

8.224 Efficacy Results**8.2241 VAS Scores on Day 6 Overall**

The primary efficacy variable for this study was the VAS scores for pain intensity at 6:00 am, 12:00 noon, 6:00 pm, and overall (average of available measurements) on the sixth day of each double-blind treatment. The mean Day 6 VAS assessment scores, the mean differences of the two formulations in VAS assessment score and the 95% confidence intervals are summarized for the intent-to-treat population by oxycodone formulation in Table 23 and graphed in Figure 7. The mean VAS scores during SR treatment ranged from 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 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 Day 6 mean VAS scores were not significantly different at any time point, or overall ($0.147 \leq p \leq 0.889$) between the SR and IR treatments. The Day 6 means for VAS changes from baseline (and differences between formulations) and 95% confidence intervals of the differences are summarized for the intent-to-treat population by oxycodone formulation in Table 24. The mean changes from baseline for VAS scores on Day 6 were not statistically different between the SR and the IR formulations.

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Table 23: Mean VAS Assessment Score (mm) on Day 6

Time point ^b		Formulation		Least Squares Mean Difference			Mean Ratio ^e	
		Oxycodone SR	Oxycodone IR	SR-IR	95% Confidence Interval ^d		SR/IR	95% Confidence Interval ^d
					p-value ^c			
6:00 am	N	79	79					
	Mean ^a	39.63	42.43	-2.815	(-6.58, 0.95)		0.147	0.934 (0.84, 1.02)
	S.E.	2.991	2.933	1.920				
12:00 noon	N	79	80					
	Mean ^a	39.48	38.08	1.256	(-2.53, 5.05)		0.518	1.033 (0.93, 1.13)
	S.E.	2.590	2.418	1.934				
6:00 pm	N	79	79					
	Mean ^a	41.94	40.20	1.884	(-1.90, 5.67)		0.332	1.047 (0.95, 1.14)
	S.E.	2.956	2.582	1.931				
Overall ^f	N	79	80					
	Mean ^a	40.35	40.33	0.216	(-2.80, 3.23)		0.889	1.005 (0.93, 1.08)
	S.E.	2.649	2.431	1.537				

- ^a VAS = Visual Analog Scale for pain intensity on a scale of 0 (no pain) to 100 (worst possible pain).
- ^b Refers to Day 6 of the indicated double-blind treatment.
- ^c Includes patients whose VAS assessment scores were obtained during both double-blind treatments.
- ^d Although expressed using a comma per statistical convention, this interval is interpreted as the range between these two values.
- ^e p-value based on comparison between oxycodone SR and oxycodone IR.
- ^f Overall = Sum of the scores at all three time points divided by the number of time points with non-missing data.

Figure 7: Mean VAS Score (mm) on Day 6

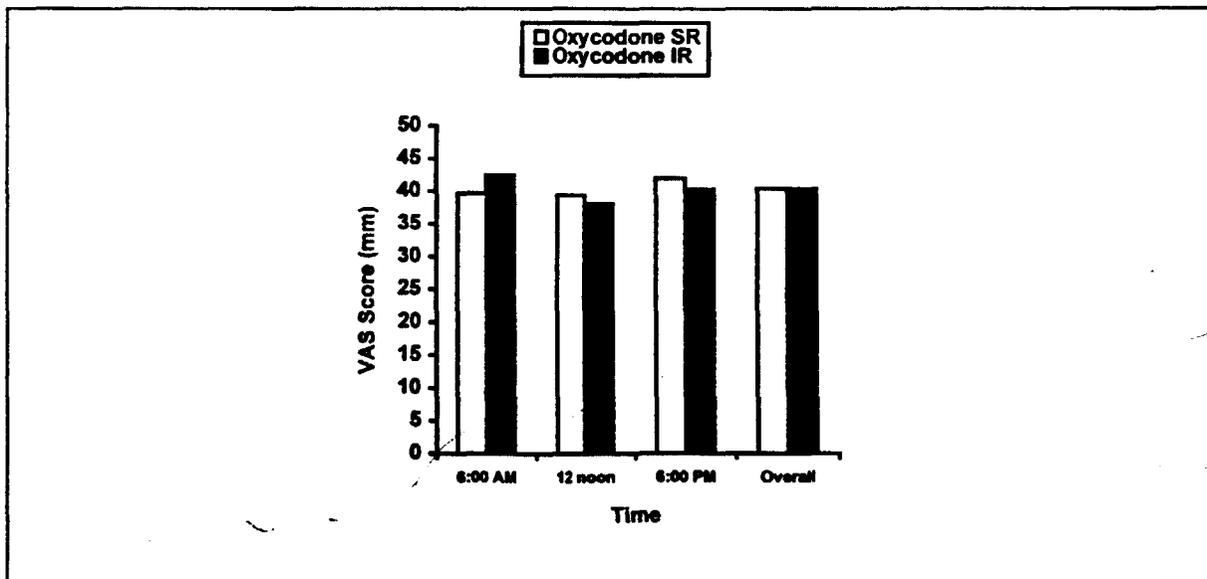


Table 24: Mean Change From Baseline for VAS Score (mm) on Day 6
Intent-to-Treat Population

