

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-932

CHEMISTRY REVIEW(S)

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG
PRODUCTS, HFD-170

Review of Chemistry, Manufacturing, and Controls

NDA #20-932

REVIEW #1

DATE REVIEWED: 2.11.98

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
SUBMISSION	12-22-97	12-29-97	1-8-98

NAME & ADDRESS OF APPLICANT:

Roxane Laboratories, 1809 Wilson Road, Columbus, Ohio 43228, Sean Alan Reade, Director of RA, tel 614-276-4000 ext 2345.

DRUG PRODUCT NAME

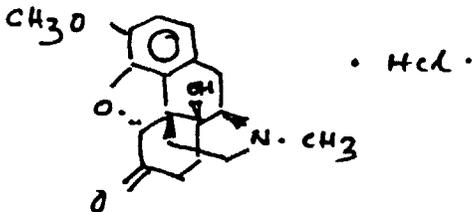
Proprietary: Roxicodone SR (CII)
Established: Oxycodone HCl SR Tablets
Code Name/#: 124-90-3 (oxycodone hydrochloride)
Chem.Type/Ther.Class: S

PHARMACOL. CATEGORY: Narcotic analgesic for the management of moderate to severe pain.

DOSAGE FORM: Tablets for bid dosing.
STRENGTHS: 10 and 30 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

4,5 alpha-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride; C₁₈H₂₁N₀₄. Hcl; MW= 351.83; Freely soluble in water (1 gm per 10 ml); and octanol to water partition = 0.7.



NDA 20-932

Validation of the regulatory methods has not been completed.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-932

PHARMACOLOGY REVIEW(S)

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

NDA: #20-932 original: December 29, 1997

Information to sponsor Yes (x) No ()

Completion Date: April 24, 1998

Sponsor: Roxane Laboratories, Inc.
Columbus, Ohio

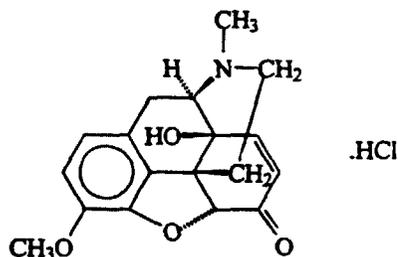
Manufacturers of Drug Substance:

Noramco of Delaware, Inc - Wilmington, Delaware
Mallinckrodt, Inc - St. Louis, Missouri

Trade Name: Roxicodone™ SR

Drug Name: oxycodone hydrochloride -
sustained release

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



Relevant IND/NDA/DMF:

NDA 20-553 - Oxycontin™

Oxycodone hydrochloride

C₁₈H₂₁NO₄.HCl

MW 351.83

Drug Class: narcotic analgesic

Indication: management of moderate to severe pain where use of
an opioid analgesic is appropriate for more than a few days

Clinical Formulation (and components):

oxycodone (10mg, 30 mg), colloidal silicon dioxide NF,
hydroxypropyl methylcellulose USP, lactose NF, sodium
polystyrene sulfonate USP, stearic acid NF, D&C Yellow No 10.

Route of Administration: oral tablets

Proposed Marketing/Clinical Dose: 10 mg, 30 mg

Studies Reviewed within this Submission: None submitted.

Introduction/Drug History: Oxycodone is a semi-synthetic
morphine-like alkaloid which has been marketed for nearly 80

NDA #20-932

years. The analgesic activity in animals may be greater than morphine on a mg/kg basis but the effects of morphine and oxycodone are similar in the cardiovascular system, gastrointestinal tract and renal function. Oxycodone, like morphine, directly suppresses the brain stem respiratory center and reduces its reaction to blood carbon dioxide tension, producing respiratory depression. Oxycodone also depresses the cough reflex by direct action of the medullary cough center.

Oxycodone was recently reviewed in NDA 20-553 and no new non-clinical data of significance has been found or submitted.

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

RECOMMENDATIONS

This compound is approvable from the pharmacology/toxicology perspective.

Labeling -

NDA #20-932

/S/

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

-^ /S/

April 27, 1998

~~Team Leader: Dou Huey Jean, Ph.D.~~

cc: NDA #20-932
HFD 170/Div File
HFD 170 /Blatt H
HFD 170/HGeyer

NDA 20-932

A carcinogenicity review was not conducted. This drug substance has been on the market for decades.

NDA 20-932

This drug was not evaluated by the Executive CAC (Carcinogenicity Assessment Committee).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-932

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA 20-932

Drug name: Roxicodone SR (oxycodone hydrochloride)

Applicant: Roxane Labs, Inc.

Drug class: 3S

Indication: Chronic moderate-to-severe pain (cancer or non-cancer pain)

Volumes reviewed: 1.1 1.75-101 dated 29 December 1997

(Received HFD-170 31 December 1997)

Reviewer: Z. Jonathan Ma, Ph.D., HFD-720

User fee date: 29 October 1998

Project manager: Bonnie McNeal

Medical reviewer: Monte L. Scheinbaum, Ph.D., M.D.

1. INTRODUCTION

A sustained-release (SR) formulation of oxycodone (Roxicodone SR) has been developed by Roxane Laboratories, Inc. for the indication of treatment for chronic moderate-to-severe pain. This NDA is intended for an approval for the marketing of 10 and 30 mg tablets of this sustained formulation.

This submission contains study reports from three clinical trials conducted by the sponsor. They are Studies CBI-961/962, CBI-1252 and CBI-963.

Study CBI -963 was a 30-day, open-label, multi-center observational study assessing the safety of Roxicodone SR in patients experiencing chronic pain. This safety study has been reviewed by the medical officer and will not be discussed in this review.

This statistical review is to focus on Studies CBI-961/962 and CBI-1251, which were randomized, double-blind, double-dummy, active-controlled, multi-center crossover studies, comparing the efficacy and safety of oxycodone SR (10 mg or 30 mg tablets, administered every 12 hours) to oxycodone IR (5 mg tablets, administered every 6 hours).

Section 2 of this review briefly describes the study designs of the two clinical trials. Detailed analyses on efficacy and safety data from the reported trials are to be discussed in sections 3 and 4, followed by the Discussion and Conclusion sections. Lastly, some labeling recommendations are offered.

2. STUDY DESIGN

The sponsor conducted two randomized, double-blind, double-dummy, active-controlled, multi-site crossover studies (Studies CBI-961/962 and CBI-1252) to compare the efficacy of oxycodone SR (Roxicodone SR 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.

As outlined in Table 2.1, the two studies were very similar in study design. Oxycodone IR were used for active-control and rescue medication in both studies. Also, both studies had a 2- to 7-day stabilization period followed by a treatment period, which consisted of 14 days of crossover treatment period, where patients were randomized to receive either oxycodone IR for 7 days followed by oxycodone SR for 7 days, or vice versa. The primary and secondary efficacy endpoints were also similarly defined in the two studies.

One major difference between the two trials was the type of pain under study. Study CBI-961/962 was also referred to as the cancer pain study because all patients recruited in this study suffered from chronic cancer pain. And Study CBI-1252 was also referred to as the non-cancer pain study because it studied patients mainly with chronic non-cancer pain (except one patient).

The inclusion/exclusion criteria were also mostly the same except that Study CBI-961/962 required subjects with a pain intensity of VAS \leq 50 mm at baseline and Study CBI-1252 a VAS \leq 70 mm at baseline.

