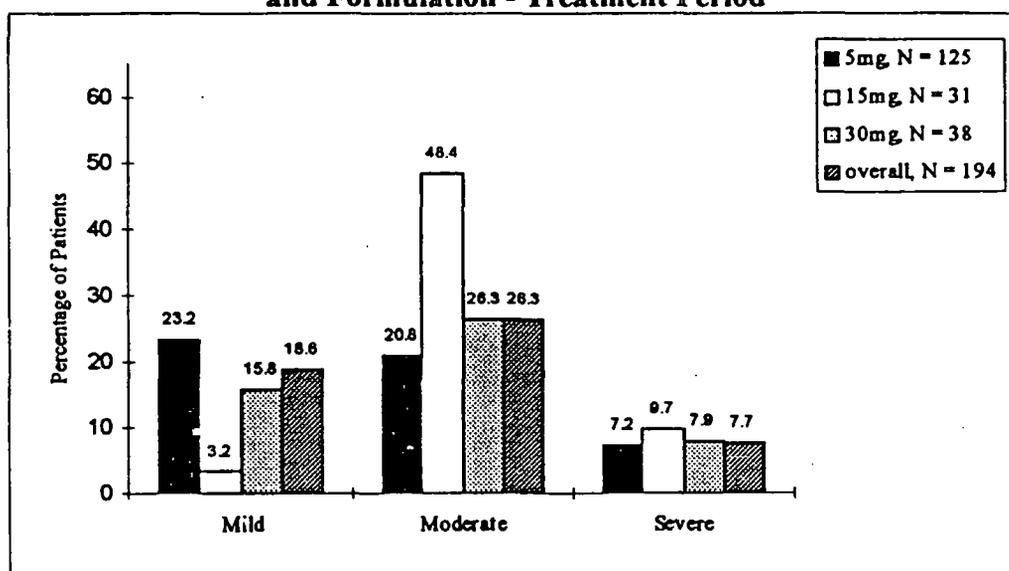
The body system with the highest incidence of drug-related adverse events was the digestive system (18%; 34/194) followed by the nervous system (11%; 21/194) and the body as a whole (8%; 15/194). The more common drug-related adverse events experienced during the treatment period consisted of constipation (8%; 15/194), nausea

(8%; 15/194), pruritus (5%; 9/194), headache (4%; 7/194), vomiting (3%; 6/194), insomnia (3%; 6/194), and somnolence (3%; 5/194). No unexpected drug-related adverse events were reported during these studies and the drug-related adverse events seen in these studies were typical of this type of drug in reviewer's opinion.

Incidence of Adverse Events by Severity

Overall, 26% of the patients experienced moderate drug-related events, 18% experienced mild drug-related events, and less than 10% of the patients reported severe drug-related adverse events during the treatment period. The number of moderate drug-related adverse events was highest in the 15-mg group and the number of moderate adverse events was highest in the 30-mg group (Figure 8).

Figure 8.
Incidence of Patients (%) Experiencing Drug-Related Adverse Events by Severity and Formulation - Treatment Period



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Since the sample size in the study XIR0596 is small, especially in the treatment phase (N=69), analyses of adverse events based on the single study of 0596 by gender, age, race, etiology of pain, special populations and doses were unlikely to produce meaningful results. For example, incidence of adverse events by body system by total daily dose is presented below (Table 30). It appears there is no clear dose-response pattern likely due to small sample size in each dose category. Therefore, analyses in the following sections are based upon the pooled safety data from the IR 5-, 15- and 30-mg studies.

Table 30.
Incidence of Adverse Events (≥ 5%) by Body System by Total Daily Dose (mg) During the Treatment Period - Study XIR0596

Body System COSTART Term ^a	Number (%) of Patients		
	≤ 80 mg (N=20)	> 80 - 120 mg (N=25)	> 120 mg (N=24)
Body as a Whole	7 (35%)	5 (20%)	3 (13%)
Cardiovascular System	1 (5%)	0 (0%)	0 (0%)
Digestive System	10 (50%)	6 (24%)	5 (21%)
Hemic and Lymphatic System	1 (5%)	0 (0%)	0 (0%)
Metabolic and Nutritional System	0 (0%)	1 (4%)	0 (0%)
Nervous System	1 (5%)	7 (28%)	4 (17%)
Respiratory System	3 (15%)	2 (8%)	1 (4%)
Skin and Appendages	1 (5%)	2 (8%)	5 (21%)