Time Point ^a		Oxycodone		Least Squares Mean Difference		p-value ^e
		SR	IR	SR-IR	95% Confidence Interval ^d	
6:00 am	N	78	77			
	Mean Change in VAS ^b	-0.88	-1.06	0.873	(-5.84, 7.59)	0.799
	S.E.	2.017	2.286	3.426		
12:00 noon	N	73	75			
	Mean Change in VAS ^b	0.67	-4.36	4.968	(-1.81, 11.75)	0.156
	S.E.	1.989	2.030	3.458		
6:00 pm	N	63	70			
	Mean Change in VAS ^b	-1.21	-1.30	-0.552	(-8.34, 7.24)	0.890
	S.E.	2.699	1.786	3.975		
Overall ^f	N	78	78			
	Mean Change in VAS ^b	-0.07	-2.42	2.368	(-2.73, 7.46)	0.365
	S.E.	1.702	1.527	2.600		

Baseline for Period 1 is 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.

- ^a VAS = Visual Analog Scale score for pain intensity on a scale of 0 (no pain) to 100 (worst possible pain).
- ^b Refers to Day 6 of the indicated double-blind treatment.
- ^c Although expressed using a comma per statistical convention, this interval is interpreted as the range between these two values.
- ^d P-value based on comparison between oxycodone SR and oxycodone IR.
- ^e Overall = sum of the scores at all three time points divided by the number of time points with non-missing data.

8.2242 Days 1 to 5 VAS Scores

The mean VAS assessment scores for Days 1 through 5, as well as the differences between formulation scores, and 95% confidence intervals are summarized by oxycodone formulation in Table 25. Ratios of mean VAS assessment scores and the corresponding 95% confidence intervals are also shown according to study day. There were no significant differences between treatments at any of the three time points or in the overall assessments for any of the five days.