Table 2.1 Study Design of CBI-961/962 and CBI-1252		
	CBI-961/962	CBI-1252
Overall Design	Randomized, Double-blind, Double-dummy, Active-controlled, Multi-Site, 2-period Crossover	
Study Formulation	Oxycodone SR tablets (10 mg or 30 mg /12 hrs)	
Reference Formulation	Oxycodone IR tablets (5 mg/6 hrs)	
Rescue Medication	Oxycodone IR (5 mg)	
Crossover Treatment Period	14 days (7 days for each formulation)	
Primary Endpoints	VAS prior to 6:00 am, 12:00 noon and 6:00 pm on Day 6	
Secondary Endpoints	VAS on Day 1-5 Global VAS Ratio of mean VAS (SR/IR) Use of rescue medication Integrated analysis of VAS and rescue medication	
Stabilization Drug	Oxycodone IR or SR	Oxycodone SR
Sample Size*	69/49*	114/86*
No. of Sites	15	13
Baseline VAS for Inclusion	\leq 50 mm	\leq 70 mm
Type of Pain	Chronic Cancer Pain	Chronic Non-cancer Pain

*Sample Size represents number of patients on stabilization period/double-blind period.

Inclusion/Exclusion Criteria

Inclusion criteria - each patient was to:

- Have a diagnosis of chronic pain of cancer origin.
- Be male or female 18 years of age or older (if female and of child-bearing potential, the patient was to be practicing suitable means of birth control).
- Have a pain intensity VAS assessment score ≤ 50 mm for CBI-961/962 or ≤ 70 mm for CBI-1252 (0 = no pain, 100 = worst pain possible) for pain over the 24 hours prior to being randomized.
- Currently be treated adequately for chronic pain of cancer origin associated with a TDD of at least 20 mg of oral oxycodone.
- Have a life expectancy of at least 8 weeks.
- Be able to ingest and tolerate oral medications (without emesis).
- Require no more than two breakthrough doses of analgesic during the 24-hour period prior to being randomized.

Exclusion criteria - each patient was not to:

- Be pregnant or lactating.
- Have had surgery in the month prior to stabilization or be scheduled for surgery at any time during the Stabilization Period or at any time during the trial.
- Have a history of allergic, anaphylactic, hypersensitivity, idiosyncratic, or other adverse reaction to opioids or opioid-like medications, as determined by the investigator.
- Have a physical or mental disorder that may prohibit completion of study measures.
- Have a condition that may interfere with the absorption, distribution, metabolism, or excretion of study medications.
- Be scheduled to receive a course of radiation therapy within 14 days prior to the Screening Visit, at any time during the Stabilization Period, or at any time during the trial.
- Be receiving radiation therapy for pain palliation or be anticipating the need for such therapy during the course of the study.
- In the investigator's opinion, be judged to have a history of noncompliance with prescribed therapy (medications) or believed to be unable to keep records (diaries) or scheduled clinic appointments.
- Have any clinically significant medical condition that would, in the investigator's opinion, compromise patient safety or preclude treatment with oxycodone.
- Have received any investigational drug within 30 days prior to screening.

Dose Determination and Efficacy Measurements

The total daily dose (TDD) of oxycodone was decided based on previous opioid medication history and standard conversion to oxycodone equivalence. Patients were allowed to titrate the TDD of oxycodone to a comfort level. The TDD of oxycodone taken during the stabilization

periods (including scheduled and rescue doses) of the studies was used to determine the TDD to be taken during the double-blind treatment periods of the studies.

Visual Analog Scale (VAS, 0–100 mm) scores were used to record the pain intensity experienced by patients just prior to the 6:00 am, 12:00 noon, and 6:00 pm doses every day during the double-blind treatment period.

Patients also recorded doses of rescue medication (oxycodone IR) taken for breakthrough pain. The dose of rescue medication was determined by the investigator based on the patient's TDD. In addition, patients recorded global VAS scores for overall effectiveness of the study drug at the end of each double-blind treatment, where 0 = poor pain control and 100 = excellent pain control.

Primary Efficacy Endpoints

- VAS score for pain intensity at 6:00 am, 12:00 noon, and 6:00 pm, and overall (i.e., the average of all available scores) on Day 6 of each double-blind treatment (oxycodone IR or oxycodone SR)

Secondary Efficacy Endpoints include

- VAS score at 6:00 am, 12:00 noon, and 6:00 pm, and overall on Days 1-5 and the last measurement after Study Day 3, i.e., after patients stabilized to the new drug
- The number and percent of patients who required rescue medication
- The average daily dose of rescue medication
- The average number of doses of rescue medication
- Integrated assessment of VAS scores and rescue medication (“summed percent difference”) for Days 1 through 6
- Global VAS scores for overall effectiveness of study drug

3. EFFICACY ANALYSES

The intent-to-treat population included all patients who were randomized, received at least one dose of double-blind study drug, and recorded at least one VAS or took at least one dose of rescue drug.

Patient Population

For Study CBI-961/962, of 69 patients enrolled, 20 did not complete the stabilization period and, hence, a total of 49 patients were randomized to receive one of two treatment sequences during the double-blind treatment period. Among them, 22 patients received SR/IR sequence and 25 received IR/SR sequence. Two patients did not provide dosing information and therefore were excluded from the efficacy analyses.

For Study CBI-1252, of 114 patients enrolled, 28 did not complete the stabilization period and, hence, a total of 86 patients were randomized to receive one of two treatment sequences during the double-blind treatment period. Among them, 42 patients received SR/IR sequence and 44 for IR/SR sequence. One patient did not provide dosing information and therefore was excluded from the efficacy analyses.

The disposition of patients, by exposure to each formulation, is presented in Table 3.1.

	CBI-961/962			CBI-1252			Total
Enrolled in Stabilization Period	69			114			183
Randomized to double-blind treatment	49			86			135
	<u>IR</u>	<u>SR</u>	<u>Total</u>	<u>IR</u>	<u>SR</u>	<u>Total</u>	
Received double-blind study medication	43	44	47	82	82	85	132
Discontinued double-blind treatment	5	5	10	3	4	7	17
Completed double-blind treatment	-	-	37	-	-	78	115
Included in the intent-to-treat analysis	43	44	47	82	82	85	132

Source: Table 2.2.1.1., Page 23 Vol 96.

The demographics and baseline characteristics of all randomized patients in both studies are presented in Table 3.2

Characteristic	CBI-961/962	CBI-1252	Total
Age (yrs)			
N	49	86	135
Mean (S.D.)	57.6 (13.7)	48.4 (13.4)	51.7 (14.2)
Range			23-86
Gender			
Male	20 (41%)	38 (44%)	58 (43%)
Female	29 (59%)	48 (56%)	77 (57%)
Race			
White	36 (74%)	83 (97%)	119 (88%)
Non-white	13 (26%)	3 (3%)	16 (12%)
Weight (lbs)			
N	45	86	131
Mean (S.D.)	168 (55)	174 (38)	172 (44)
Range			
Stabilized TDD (mg) of Oxycodone			
N	49	86	135
Mean (S.D.)	94.8 (84.7)	65.9 (98.8)	76.4 (94.6)
Range			
Baseline VAS (mm)			
N	47	82	129
Mean (S.D.)	23.7 (18.8)	41.1 (20.7)	34.8 (21.6)
Range			
Patients by Pain Etiology			
Cancer	49 (100%)	1 (1%)	50 (37.0)
Non-cancer	0	85 (99%)	85 (63.0)

Source: Table 2.2.1.2. Page 25, Vol 96.

As mentioned previously, the two study populations were different in terms of pain etiology. While all patients in CBI-961/962 suffered from chronic cancer pain, all patients but one patient in CBI-1252 suffered from chronic non-cancer pain.