^a The individual adverse event COSTART term is included if the incidence is ≥5% for any study

Study Presented: XIR0596

Data Source: The sponsor's Table Q

SECTION 8.4.2 ADVERSE EVENTS BY GENDER

Of the 453 patients in the stabilization period, 194 (43%) patients were male and 259 (57%) patients were female. The overall incidence of adverse events reported by male and female patients was virtually the same. Sixty-three (63%; 122/194) percent of the male patients experienced adverse events compared to 59% (153/259) of the female patients. The incidence of adverse events in the 15-mg group was somewhat higher (M:77.8%, F: 72.4%) than that reported in the 5-mg (M: 57.6%, F: 56.7%) or 30-mg groups (M:71.4%, F: 69.2%) for both males and females.

Of the 194 patients in the treatment period, 93 (48%) patients were male and 101 (52%) patients were female. The incidence of adverse events for females was slightly higher during the treatment period compared to males. Overall, 57% (58/101) of the female patients and 47% (44/93) of the male patients experienced adverse events. The incidence of adverse events in the 15-mg group was slight higher (M:61.5%, F: 61.1%) than that reported in the 5-mg (M: 40.4%, F: 58.9%) or 30-mg groups (M:53.6%, F: 40.0%) for both males and females.

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SECTION 8.4.3 ADVERSE EVENTS BY AGE

The incidence of adverse events was examined by age (<65 and ≥65 years). There was no data on pediatric subjects. Of the 453 patients in the stabilization period, 358 (79%) patients were under the age of 65 years and 95 (21%) patients were 65 years of age or older. Generally, the incidence of adverse events was slightly higher for patients under 65 years than those 65 years or older, except for the 15-mg group. Overall, 63% (224/358) of the patients under the age of 65 years reported adverse events during the stabilization period compared with 54% (51/95) of the patients 65 years or older. The incidence of headache was also higher in patients who were under the age of 65 years (15% compared with 6%). The incidence of dizziness was 9% higher for patients 65 years or older (16%; 15/95) than for patients who were under the age of 65 years (7%; 25/358). No other apparent differences (>10 percentage point difference) in the incidence of adverse events were seen between the two age groups.

Of the 194 patients in the treatment period, 155 (80%) patients were under the age of 65 years and 39 (20%) patients were 65 years of age or older. The incidence of adverse events reported by patients 65 years or older was higher than that seen in patients under the age of 65 years during the treatment period. Overall, 67% (26/39) of the patients 65 years or older reported adverse events during the treatment period compared to 49% (76/155) of the patients who were under the age of 65 years. The incidence of adverse events among the formulation groups was similar, but somewhat higher for the 15-mg group in patients under 65 years and for the 30-mg group in patients 65 years or older. No apparent differences (>10 percentage point difference) in the incidence of adverse events were seen between the two age groups. However, the incidence was slightly higher for the patients who were 65 years or older for the following body systems: cardiovascular system, digestive system, hemic and lymphatic system, metabolic and nutritional system, musculoskeletal system, nervous system, respiratory system, and skin and appendages; and for the following events: asthenia, constipation, vomiting (and for combined nausea and vomiting), dyspepsia, and dizziness.

SECTION 8.4.4 ADVERSE EVENTS BY RACE

Of the 453 patients in the stabilization period, majority were Caucasian (415/453; 92%). Thirty-four (8%) patients were Black and 4 (1%) patients were Native American, Asian, or another race. The incidence of constipation (21%; 7/34 compared to 10%; 43/415) and vomiting (21%; 7/34 compared to 11%; 46/415) was higher in black patients compared to Caucasian patients. However, it is difficult to determine whether these differences are due to differences in race or sample size (i.e., 415 patients compared to 34 patients).

Of the 194 patients in the treatment period, majority were Caucasian (179/194; 92%). Thirteen (7%) patients were Black and 2 (1%) patients were Native American, Asian, or other. The incidence of adverse events reported by Caucasian patients was higher in about half of the instances. Due to the differences in sample size, it is difficult to

determine if these differences are due to actual racial differences or sample size (i.e., 179 patients compared to 13 patients).