Table 25: Mean VAS Assessment Score (mm) on Days 1 through 5

Time point		(Intent-to-Treat Population)		Least Squares Mean Difference			Mean Ratio	
		Oxycodone SR	Oxycodone IR	SR-IR	95% Confidence Interval	p-value	SR/IR	95% Confidence Interval
Day 1								
6:00 am	N	50	51					
	Mean (S.E.)	45.38 (3.857)	41.31 (3.573)	4.125 (4.663)	(-5.02, 13.27)	0.391	1.104	(0.87, 1.33)
12:00 noon	N	63	69					
	Mean (S.E.)	43.76 (2.639)	37.46 (2.599)	2.995 (2.300)	(-1.51, 7.50)	0.199	1.075	(0.96, 1.19)
6:00 pm	N	82	82					
	Mean (S.E.)	44.34 (2.878)	43.18 (2.775)	0.966 (1.999)	(-2.95, 4.88)	0.630	1.022	(0.93, 1.11)
Overall	N	82	82					
	Mean (S.E.)	43.41 (2.636)	42.03 (2.497)	1.061 (1.614)	(-2.08, 4.24)	0.505	1.025	(0.95, 1.10)
Day 2								
6:00 am	N	79	82					
	Mean (S.E.)	43.32 (3.053)	42.74 (3.034)	0.359 (1.879)	(-3.32, 4.04)	0.849	1.008	(0.92, 1.09)
12:00 noon	N	79	82					
	Mean (S.E.)	39.73 (2.647)	40.66 (2.484)	-0.846 (1.617)	(-4.01, 2.32)	0.602	0.979	(0.90, 1.06)
6:00 pm	N	79	82					
	Mean (S.E.)	42.05 (2.711)	44.32 (2.704)	-2.538 (1.690)	(-5.85, 0.77)	0.137	0.943	(0.87, 1.02)
Overall	N	79	82					
	Mean (S.E.)	41.70 (2.606)	42.57 (2.540)	-1.009 (1.372)	(-3.70, 1.68)	0.465	0.976	(0.91, 1.04)
Day 3								
6:00 am	N	79	81					
	Mean (S.E.)	42.91 (3.010)	44.88 (2.879)	-1.923 (2.124)	(-6.09, 2.24)	0.368	0.957	(0.87, 1.05)
12:00 noon	N	79	81					
	Mean (S.E.)	40.22 (2.524)	40.05 (2.440)	0.090 (1.864)	(-3.56, 3.74)	0.962	1.002	(0.91, 1.09)
6:00 pm	N	79	81					
	Mean (S.E.)	43.28 (2.896)	42.31 (2.748)	0.628 (2.104)	(-3.49, 4.75)	0.766	1.015	(0.92, 1.11)
Overall	N	79	81					
	Mean (S.E.)	42.14 (2.586)	42.41 (2.449)	-0.402 (1.642)	(-3.62, 2.82)	0.807	0.991	(0.92, 1.07)
Day 4								
6:00 am	N	79	81					
	Mean (S.E.)	40.39 (3.103)	42.04 (2.985)	-1.910 (1.606)	(-5.06, 1.24)	0.238	0.955	(0.88, 1.03)
12:00 noon	N	79	81					
	Mean (S.E.)	39.13 (2.738)	40.44 (2.540)	-1.872 (2.170)	(-6.12, 2.38)	0.391	0.954	(0.85, 1.06)
6:00 pm	N	78	80					
	Mean (S.E.)	42.67 (3.034)	41.39 (2.717)	0.053 (2.236)	(-4.33, 4.44)	0.981	1.001	(0.90, 1.11)
Overall	N	79	81					
	Mean (S.E.)	40.56 (2.738)	41.45 (2.507)	-1.269 (1.716)	(-4.63, 2.09)	0.462	0.969	(0.89, 1.05)
Day 5								
6:00 am	N	79	81					
	Mean (S.E.)	41.11 (3.054)	43.94 (2.903)	-2.846 (1.896)	(-6.56, 0.87)	0.138	0.935	(0.85, 1.02)
12:00 noon	N	79	81					
	Mean (S.E.)	40.67 (2.576)	38.65 (2.476)	1.987 (1.702)	(-1.35, 5.32)	0.247	1.052	(0.96, 1.14)
6:00 pm	N	79	80					
	Mean (S.E.)	42.80 (2.851)	43.78 (2.839)	-1.000 (1.781)	(-4.49, 2.49)	0.576	0.977	(0.90, 1.06)
Overall	N	79	81					
	Mean (S.E.)	41.53 (2.644)	42.06 (2.484)	-0.620 (1.412)	(-3.39, 2.15)	0.662	0.985	(0.92, 1.05)

8.2243 VAS Assessment Scores at Endpoint

The mean VAS scores at endpoint (the last day on which a VAS score was recorded on Day 4 or later), the mean difference of the scores for each formulation, and the 95% confidence interval of the difference are summarized for the intent-to-treat population in Table 26. The ratio of the mean VAS scores of the two formulations and the corresponding 95% interval of the ratio are also summarized at each time point. The differences in mean VAS scores at endpoint for the SR and IR formulations (overall, and at the three time points) were not statistically significant. Mean changes from baseline in VAS scores at endpoint were also not statistically different ($0.203 \leq p \leq 0.821$).

**Table 26: Mean Endpoint VAS Assessment Score (mm)
(Intent-to-Treat Population)**

Time point		Oxycodone		Least Squares Mean Difference			Mean Ratio	
		SR	IR	SR-IR	95% Confidence Interval	p-value	SR/IR	95% Confidence Interval
Endpoint 6:00 am	N	79	81					
	Mean	40.30	41.79	-0.897	(-4.27, 2.48)	0.604	0.979	(0.90, 1.06)
	S.E.	2.950	3.044	1.721				
12:00 noon	N	79	81					
	Mean	39.54	39.62	0.821	(-2.62, 4.46)	0.660	1.021	(0.93, 1.11)
	S.E.	2.652	2.603	1.857				
6:00 pm	N	79	81					
	Mean	41.72	43.25	-1.064	(-5.15, 3.03)	0.612	0.975	(0.88, 1.07)
	S.E.	3.007	2.677	2.087				
Overall	N	79	81					
	Mean	40.52	41.55	-0.380	(-3.25, 2.49)	0.796	0.991	(0.92, 1.06)
	S.E.	2.675	2.496	1.462				

8.2244 Global VAS Assessment for Overall Effectiveness of Study Drug

The mean global VAS scores for the SR and IR formulations were comparable, 61.53 mm (SE= 2.702) for SR; 58.27 mm (SE= 2.598) for IR for patients who received both treatments. The difference between formulations was not statistically significant ($p=0.361$), indicating that IR and SR were similarly effective in controlling pain for these patients. Distribution of global VAS scores are displayed in Table 27. Global VAS scores ranged from 0 mm (poor pain control) to 100 mm (excellent pain control). There were 56/78 (71.8%) of patients while on SR and 54/79 (68.4%) patients while on IR who recorded VAS scores at or above 50 mm indicating good pain control.