As a possible consequence, the patients from the cancer pain study (CBI-961/962) tended to be older and required a higher TDD of oxycodone on average (i.e., 94.8 vs 65.9 mg for CBI-961/962 and CBI-1252, respectively). The difference in the average VAS score at baseline (23.7

vs 41.1 mm for the two studies, respectively) reflected the difference in the inclusion criteria regarding the VAS score on pain intensity mentioned earlier.

Primary Efficacy Analyses

The sponsor employed ANOVA models to analyze the data from the two crossover trials. The interaction terms were tested for significance according to pre-specified procedures in these models. The majority of the interactions were not statistically significant ($p > 0.10$) and no consistent significant interaction effect was noted. Therefore, they were all dropped from the models. Also, no significant sequence effect was noted in the sponsor's report. The final ANOVA model included terms for sequence, patients within sequence, treatment, and period, which is a standard model for crossover trials.

All efficacy endpoints were analyzed following a similar procedure and the results were displayed following a similar format. After discussing with the Agency, the sponsor decided to calculate the confidence intervals of the mean differences in VAS score when comparing the efficacy of the two formulations. Per the Agency's recommendation, the change in VAS on Day 6 was added to the primary endpoint list. This review will also include the analyses on the rescue medication use and the integrated assessment on Day 6 in the primary efficacy analyses.

VAS Score on Day 6

The mean VAS scores on Day 6 for each formulation, the least squares mean difference of the scores, mean ratio of the scores, and the 95% confidence intervals of the difference and the mean ratios are summarized for the intent-to-treat population in Table 3.3. The sponsor's report did not make it clear how the confidence intervals were calculated for the mean ratios.

Table 3.3: Mean VAS Score (mm) on Day 6								
Time Point		Oxycodone		Least Squares Mean Difference			Mean Ratio	
		SR	IR	SR-IR	95% C.I.	p value	SR/IR	95% C.I.
CBI-961/962 (Cancer Pain)								
6:00 am	N	39	38					
	Mean (S.E.)	25.2 (3.4)	24.1 (3.7)	0.48 (2.8)	(-5.0, 6.0)	0.87	1.02	(0.80, 1.23)
12:00 noon	N	36	37					
	Mean (S.E.)	23.0 (3.3)	22.4 (3.3)	-1.09 (2.3)	(-5.6, 3.4)	0.64	0.96	(0.77, 1.14)
6:00 pm	N	36	37					
	Mean (S.E.)	22.9 (3.5)	26.0 (3.7)	-5.3 (2.6)	(-10.4, -2)	0.049	0.81	(0.62, 0.99)
Overall	N	39	38					
	Mean (S.E.)	25.3 (3.3)	24.6 (3.0)	-1.3 (2.1)	(-5.5, 2.9)	0.54	0.95	(0.79, 1.11)
CBI-1252 (Non-Cancer Pain)								
6:00 am	N	79	79					
	Mean (S.E.)	39.6 (3.0)	42.4 (2.9)	-2.82 (1.9)	(-6.6, 1.0)	0.15	0.93	(0.84, 1.02)
12:00 noon	N	79	80					
	Mean (S.E.)	39.5 (2.6)	38.1 (2.4)	1.26 (1.9)	(-2.5, 5.1)	0.52	1.03	(0.93, 1.13)
6:00 pm	N	79	79					
	Mean (S.E.)	41.9 (3.0)	40.2 (2.6)	1.88 (1.9)	(-1.9, 5.7)	0.33	1.05	(0.95, 1.14)
Overall	N	79	80					
	Mean (S.E.)	40.4 (2.6)	40.3 (2.4)	0.22 (1.5)	(-2.8, 3.2)	0.89	1.01	(0.93, 1.08)

• Overall = sum of the scores at all three time points divided by the number of non-missing observations.

Source: Table 2.3.1.1.1.1., Page 43, Vol 96

One statistically significant difference in VAS scores occurred at the 6:00 pm time point in Study CBI-961/962, where the SR formulation actually had a lower mean VAS score than the IR formulation (difference=5.3, p=0.049). However, the sponsor did not consider the difference as a clinically meaningful one, which was defined as 8 mm by the sponsor.

No statistically significant difference was observed at the other two time points in Study-961/962 or the three time points in Study CBI-1252 on Day 6.

Change in VAS from Baseline on Day 6

The mean change from baseline in VAS score on Day 6 was similarly analyzed, as the results shown in Table 3.4. In order to be included in analyses for mean change, a patient had to have both a "baseline" score and a score at the specified time point. Baseline for Period 1 was the VAS score for each time point recorded at the end of stabilization and for Period 2 the last VAS score for each time point recorded in Period 1. Alternatively, the score from the end of stabilization could have been used as the baseline score for both periods. Since the VAS scores were generally similar along the trial period, no significantly different outcome should be expected.

Table 3.4: Mean Change From Baseline for VAS Score (mm) on Day 6						
		Oxycodone		Least Squares Mean Difference		
Time Point		SR	IR	SR-IR	95% C. I.	p-value
CBI-961/962 (Cancer Pain)						
6:00 am	N	38	37			
	Mean Chg (S.E.)	0.89 (2.4)	1.62 (2.5)	-0.63 (3.9)	(-8.3, 7.1)	0.87
12:00	N	34	34			
	Mean Chg (S.E.)	-0.21 (2.5)	-1.12 (2.8)	2.89 (4.3)	(-5.6, 11.4)	0.51
noon	N	31	27			
	Mean Chg (S.E.)	3.81 (2.8)	4.74 (2.6)	1.23 (4.8)	(-8.2, 10.6)	0.80
6:00 pm	N	38	37			
	Mean Chg (S.E.)	1.57 (2.0)	0.74 (2.1)	0.98 (3.3)	(-5.4, 7.4)	0.77
CBI-1252 (Non-Cancer Pain)						
6:00 am	N	78	77			
	Mean Chg (S.E.)	-0.88 (2.0)	-1.06 (2.3)	0.87 (3.4)	(-5.8, 7.6)	0.80
12:00	N	73	75			
	Mean Chg (S.E.)	0.67 (2.0)	-4.36 (2.0)	4.97 (3.5)	(-1.8, 11.8)	0.16
noon	N	63	70			
	Mean Chg (S.E.)	-1.21 (2.7)	-1.30 (1.8)	-0.55 (4.0)	(-8.3, 7.2)	0.89
6:00 pm	N	78	78			
	Mean Chg (S.E.)	-0.07 (1.7)	-2.42 (1.5)	2.37 (2.6)	(-2.7, 7.5)	0.37

* Overall = sum of the scores at all three time points divided by the number of non-missing observation.
Source: Table 2.3.1.1.1.2. Page 46, Vol 96.

Neither studies had a statistically significant difference from the comparisons between the SR and IR formulations ($0.16 \leq p \leq 0.89$).

Use of Rescue Medication (Oxycodone IR) - Day 6

Overall use of rescue medication for breakthrough pain on Day 6 is summarized in Table 3.5.

Table 3.5: Overall use of rescue medication on Day 6

		No. of Patients	No. Taking Rescue Medication	Total No. of Doses	Average Dose (mg)
CBI-961/962	IR	37	16 (43%)	35	22.9
	SR	38	15 (39%)	27	19.3
CBI-1252	IR	80	66 (76%)	144	8.3
	SR	79	60 (83%)	136	8.8

Source: Table 2.3.1.1.2.1, Page 47, Vol 96.

In Study CBI-961/962, the overall use of rescue medication was slightly higher while patients were taking the IR formulation. This difference was not considered clinically meaningful by the sponsor.

In Study CBI-1252, the overall use of rescue medication was slightly higher while patients were taking the SR formulation. This difference was not considered clinically meaningful by the sponsor.