SECTION 8.4.5 ADVERSE EVENTS BY ETIOLOGY OF PAIN

The majority (77%) of patients were being treated for chronic non-malignant pain. Of the 453 patients in the stabilization period 104 (23%) patients had malignant pain and 349 (77%) patients had non-malignant pain. Overall, the incidence of adverse events reported by patients with chronic malignant and non-malignant pain was similar during the stabilization period. Sixty-six (66%; 69/104) of the patients with malignant pain reported adverse events and 59% (206/349) of the patients with non-malignant pain reported adverse events. The incidence of adverse events were similar for the 15- and 30-mg groups and was slightly higher than that reported in the 5-mg group among patients with malignant and non-malignant pain. The incidence of adverse events affecting the digestive system was higher for patients who had malignant pain (43%) than those who had chronic non-malignant pain (32%). Within the digestive system the incidence of nausea (29%; 30/104 compared to 18%; 62/349) and the incidence of vomiting (20%; 21/104 compared to 9%; 32/349) were also higher for patients who had malignant pain.

Of the 194 patients in the treatment period, 59 (30%) patients had malignant pain and 135 (70%) patients had non-malignant pain. Overall, the incidence of adverse events was somewhat higher for patients with malignant pain. Sixty-three (63%; 37/59) percent of the patients with malignant pain experienced adverse events compared to 48% (65/135) of the patients with non-malignant pain. The incidence of adverse events affecting the digestive system was higher for patients with malignant pain (34%; 20/59) compared with those with non-malignant pain (19%; 25/135). Patients who were being treated for chronic malignant pain may have also been receiving chemotherapeutic agents that may have contributed to the increased incidence rates seen in this group.

SECTION 8.4.6 ADVERSE EVENTS IN PATIENTS WITH HEPATIC INSUFFICIENCY, OR PATIENTS WITH RENAL INSUFFICIENCY, OR RELATED PREGNANCY NURSING, LABOR AND DELIVERY

The to-be-marketed 15- and 30-mg tablets have not been evaluated in these special populations. The sponsor provided some information based on reference to Drug Facts and Comparisons, information available under the Freedom of Information Act and publications in literature. The following is a condensation of these information.

In studies conducted previously in patients with hepatic impairment, the plasma concentrations of oxycodone were higher than those in patients with normal hepatic function. The initiation of therapy at one-third to one-half of the usual doses and careful titration is warranted for patients with hepatic impairment.

In studies conducted previously in patients with renal impairment, as evidenced by decreased creatinine clearance (< 60 ml/min), the concentrations of oxycodone in the plasma were higher than in subjects with normal renal function. Dose initiation in patients with renal impairment should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

No adequate and well-controlled studies have been conducted in pregnant women. Opioids cross the placental barrier and the transfer is rapid. Neonates whose mothers have been taking oxycodone on a chronic basis may exhibit respiratory depression or withdrawal symptoms, either at birth or in the nursery. Withdrawal symptoms may include irritability, excessive crying, yawning, sneezing, increased respiratory rate, tremors, hyperreflexia, fever, vomiting, increased stools, and diarrhea.

Oxycodone is not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn. It is advisable to have naloxone available if opioids are administered during labor and delivery

SECTION 8.5 OTHER SAFETY FINDINGS

SECTION 8.5.1 CLINICAL LABORATORY EVALUATIONS

Since exposure to oxycodone IR during studies CBI-961/962, CBI-963, and CBI-1252 was not exclusive throughout the study, these studies have not been included in the laboratory evaluation for oxycodone IR. Laboratory tests were only conducted in Study XIR0696 if the laboratory tests conducted at the end of the XIR0596 study were done more than 14 days prior to entry into the XIR0696 study. End-of-study laboratory tests were not conducted in extension study XIR0696. Therefore, the clinical laboratory data presented in this section is from Study XIR0596 only.

Determination of clinically relevant abnormal laboratory values was based on investigators' assessments and the following criteria. The following criteria for clinically relevant laboratory tests were provided by the sponsor 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 x 10 ⁶ /mm ³
Platelet	< 100 x 100/mm ³
Bilirubin	>1.5 x ULN (upper limit of normal)
ALT	> 2 x ULN
AST	> 2 x ULN
BUN	> 36 mg/dL
Creatinine	> 2 mg/dL

Based on these criteria, only 6 patients experienced clinically relevant abnormal values at baseline (1 RBC, 2 HGB, 1 platelet count, and 1 HCT), and one patient experienced clinically relevant abnormal values (HGB) at the final visit (Table 31).