Integrated Assessment of VAS Scores and Rescue Medication Use - Day 6

Recommended by the Agency, a combined endpoint involving both VAS scores and rescue medication use (RMU) was used to assess the two factors simultaneously. A patient summated percent difference was defined as:

$$\frac{\text{Patient VAS Rank} - \text{Mean Rank}}{\text{Mean Rank}} + \frac{\text{Patient RMU Rank} - \text{Mean Rank}}{\text{Mean Rank}}$$

where Mean Rank was calculated as (n+1)/2 and n represented the total number of patients under observation at the time point. Lower patient ranks indicate less pain on the VAS scale and less rescue medication usage, hence a more efficacious response to oxycodone treatment.

For Day 6, the integrated assessment of VAS scores and rescue medication use over the 6 hours preceding each VAS score (summated percent difference) was also analyzed using ANOVA model and the results from the two controlled studies were summarized in Table 3.6 below.

Table 3.6: Integrated Assessment of VAS Scores (mm) and Rescue Medication (Oxycodone IR) Use				
Summated Percent Difference on Day 6				
Time Point		Summated % Difference*		p-value
		Oxycodone SR	Oxycodone IR	
CBI-961/962 (Cancer Pain)				
6:00 am	N	39	38	0.62
	Mean (S.E.)	2.66 (9.9)	-2.73 (10.4)	
12:00 noon	N	36	37	0.76
	Mean (S.E.)	0.23 (11.5)	-0.22 (12.5)	
6:00 pm	N	36	37	0.18
	Mean (S.E.)	-8.75 (13.0)	8.51 (14.0)	
Overall**	N	39	38	0.55
	Mean (S.E.)	-3.19 (12.5)	3.27 (13.6)	
CBI-1252 (Non-Cancer Pain)				
6:00 am	N	79	79	0.31
	Mean (S.E.)	-3.02 (8.5)	3.02 (8.8)	
12:00 noon	N	79	80	0.41
	Mean (S.E.)	-3.45 (9.8)	3.41 (9.3)	
6:00 pm	N	79	79	0.38
	Mean (S.E.)	3.55 (9.5)	-3.55 (8.8)	
Overall**	N	79	80	0.37
	Mean (S.E.)	-3.89 (10.8)	3.84 (10.0)	

* Sum of the percent differences calculated by subtracting the combined mean rank from each patient's VAS rank and rescue medication use rank.

** Overall is based on the average VAS score across all three time points and the number of doses of rescue medication between 12:00 am and 6:00 pm.

Source: Table 2.3.1.1.3.1., Page 49, Vol 96

Analysis of Subgroups

The sponsor also performed subgroups analyses on the primary efficacy endpoints (VAS score and change in VAS score on Day 6) based on sex (male and female), race (white and non-white), age (<65 and ≥65), and baseline TDD (< 40 mg/day, ≥ 40-60 mg/day, > 60-80 mg/day, > 80-120 mg/day, > 120 mg/day) of oxycodone. Most of the tests on the difference between the IR and SR formulations turned out to be not statistically significant. The only statistically significant test was found in non-white and the sponsor considered the difference not clinically significant due to the small sample size.

Secondary Efficacy Analyses

Secondary efficacy variables were mean VAS scores on Days 1-5 and the last measurement after Day 3 (i.e., endpoint after having achieved steady-state levels) of each treatment and the mean global VAS scores for overall drug effectiveness. The use of rescue medication for breakthrough pain was also examined. In addition, an integrated analysis of VAS scores and the use of rescue medication was performed.

VAS Score Days 1 - 5

For Study CBI-961/962, 4 significant differences in VAS scores were found between the SR and IR formulations in a total 20 time points (three time points a day plus Overall for five days). The p values were, respectively, 0.04, 0.02 and 0.02 for 6:00AM, 12:00 noon and Overall on Day 1,

and 0.01 for 12:00 noon on Day 5. The differences in VAS ranged from 4.7 to 7.1 mm and were considered not clinically significant by the sponsor.

The mean changes from baseline in VAS scores on Days 1- 4 were not statistically different ($0.058 \leq p \leq 0.952$). The fluctuations from baseline in mean VAS scores were minor for both formulations. Mean changes from baseline ranged from -0.98 mm to 5.97 mm for the SR formulation and from -2.53 mm to 4.60 mm for the IR formulation.

On Day 5, a significant difference ($p=0.047$) was seen between the formulations in the mean change of Overall VAS scores, while the mean changes from baseline were not statistically different ($0.064 \leq p \leq 0.666$) between SR and IR at the three individual time points. The mean change for the SR formulation ranged from 2.68 mm to 4.97 mm and the change for the IR formulation ranged from -3.49 mm to 1.21 mm.

For Study CBI-1252, neither the mean VAS scores nor the mean change from baseline in VAS scores on Days 1 through 5 were found to be statistically different ($0.071 \leq p \leq 0.964$) between the SR and the IR formulations. The fluctuations from baseline in mean VAS scores were minor for both formulations, and ranged from -2.11 mm to 4.72 mm for the SR formulation, and -3.84 mm to 1.68 mm for the IR formulation.

VAS Score Endpoint

In both studies, no statistically significant difference was found in either VAS score or the change in VAS score at endpoint between the SR and IR formulations.

For Study CBI-961/962, the mean changes from baseline ranged from 1.13 mm to 5.34 mm for the SR formulation and from 2.19 mm (overall) to 3.82 mm for the IR formulation. For Study CBI-1252, the mean changes from baseline ranged from -0.63 mm to 0.73 mm for the SR formulation and from -2.43 mm to 0.99 mm for the IR formulation.

Summary of Overall VAS Scores

The mean overall VAS scores for Days 1 through 6, and at endpoint are summarized by individual study in Table 3.7.

	Study CBI-961/962 (Cancer Pain)						Study CBI-1252 (Non-cancer Pain)					
	SR			IR			SR			IR		
	N	Mean	S.E.	N	Mean	S.E.	N	Mean	S.E.	N	Mean	S.E.
Day 1	45	28.3	3.0	43	24.3	2.8	82	43.4	2.6	82	42.0	2.5
Day 2	44	23.6	3.0	41	26.1	3.2	79	41.7	2.6	82	42.6	2.5
Day 3	45	25.2	3.2	41	25.1	2.9	79	42.1	2.6	81	42.4	2.4
Day 4	43	26.9	3.2	39	25.8	3.1	79	40.6	2.7	81	41.5	2.5
Day 5	42	27.6	3.3	39	22.7	3.0	79	41.5	2.6	81	42.1	2.5
Day 6	39	25.3	3.3	38	24.6	3.0	79	40.4	2.6	80	40.3	2.4
Endpoint	43	26.7	3.2	40	26.4	3.1	79	40.5	2.7	81	41.6	2.5

Source: Table 2.3.1.2.3.1., Page 72, Vol 96.

For Study CBI-961/962, mean overall VAS scores remained fairly consistent for both formulations over the six study days and endpoint. Mean overall VAS scores for each oxycodone formulation were comparable on each study day. The largest difference was seen on Day 5 (27.62 mm for SR; 22.68 mm for IR); however this difference was not statistically significant ($p=0.067$).

For Study CBI-1252, mean overall VAS scores ranged from 40.33 to 43.41 mm for either oxycodone formulation over the six study days and at endpoint. Mean overall VAS scores for each oxycodone formulation were comparable on each study day. No statistically significant differences were seen on any study day.

Use of Rescue Medication (Oxycodone IR)

The number and percentage of patients experiencing breakthrough pain that required rescue medication while on either formulation of oxycodone is presented by time interval (i.e. Days 1-3, Days 4-6, and Days 1-6 of either treatment) for the intent-to-treat population in Table 3.8.