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Table 31.
Clinically Significant Abnormal Blood Chemistry and Hematology Values at Baseline and/or the
Final Visit - Study XIR0596

Laboratory Test	N ^a	Mean (±SD) Baseline	Mean (±SD) Final Visit	Change (±SD) [Final ^b -Screening]
Blood Chemistry				
ALT (IU/L)				
15 mg	32	24.31 (±19.66)	25.72 (±21.84)	1.41 (±13.56)
30 mg	35	28.89 (±32.76)	29.94 (±33.36)	1.06 (±6.61)
AST (IU/L)				
15 mg	32	23.47 (±11.15)	26.78 (±16.88)	3.31 (±8.30)
30 mg	35	25.83 (±18.47)	26.77 (±20.96)	0.94 (±10.14)
BUN (mg/dL)				
15 mg	33	14.64 (±7.34)	13.58 (±6.02)	-1.06 (±5.83)
30 mg	35	14.45 (±5.70)	13.83 (±5.99)	-0.62 (±3.51)
Creatinine (mg/dL)				
15 mg	33	0.87 (±0.26)	0.91 (±0.23)	0.04 (±0.13)
30 mg	35	0.92 (±0.19)	0.97 (±0.19)	0.05 (±0.12)
Total Bilirubin (mg/dL)				
15 mg	32	0.51 (±0.16)	0.53 (±0.20)	0.02 ±0.12)
30 mg	35	0.56 (±0.21)	0.49 (±0.17)	-0.07 (±0.15)
Hematology				
Hematocrit (%)				
15 mg	32	40.58 (±5.92)	40.44 (±5.69)	-0.13 (±4.45)
30 mg	35	43.25 (±4.08)	42.05 (±4.00)	-1.20 (±3.02)
Hemoglobin (g/dL)				
15 mg	32	13.68 (±2.13)	13.53 (±1.90)	-0.15 (±1.43)
30 mg	35	14.63 (±1.52)	14.19 (±1.58)	-0.44 (±0.80)
Platelet (x10 ³ /mm ³)				
15 mg	31	243.94 (±84.89)	242.45 (±68.21)	-1.48 (±83.20)
30 mg	34	265.97 (±106.25)	277.77 (±112.01)	11.80 (±53.93)
RBC (x10 ⁶ /mm ³)				
15 mg	32	4.40 (±0.72)	4.37 (±0.67)	-0.03 (±0.46)
30 mg	35	4.76 (±0.56)	4.76 (±0.56)	-0.16 (±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

Data Source: Sponsor's Table 7.1.1

SECTION 8.5.2 VITAL SIGNS

Since exposure to oxycodone IR during studies CBI-961/962, CBI-963, and CBI-1252 was not exclusive throughout the study these studies have not been included in the vital sign evaluation for oxycodone IR. There did not appear to be any clinically relevant

changes in vital signs during the XIR0596 study and during the extension XIR0696 study.

Overall during the stabilization periods of the pooled studies, one patient experienced hypertension (30-mg group) which was considered by the investigator to be related to the study medication. Five patients experienced tachycardia (no data on heart rates provided, 4 patients in the 5-mg group and 1 patient in the 30-mg group). Of these, four were considered by the investigator to be related to the study medication.

During the treatment periods of the pooled studies, one patient experienced hypotension that was considered by the investigator to not be related to the study medication. One patient experienced tachycardia, which was considered by the investigator to be related to the study medication. Both of these events were reported by patients in the 5-mg tablet formulation group .

SECTION 8.6 DOSE-RESPONSE ADVERSE EXPERIENCE INFORMATION

Of the 453 patients in the stabilization period, 210 (46%) patients averaged a total daily dose that was less than 60 mg/day, 161 (36%) patients averaged a total daily dose between 60 and 120 mg/day, and 82 (18%) patients averaged a total daily dose that was greater than 120 mg/day. Overall, there was very little difference in the incidence of adverse events by dose level. The incidence of adverse events for patients who averaged a TDD <60 mg/day, between 60 and 120 mg/day, and greater than 120 mg/day was 57% (119/209), 64% (103/161), and 65% (53/82), respectively. The incidence rates that increased with increasing dose during the stabilization period consisted of increases in the digestive and skin and appendages body systems and increases for the events of nausea, dry mouth, and insomnia. With the exception of the incidence of adverse events occurring in the digestive system, specifically for the event of nausea, a clear dose-response with respect to incidence of adverse events was not apparent.