Table 3.8: Number of Patients Experiencing Breakthrough Pain Requiring Rescue Medication (Oxycodone IR)

		CBI-961/962 (Cancer Pain)		CBI-1252 (Non-Cancer Pain)	
		SR		SR	
		>1 dose	0 doses	>1 dose	0 doses
IR	≥1 dose	21 (53%)	4 (10%)	68 (86%)	3 (4%)
	0 doses	6 (15%)	9 (23%)	2 (3%)	6 (8%)
		$\chi^2=0.40, p=0.53$		$\chi^2=0.20, p=0.66$	
Days 1 to 3	≥1 dose	17 (44%)	5 (13%)	68 (87%)	5 (6%)
	0 doses	8 (21%)	9 (23%)	3 (4%)	2 (3%)
		$\chi^2=0.69, p=0.41$		$\chi^2=0.50, p=0.48$	
IR	≥1 dose	25 (63%)	3 (8%)	76 (96%)	1 (1%)
	0 doses	5 (13%)	7 (18%)	0 (0%)	2 (3%)
		$\chi^2=0.50, p=0.48$		$\chi^2=1.0, p=0.32$	
Days 1 to 6	≥1 dose	25 (63%)	3 (8%)	76 (96%)	1 (1%)
	0 doses	5 (13%)	7 (18%)	0 (0%)	2 (3%)
		$\chi^2=0.50, p=0.48$		$\chi^2=1.0, p=0.32$	

* Includes only patients who took both formulations of oxycodone.
Source: Table 2.3.1.2.4.1., Page 74, Vol 96.

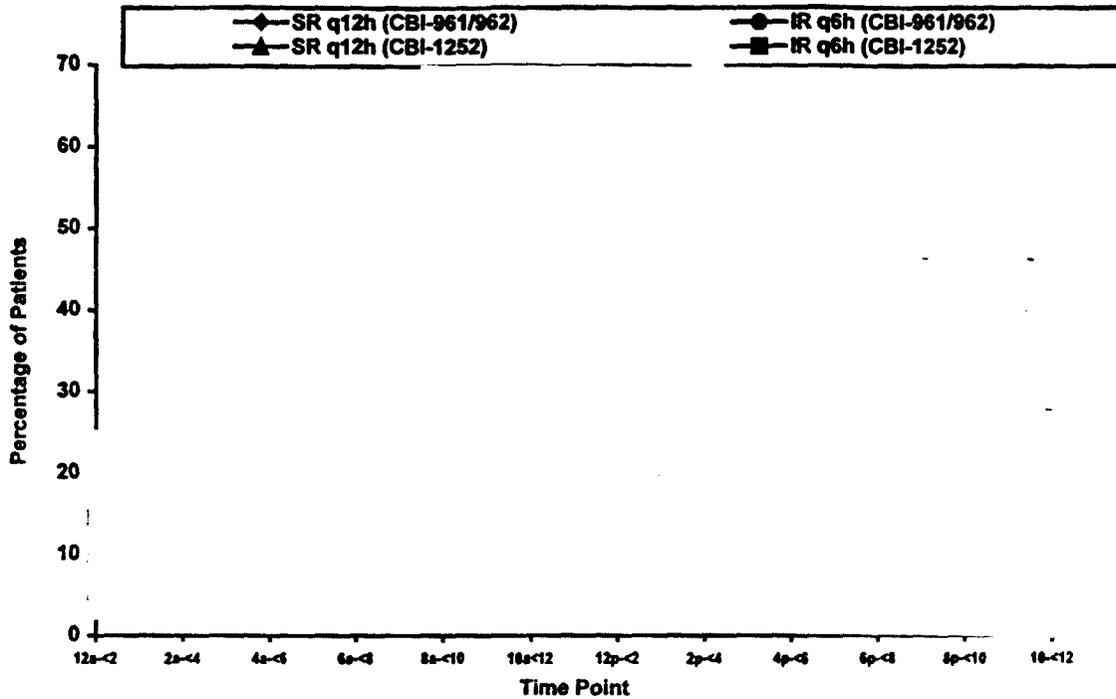
The results of the McNemar's tests consistently showed no statistically significant association between drug formulation and the need for rescue medication during the study days of each trial. The percentage of patients requiring rescue medication while receiving either formulation was higher in Study CBI-1252 (76/79; 96%) than in Study CBI-961/962 (25/40; 63%).

The pattern of the usage of rescue medication was similar following administration of oxycodone SR (administered at 6:00 am and 6:00 pm) or oxycodone IR (administered at 12:00 am, 6:00 am, 12:00 pm, and 6:00 pm). Regardless of whether patients took active drug or placebo, both the percentage of patients who took rescue medication for breakthrough pain and the number of doses taken decreased during the 2-hour interval following the administration of study drug and increased during the next 4 hours until study drug was again administered. This information is graphically displayed in Figure 3.1 for all study days averaged together.

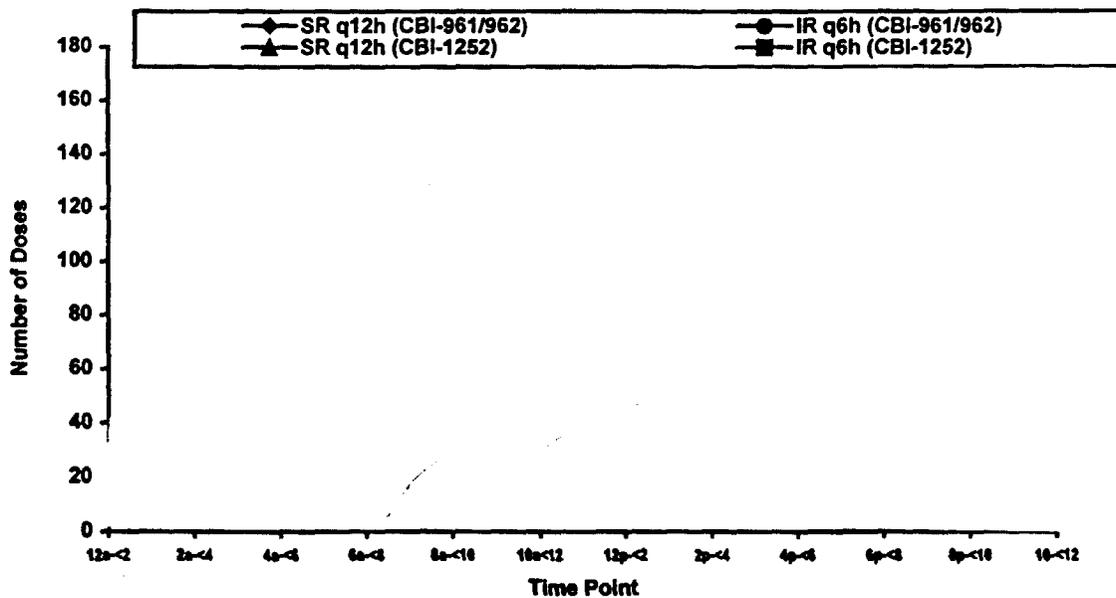
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Figure 3.1: Rescue Medication Use for Breakthrough Pain Every 2 Hours During Double-Blind Treatment

Percentage of Patients Who Took Rescue Medication



Number of Doses of Rescue Medication Taken



Integrated Assessment of VAS and Rescue Medication Use (Days 1 - 5)

For Study CBI-961/962, the only statistically significant difference between the two formulations was observed at 12:00 noon on Day 5 ($p=0.034$), where IR had a lower mean value for summated percent difference. For Study CBI-1252, no statistically significant difference was observed.

Global VAS Score

Global Visual Analog Scale score was recorded by patients to measure overall effectiveness of drug in controlling pain intensity (0 = poor pain control, 100 = excellent pain control) over each 7-day double blind treatment period.

The number and percentage of patients who recorded global VAS scores between 90 and 100 mm, between 70 and 90 mm, between 50 and 70 mm, and less than 50 mm for each formulation in the two controlled studies are displayed in Table 3.9. The mean global VAS for each formulation, the difference in these scores between formulations, and the 95% confidence interval are also displayed.

Table 3.9: Mean Global VAS Score (mm)					
VAS Interval (mm)	SR	IR	LS Mean Difference	95% C.I.	p-value
CBI-961/962 (Cancer Pain)					
Percentage					
≥90	7 (23%)	5 (17%)			
≥70 - <90	8 (27%)	9 (31%)			
≥50 - <70	3 (10%)	5 (17%)			
<50	12 (40%)	10 (35%)			
N	30	29			
Mean	60.7	60.0	-2.05	(-15.1, 11.0)	0.76
S.E.	5.6	5.2	6.6		
CBI-1252 (Non-Cancer Pain)					
Percentage					
≥90	9 (12%)	6 (8%)			
≥70 - <90	25 (32%)	21 (27%)			
≥50 - <70	22 (28%)	27 (34%)			
<50	22 (28%)	25 (32%)			
N	78	79			
Mean	61.5	58.3	2.89	(-3.3, 9.1)	0.36
S.E.	2.7	2.6	3.1		

Source: Table 2.3.1.2.6.1., Page 85, Vol 96.

4. SAFETY ANALYSES

This review only focuses on the adverse events occurred during the double-blind treatment period because the stabilization period did not offer valid ground for comparisons between the two formulations. The adverse experiences reported during the treatment period for patients in both clinical studies was summarized by the sponsor as follows.

Table 4.1: Summary of Adverse Experiences CBI-961/962 and CBI-1252 Pooled Data Double-Blind Treatment Period			
Number of Patients:	Number (%) of Patients		
	Oxycodone SR (N=126)	Oxycodone IR (N=125)	Total (N=132)
With One or More Adverse Experiences	65 (52%)	59 (47%)	87 (66%)
With Drug-Related Adverse Experiences	35 (28%)	33 (26%)	53 (40%)
With Serious Adverse Experiences	4 (3%)	2 (2%)	6 (5%)
With Serious Drug-Related Adverse Experiences	0	0	0
Who Died	0	0	0
Who Discontinued Due to Adverse Experiences	4 (3%)	4 (3%)	8 (6%)

Source: Table 4.1.2.1., Page 27, Vol 98.

The number and percentage of patients reporting one or more adverse experiences while on either formulation of oxycodone are summarized in Table 4.2. Of the 119 patients who received both formulations, 21% reported adverse experiences while receiving SR but not while receiving IR, 14% had adverse experiences while receiving IR but not while receiving SR, 31% reported adverse experiences on both formulations, and 34% did not report adverse experiences on either formulation. While the incidence of adverse experiences was higher for the SR formulation than for the IR formulation, the difference was not statistically significant ($p=0.22$).

Table 4.2: Summary of Clinical Adverse Experiences (AEs) While on Either Formulation of Oxycodone Controlled Clinical Studies – Double-Blind Treatment Period (CBI-961/962 and -1252)				
		<u>Oxycodone SR</u>		Total
<u>Oxycodone IR</u>		≥ 1 AE	No AEs	
	≥ 1 AE	37 (31%)	17 (14%)	54
	No AEs	25 (21%)	40 (34%)	65
	Total	62	57	119

$\chi^2 = 1.52, p=0.22$

Source: Table 4.1.2.2., Page 28, Vol 98.

The adverse experiences that occurred in $\geq 3\%$ of the patients receiving either oxycodone SR or IR, regardless of relationship to study drug, during the double-blind treatment period are presented in Table 4.3. The corresponding rates for adverse experiences considered by the investigator to be possibly, probably, or highly probably drug related are also presented.

Table 4.3: Number of Patients With Most Common (≥3%) Adverse Experiences (AEs) by Body System and COSTART Term CBI-961/962 and CBI-1252 Pooled Data Double-Blind Treatment Period						
Body System COSTART Term	Number (%) of Patients					p-value
	Oxycodone SR (N=126)		Oxycodone IR (N=125)		Total (N=132)	
	All AEs	Drug-Related AEs	All AEs	Drug-Related AEs	All AEs	
Any Adverse Experience	65 (52%)	35 (28%)	59 (47%)	33 (26%)	87 (66%)	0.22
Body As A Whole	27 (21%)	13 (10%)	20 (16%)	8 (6%)	39 (30%)	0.25
Abdominal Pain	5	1	2	1	6	
Asthenia	3	2	4	1	7	
Headache	12	10	5	3	14	
Pain	4	0	1	0	5	
Cardiovascular System	4 (3%)	1 (1%)	4 (3%)	1 (1%)	7 (5%)	1.00
Digestive System	34 (27%)	18 (14%)	22 (18%)	15 (12%)	48 (36%)	0.12
Constipation	5	4	3	3	8	
Diarrhea	8	3	1	0	9	
Dyspepsia	3	0	4	3	7	
Nausea	10	7	9	8	18	
Vomiting	10	6	8	4	17	
Hemic & Lymphatic System	3 (2%)	0	1 (1%)	0	4 (3%)	0.31
Metabolic & Nutritional System	6 (5%)	1 (1%)	4 (3%)	1 (1%)	10 (8%)	0.31
Musculoskeletal System	8 (6%)	0	6 (5%)	0	12 (9%)	0.39
Myalgia	4	0	3	0	5	
Nervous System	18 (14%)	12 (10%)	15 (12%)	8 (6%)	26 (20%)	0.70
Dizziness	5	3	4	2	8	
Nervousness	4	2	0	0	4	
Somnolence	4	4	4	3	8	
Respiratory System	5 (4%)	1 (1%)	5 (4%)	1 (1%)	9 (7%)	0.74
Skin & Appendages System	6 (5%)	3 (2%)	7 (6%)	5 (4%)	12 (9%)	0.78
Pruritus	3	3	5	5	7	
Special Senses	1 (1%)	0	0	0	1 (1%)	0.32
Urogenital System	4 (3%)	1 (1%)	1 (1%)	0	4 (3%)	0.18

P-value based on McNemar's test and includes patients who took at least one dose of both oxycodone SR and oxycodone IR. Comparison is between "All AEs" for oxycodone SR and oxycodone IR.

Among the body systems, the highest incidence of adverse experiences occurred in the "body as a whole", "nervous system", and "digestive system" categories. Based on previous human experience with oxycodone, adverse experiences might be expected to occur in these body systems. For both formulations, the most commonly reported adverse experiences were headache, nausea, and vomiting. These experiences are commonly associated with opioid therapy.

The total number of patients experienced AEs were similar between the two formulations, 65 (52%) and 59 (47%) for SR and IR, respectively. For drug-related AEs, the incidence reduced to 35 (28%) and 33 (26%) for the two formulations, respectively.

On the other hand, however, for individual body system the incidence of AEs appeared to be mostly higher for SR than IR. The difference between the two formulations becomes more notable for body systems with relatively higher AE incidences, such as "body as a whole" (21% vs. 16% for SR and IR, respectively), and "digestive system" (27% vs. 17%, respectively).