Of the 194 patients in the treatment period, 52 (27%) patients averaged a total daily dose that was less than 60 mg/day, 85 (44%) patients averaged a total daily dose between 60 and 120 mg/day, and 54 (28%) patients averaged a total daily dose that was greater than 120 mg/day. The overall incidence of adverse events by TDD was similar and did not indicate a dose-response with respect to the overall incidence of adverse events. Overall, patients who averaged a TDD between 60 and 120 mg/day had the highest incidence of adverse events (59%; 50/85) followed by patients who averaged a TDD less than 60 mg/day (54%; 28/52) and patients who averaged a TDD greater than 120 mg/day (43%; 23/54). The apparent dose-response seen during the stabilization period for the digestive system, specifically for nausea, was not seen during the treatment period.

SECTION 8.7 ADVERSE/DRUG-RELATED EFFECTS OF CONCERN

Respiratory depression is the chief hazard from all opioid agonist preparations. Of the 194 patients who received oxycodone IR during the treatment period, a total of 12

patients (6%) reported events involving the respiratory system. These events consisted of bronchitis, increased cough, dyspnea, epistaxis, laryngismus, lung disorder, pharyngitis, rhinitis, and sinusitis. Ten of the 12 patients reported adverse events in the respiratory system that were not considered by the investigator to be related to oxycodone administration. The reviewer agrees. Only two patients reported drug-related adverse events of the respiratory system. These events were dyspnea and laryngismus. There were no reports of respiratory depression in this clinical program even following high doses (up to 680 mg/day).

Oxycodone IR, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents that compromise vasomotor tone. In this clinical program, no patients experienced hypotension during the stabilization period. One patient (0.5%) reported hypotension while receiving 5-mg IR tablets during the treatment period. The hypotension, which was intermittent over a 5-day period, was assessed by the investigator as unlikely-related to study drug. During the stabilization and treatment periods of the pooled studies, 40 and 7 patients reported dizziness, respectively. A total of 54 events of dizziness were reported during both the stabilization and treatment periods.

Because of the potential effects of oxycodone on the central nervous system, reports of accidental injury were examined for the occurrence of accidental falls. Three patients reported accidental injuries following treatment with the 15- and 30-mg tablets, two of which could be attributed to accidental falls. One was considered by the investigator to have a possible relation to administration of the study medication.

Opioid analgesics are associated with central nervous system (CNS) depressant and stimulating effects. Of the 194 patients in the treatment period, 29 patients (15%) reported events of the nervous system: 16 patients (13%; 16/125) in the 5-mg group, 5 patients (16%; 5/31) in the 15-mg group, 8 patients (21%; 8/38) in the 30-mg group. Dizziness (4%; 7/194), insomnia (4%; 8/194), and somnolence (3%; 6/194) were the most frequently reported adverse events during the treatment period.

Opioid analgesics are associated with digestive system effects. Of the 194 patients in the treatment period, 45 patients (23%; 45/194) reported events in the digestive system. The incidence of patients experiencing adverse events in the digestive system for the 5-, 15-, and 30-mg groups was 21% (26/125), 32% (10/31), and 24% (9/38), respectively. Constipation, dyspepsia, nausea, and vomiting were the most commonly reported adverse events of the digestive system. The incidence of constipation was higher for patients in the 15- and 30-mg groups compared with patients in the 5-mg group. Four percent (5/125), 13% (4/31), and 16% (6/38) of the patients in the 5-, 15-, and 30-mg groups, respectively experienced constipation. Nausea and vomiting are common as an early undesirable effect of chronic opioid therapy. The incidence of nausea was highest among patients in the 15-mg group. The incidence of nausea was 7% (9/125), 16% (5/31), and 5% (2/38) for patients in the 5-, 15-, and 30-mg treatment groups, respectively. The incidence of vomiting was lowest among patients in the 30-mg treatment group. Only 3% (1/38) of the patients in the 30 mg group reported vomiting compared to 7% (9/125) and 10% (3/31) of the patients in the 15- and 30-mg groups, respectively.

Oxycodone may trigger the release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release include pruritus, flushing, and sweating.

Of the 194 patients in the treatment period, 15 patients (8%) reported events relating to the skin and appendages. The incidence of adverse events between the 5-, 15-, and 30-mg groups was 6% (8/125), 13% (4/31), and 8% (3/38), respectively.

Acute overdose with oxycodone IR can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death. Overdose was reported by one patient in spontaneous post-marketing reports for oxycodone IR. One patient in the XIR0596 experienced a serious adverse event classified as an overdose. This patient reportedly became confused and took too many tablets. The study medication was stopped when the signs and symptoms of the overdose were reported to the investigational site and the symptoms resolved without further treatment.