The sponsor did not make direct comparisons on the frequency of AEs between the SR and IR formulations in their safety report. To obtain such information, this reviewer performed necessary calculations based on the data provided in the Appendix section of the sponsor's submission. Tables 4.4 and 4.5 show the AE frequency data for the two studies CBI-961/962 and CBI-1252, respectively.

**Table 4.4: Number and Frequency of Patients With Any AEs
by Body System and COSTART Term
CBI-961/962 (Cancer Pain)
Double-Blind Treatment Period**

Body System COSTART Term	SR N=44		IR N=43		Overall N=47
	No. of Pt.	Frequency of Pt.	No. of Pt.	Frequency of Pt.	(SR+IR) No. of Pt.
Total	24 (55%)	61	22 (51%)	37	32 (68%)
Body As A Whole	12 (27%)	14	8 (19%)	10	18 (38%)
Cardiovascular System	2 (5%)	2	1 (2%)	1	2 (4%)
Digestive System	15 (34%)	20	9 (21%)	10	21 (45%)
Hemic & Lymphatic System	2 (5%)	2	1 (2%)	1	3 (6%)
Metabolic & Nutritional System	3 (7%)	4	1 (2%)	2	4 (9%)
Musculoskeletal System	1 (2%)	1	2 (5%)	2	3 (6%)
Nervous System	6 (14%)	9	4 (9%)	5	8 (17%)
Respiratory System	3 (7%)	4	2 (5%)	3	5 (11%)
Skin & Appendages System	3 (7%)	3	3 (7%)	3	5 (11%)
Special Senses	1 (2%)	1	0 (0%)	0	1 (1%)
Urogenital System	1 (2%)	1	0 (0%)	0	1 (1%)

Data Source: Table 13.4, Vol 76

**Table 4.5: Number and Frequency of Patients With Any AEs
by Body System and COSTART Term
CBI-1252 (Non-Cancer Pain)
Double-Blind Treatment Period**

Body System COSTART Term	SR N=82		IR N=82		Overall N=85
	No. of Pt.	Frequency of Pt.	No. of Pt.	Frequency of Pt.	(SR+IR) No. of Pt.
Total	41 (50%)	86	37 (45%)	65	55 (65%)
Body As A Whole	15 (18%)	18	12 (15%)	13	21 (25%)
Cardiovascular System	2 (2%)	2	3 (4%)	4	5 (6%)
Digestive System	19 (23%)	25	13 (16%)	17	27 (32%)
Hemic & Lymphatic System	1 (1%)	1	0 (0%)	0	1 (1%)
Metabolic & Nutritional System	3 (4%)	5	3 (4%)	4	6 (7%)
Musculoskeletal System	7 (9%)	9	4 (5%)	4	9 (11%)
Nervous System	12 (15%)	17	11 (13%)	15	18 (21%)
Respiratory System	2 (2%)	2	3 (4%)	3	4 (5%)
Skin & Appendages System	3 (4%)	4	4 (5%)	4	7 (8%)
Urogenital System	3 (4%)	3	1 (1%)	1	3 (4%)

Data Source: Table 13.4, Vol 86

In Tables 4.4 and 4.5, the frequency of patients with AEs was calculated by adding up the AEs occurrences for all sub-categories under each body system. It appeared that most frequencies are larger than the numbers of patients with AEs under the same category because a patient may have experienced more than one type of AEs.

For Study CBI-961/962 (cancer pain), while the numbers of patients with AEs were 24 and 22 for the SR and IR, respectively, the frequencies were 61 and 37, respectively. Therefore, the average frequency of AEs per patient was $61/24=2.54$ and $37/22=1.68$ for SR and IR, respectively. The percentage increase in AE frequency from IR to SR formulation was $2.54/1.68 - 1 = 51\%$.

For Study CBI-1252 (non-cancer pain), while the numbers of patients with AEs were 41 and 37 for the SR and IR, respectively, the frequencies were 83 and 64, respectively. Therefore, the average frequency of AEs per patient was $83/41=2.02$ and $64/37=1.73$ for SR and IR, respectively. The percentage increase in AE frequency from IR to SR formulation was $2.02/1.73 - 1 = 17\%$.

Table 4.6 shows the results from the two studies pooled data. While the numbers of patients with AEs were 65 and 59 for the SR and IR, respectively, the frequencies were 147 and 102, respectively. Therefore, the average frequency of AEs per patient was $147/65=2.26$ and $102/59=1.73$ for SR and IR, respectively. The percentage increase in AE frequency from IR to SR formulation was $2.26/1.73 - 1 = 31\%$.

Body System COSTART Term	SR N=126		IR N=125		Overall N=132
	No. of Pt.	Frequency of Pt.	No. of Pt.	Frequency of Pt.	(SR+IR) No. of Pt.
Total	65 (52%)	147	59 (47%)	102	87 (66%)
Body As A Whole	27 (22%)	32	20 (16%)	23	39 (30%)
Cardiovascular System	4 (3%)	4	4 (3%)	5	7 (5%)
Digestive System	34 (27%)	45	22 (18%)	27	48 (36%)
Hemic & Lymphatic System	3 (2%)	3	1 (1%)	1	4 (3%)
Metabolic & Nutritional System	6 (5%)	9	4 (3%)	6	10 (8%)
Musculoskeletal System	8 (6%)	10	6 (5%)	6	12 (9%)
Nervous System	18 (14%)	26	15 (12%)	20	26 (20%)
Respiratory System	5 (4%)	6	5 (4%)	6	9 (7%)
Skin & Appendages System	6 (5%)	7	7 (6%)	7	12 (9%)
Special Senses	1 (1%)	1	0 (0%)	0	1 (1%)
Urogenital System	4 (3%)	4	1 (1%)	1	4 (3%)

5. DISCUSSION

Normally, an ideal way to show efficacy and safety is to compare the study drug to a placebo in a clinical trial and demonstrate a superior efficacy and a comparable safety over placebo. However, practical concerns, mainly ethical concerns in this NDA, often prevent one from using a placebo control in such trials and active controlled trials would become the design of choice in

those situations.

In active controlled trials, one way to establish the efficacy of the study medication is to show its superiority over the active control drug under the assumption that the active control drug performs at least as well as a placebo in the trials. From a statistical point of view, this type of active controlled trials are no different from placebo controlled trials.

Nevertheless, a large portion of active controlled trials fall into another category where it is either impossible or undesirable to show superiority of the study drug over the active control drug. Instead, the sponsor hoped to establish the efficacy of the study drug by showing similarity between the study drug and the active control drug.

The sponsor's intention in this NDA was to demonstrate the efficacy of oxycodone SR indicated for the treatment of chronic pain by showing its similarity to that of oxycodone IR which is already an approved and widely used pain medication for that indication.

The sponsor concluded the following at the end of their efficacy report:

It may be concluded that oxycodone SR administered every 12 hours:

- 1. is an effective analgesic indicated for the management of moderate-to-severe pain where use of an opioid is appropriate for more than a few days;*
- 2. provides efficacy equivalent to that seen with oxycodone IR administered every 6 hours in a population of patients with chronic cancer or non-cancer pain, based on equivalence of the primary efficacy variable defined for the study (Day 6). The equivalence is supported by the secondary efficacy parameters (breakthrough pain; VAS scores; and an integrated analysis of VAS scores and breakthrough pain treatment for Days 1 through 6);*
- 3. is equally effective for the management of chronic pain in all subgroups of patients regardless of age, gender, race, or baseline dose; and*
- 4. provides effective pain control as demonstrated by a global patient pain assessment.*

Item 2 actually claims "an equivalence" between the SR and IR formulations. It seemed to this reviewer that this claim was questionable.