SECTION 8.8 DRUG-DRUG INTERACTIONS AND DRUG-DISEASE INTERACTIONS

The to-be-marketed 15- and 30-mg tablets have not been evaluated under these special conditions. The sponsor provided some information based on reference to Drug Facts and Comparisons, information available under the Freedom of Information Act and publications in literature. The following is a condensation of these information.

Opioid analgesics, including oxycodone IR, may enhance the neuromuscular-blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

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, 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.

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis.

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions, or other sources of pre-existing intracranial pressure.

SECTION 8.9 ADVERSE EFFECTS IN LONG TERM USE

Information regarding death, SAE's and overall incidence of adverse events in the Study XIR0696 has been previously discussed in Section 8.2.2 and 8.4.1 of this review.

SECTION 8.10 POST-MARKETING REPORTS

The sponsor has marketed the current formulations of single entity oxycodone (Roxicodone™), since 1982. These formulations include: Roxicodone™ 5 mg Tablets, Roxicodone™ Oral Solution (5mg/5mL), and Roxicodone Intenso™ (20 mg/ml). The following adverse events (N=10) have been reported with these formulations over the previous seven years (1991-1998) of experience.

- October 11, 1991: Report from patient on Roxicodone Intenso™ 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 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 experience (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. Roxicodone™ 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 Roxicodone™ 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 5mg 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 10mg every 2 hours as needed for pain. All three patients were given other medications for pain, but no follow up on 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 5mg QID. Patient was subsequently placed on Oxycontin 20mg q12h, Valium 5mg bid, Prozac 40mg 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 5mg 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), every 6 hours for pain from a fractured leg (administered at home by parents). 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 that patient reported that the Roxicodone 5mg 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.

SECTION 9.0 COMMENTS AND CONCLUSION

SECTION 9.0.1 SUMMARY AND COMMENTS

NDA 21,011 was submitted to seek approval for two new dosage strengths (15-mg and 30-mg tablets) of an immediate-release (IR) oxycodone hydrochloride tablet for the treatment of moderate-to-severe chronic pain on September 30, 1998. The sponsor 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). Oxycodone is a semisynthetic opioid analgesic, and like morphine binds to mu opioid receptors. The usual adult dose is 10 to 30 mg every 4 hours for IR formulations or every 12 hours for the SR formulation.

This submission is primarily a biopharmaceutics and safety submission. Efficacy with two well-controlled clinical trials is not a primary requirement for this NDA as the NDA is a line extension. It was agreed that what the sponsor needs to show is: bioequivalency to marketed products, dose strength equivalence, dose proportionality, and safety in the

target population. The new information resident in this NDA includes two biopharmaceutical studies (XIR-0396 and CBI-315-07), two clinical safety studies (XIR-0596 and XIR-0696), and fifteen reference articles relating to the clinical pharmacology, efficacy and safety of morphine products. Efficacy and safety data are extensively cross-referenced in NDA No. 20-932 (Roxycodone SR) since the 5-mg IR tablet formulation was used in these studies. Three studies (CBI-961/962, CBI-1252 and CBI-963) and forty-eight published articles from NDA 20-932 were submitted to support this application.

The evaluation of the safety data contained in this submission indicates that and the general safety and tolerability profiles were similar although the incidence of adverse events was slightly higher for patients who received oxycodone HCl 15- and 30-mg tablets, particularly in the 15-mg tablet group, compared to the currently marketed 5-mg tablet. The increased incidence in the 15-mg tablet might be due to the extra number of opioid-naive patients enrolled in this group. Administration of oxycodone HCl 15- and 30-mg tablets was not associated with adverse events beyond those known to occur with drugs of this class.

The oxycodone HCl 15- and 30-mg IR tablets appears to be effective in controlling chronic, moderate to severe pain. This effectiveness appears to be comparable to that of oxycodone IR 5-mg tablets in the similar daily dosage.

SECTION 9.0.2 CONCLUSIONS

In the opinion of this reviewer, the two new dosage strengths (15-mg and 30-mg tablets) of oxycodone HCl appears to be reasonable safe when used as recommended.

SECTION 10.0 RECOMMENDATIONS

Based on review of the data submitted, NDA-21-011 is recommended be approved with appropriate labeling.

[/S/] 8/26/99

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August 26, 1999