Equivalence means "not worse or better". Statistically, failing to show a significant difference between the two formulations does not imply an equivalence between them. Showing equivalence requires rejecting a null hypothesis of non-equivalence. A conventional way to perform an equivalence test usually involves two steps: first to specify a delta margin, and then to show that the observed difference does not exceed this pre-specified margin, i.e., the 95% confidence interval of the mean difference is within this margin. In many cases, however, a clinically meaningful delta margin is usually difficult to decide, and a particular choice can be controversial. For example, in this NDA it was difficult to justify any delta margins used for VAS pain score, total daily dose of oxycodone or rescue medication use.

Realizing these difficulties, the sponsor did not try to pre-specify the delta margins and therefore

did not directly perform any equivalence tests in this submission. Only 95% confidence intervals were calculated for mean differences and mean ratios. Since the sample sizes were not decided based on a pre-specified delta margin, the widths of the confidence intervals came out to be somewhat arbitrary. While some of the non-significant comparisons between the two formulations would have resulted from similarity, other non-significant results could be from insufficient sample sizes and, hence, insufficient power to show a difference.

Therefore, from a statistical point of view, it is not acceptable to make an equivalence claim solely based on non-significant tests.

On the other hand, the results of these two trials did seem to suggest a similarity, sometimes of a high degree, between the two formulations on many efficacy variables. In order to avoid misleading terminology, this reviewer suggests to use a vaguer word such as "similar" or "comparable" instead of "equivalent" when describing the relationship of the efficacy of the SR and IR formulations.

As discussed previously in this review, a majority of the comparisons between oxycodone SR and IR formulations on the primary and secondary efficacy endpoints were not statistically significant, including VAS pain scores, total daily dose of oxycodone and rescue medication use.

It seems reasonable to conclude that the SR formulation was indeed effective for the proposed indication, otherwise it would be hard to believe that a placebo could have produced such similar efficacy profiles on patients with chronic moderate-to-severe cancer or non-cancer pain.

Therefore, the sponsor's Items 1 and 4 above may be reasonable claims.

It should be noted, however, that the SR and IR formulation can not behave exactly the same in controlling chronic pain in reality because of their difference PK profiles. For example, although Figure 3.1 showed a very similar pattern and total dose of the rescue medication use of the two formulations, this can not be true in reality. The trough at 12:00 noon in the pattern of rescue medication use for SR formulation seemed clearly related to the placebo dose taken at 12:00 noon. In reality, such trough at 12:00 noon would not be expected to occur. This kind of dissimilarity would be another reason to avoid using the word "equivalence" for the SR and IR formulations.

Does this mean that the total daily dose of rescue medication taken by patients under the SR formulation would significantly increase from what was seen in these two trials? The answer is not clear. A possible turnout in reality would be that the trough at 12:00 noon and the peak at 2-4pm would cancel each other out and patients on SR oxycodone still end up with a similar total daily dose of rescue medication as they were in those trials.

The subgroup analyses was performed by the sponsor on the VAS scores on Day 6 and no statistically significant difference was observed based on gender, race, age and total daily dose of oxycodone. Again, since no equivalence tests were performed based on these variables, the sponsor should not use "equally effective" in the Item 3 above.

Overall, it seems reasonable to believe that the SR and IR formulations were similar in the efficacy endpoints measured in these two trials.

As of safety comparisons, normally, it is expected to observe a lower rate of adverse events under a SR formulation compared to the IR formulation because of the smoother PK profiles. However, that did not seem to be the case here. It was shown in both trials that, while the total numbers of patients with AEs were similar between the two formulations, patients under SR formulation seemed to show an increase in the frequencies of AEs compared to IR formulation.

While the increase in total AE frequency was 31% for the pooled data, the increase was 51% for the cancer pain study (CBI-961/962) and 17% for the non-cancer pain study (CBI-1252). The difference in the increase percentages, 51% vs. 17% was quite notable for the two trials. It was not clear whether this difference was associated with some underlying factors.

As indicated earlier, the patients in cancer pain trial used a much higher total daily dose of oxycodone on average than those from the non-cancer pain trial. It is not clear how much this factor has contributed to the result and the following is a tentative analysis.

In the sponsor's report, the incidence of adverse experiences was also examined by total daily dose relative to body weight (mg per kg), as summarized in Figure 5.1 and Table 5.1.

**Figure 5.1: Percentage of Patients With AEs
By Formulation and Dose by Weight
CBI-961/962 and CBI-1252 Pooled Data**

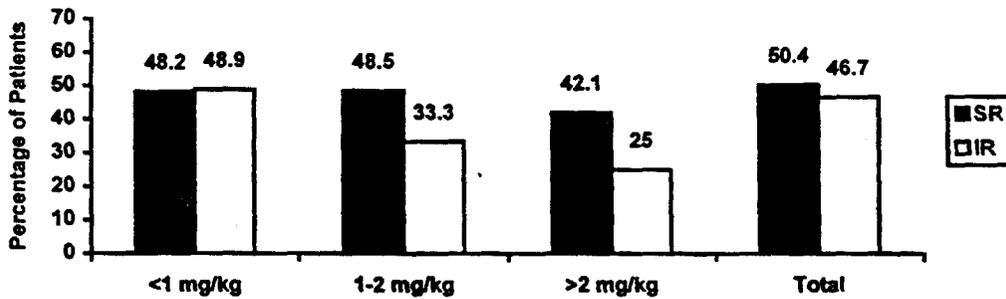


Table 5.1: Number of Patients With Adverse Experiences (AEs) by Weight and Formulation CBI-961/962 and -1252 Pooled Data								
Body System COSTART Term	Total Daily Dose of Oxycodone (mg/kg)							
	Oxycodone SR				Oxycodone IR			
	Total (N=123)	< 1 mg/kg (N=85)	1-2 mg/kg (N=33)	> 2 mg/kg (N=19)	Total (N=122)	< 1 mg/kg (N=88)	1-2 mg/kg (N=33)	> 2 mg/kg (N=16)
Any Adverse Experience ^a	62 (50%)	41 (48%)	16 (49%)	8 (42%)	57 (47%)	43 (49%)	11 (33%)	4 (25%)
Body As A Whole	21 (17%)	12 (14%)	6 (18%)	3 (16%)	15 (12%)	12 (14%)	3 (9%)	0
Digestive System	27 (22%)	20 (24%)	5 (15%)	3 (16%)	19 (16%)	14 (16%)	3 (9%)	3 (19%)
Nervous System	16 (13%)	10 (12%)	4 (12%)	2 (11%)	11 (9%)	7 (8%)	4 (12%)	0

^a Does not include patients whose weights were unavailable.

The relative hazards of AEs under SR vs. IR were $48/49=1.0$, $49/33=1.5$ and $42/25=1.7$ for dose levels < 1 mg/kg, 1-2 mg/kg and > 2 mg/kg, respectively. The two formulations appeared to be further apart in the AE incidence as the dose level increased from < 1 mg/kg to > 2 mg/kg.

6. CONCLUSIONS

Oxycodone SR appeared to be effective in controlling chronic moderate to severe pain. Its efficacy appeared to be similar or comparable to that of oxycodone IR. However, an equivalence conclusion was not supported using confirmatory statistical methods.

There was an evidence, however, that oxycodone SR formulation may cause an increase in the incidences of common adverse events. It seems that this increase mainly happened to patients who already had adverse event experience under oxycodone IR, and the increase may be related to the high level of total daily dose relative to body weight.

This reviewer recommends the approval of the sustained-release formulation of oxycodone for the indication proposed. However, cautions of a possible elevated incidence of adverse events should be given to patients who have already been shown to be sensitive to oxycodone and may use high daily dose.

7. Labeling Recommendations

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