Table 27: Global Visual Analog Scale (VAS) Score Frequency

Intent-to-Treat Population SR and IR Formulations		
Global VAS Score (range, mm)	SR Treatment n (%)	IR Treatment n (%)
N	78	79
	9 (11.5%)	6 (7.6%)
	25 (32.1%)	21 (26.6%)
	22 (28.2%)	27 (34.2%)
	22 (28.2%)	25 (31.6%)

* Global VAS score (0 mm = poor pain control; 100 mm = excellent pain control) was obtained at the last visit of each study period (or time of withdrawal) to assess overall effectiveness of oxycodone SR or IR in controlling pain in patients for whom a global VAS was recorded.

8.2245 Breakthrough Pain and Rescue Medication

The number and percentage of patients experiencing breakthrough pain while on either formulation of oxycodone are presented by interval (i.e. Days 1-3, Days 4-6, and Days 1-6 of either treatment) for the intent-to-treat population in Table 28. 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. 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. Results were similar for Days 1 through 3 and Days 4 through 6.

Table 28: Number (%) of Patients Who Experienced Breakthrough Pain (Intent-To-Treat Population^a)

<u>Days 1-3</u>			Oxycodone SR Number of Rescue Doses		Chi-Square ^b	p-value ^c
Oxycodone IR	Number of Rescue Doses	<u>≥ 1 dose</u>	<u>0 doses</u>			
				68 (86.1%)	3 (3.8%)	0.200
		<u>0 doses</u>	2 (2.5%)	6 (7.6%)		
<u>Days 4-6</u>			Oxycodone SR Number of Rescue Doses		Chi-Square ^b	p-value ^c
Oxycodone IR	Number of Rescue Doses	<u>≥ 1 dose</u>	<u>0 doses</u>			
				68 (87.2%)	5 (6.4%)	0.500
		<u>0 doses</u>	3 (3.8%)	2 (2.6%)		
<u>Days 1-6</u>			Oxycodone SR Number of Rescue Doses		Chi-Square ^b	p-value ^c
Oxycodone IR	Number of Rescue Doses	<u>≥ 1 dose</u>	<u>0 doses</u>			
				76 (96.2%)	1 (1.3%)	1.000
		<u>0 doses</u>	0 (0.0%)	2 (2.5%)		

^a Includes only patients who took both formulations of oxycodone.

^b Based on McNemar's Test.

^c Based on chi-square value.

8.2246 Total Daily Dose Rescue Medication

The mean total daily dose of rescue medication is presented by study day in Table 29. The overall total daily dose of rescue medication was approximately 14 mg per day for patients who took either formulation of oxycodone. The ANOVA analysis of overall mean total daily doses of rescue medication showed no significant differences between the SR and IR treatment groups ($p = 0.999$). The mean TDD of rescue medication taken between 6:00 pm and 6:00 am was approximately 4.1 mg per day for patients who took either formulation of oxycodone. This represents approximately one-third of the total rescue medication taken. There were no significant differences between the SR and IR treatment groups ($p = 0.956$). The standardized number of days rescue medication was taken and the average number of doses taken per day are summarized in Table 30. Results for each of these parameters were similar for the two formulations. On average, patients took approximately 1.6 to 1.7 doses of rescue medication for 5 days, regardless of formulation.

**Table 29: Mean Total Daily Dose (mg) of Rescue Medication
(Oxycodone IR)^a**

By Study Day and Overall Intent-To-Treat Population						
Study Day ^b	Oxycodone SR			Oxycodone IR		
	N	Mean	S.D.	N	Mean	S.D.
1	82	11.28	10.994	82	11.65	13.632
2	80	15.06	17.275	82	13.96	13.188
3	79	15.82	17.457	81	15.19	14.240
4	79	16.08	18.022	81	15.31	18.189
5	79	14.68	14.397	81	16.17	16.776
6	79	15.44	18.383	80	14.94	13.559
7	79	12.91	15.013	80	13.44	16.061
8	51	10.39	12.917	45	9.89	12.177
9	8	13.75	13.296	12	5.00	6.742
Overall ^c	82	13.81	14.499	82	13.82	13.308

^a Includes patients who did not take any rescue medication.

^b Relative to the first day of the indicated double-blind treatment

^c For each patient, the TDD of rescue medication taken during treatment was divided by the number of days of therapy.

**Table 30: Days and Number of Doses Rescue Medication Taken
(Intent-To-Treat Population^a)**

	Oxycodone SR	Oxycodone IR
Standardized No. of Days^b		
N	82	82
Mean	4.5	4.8
S.D.	1.907	1.680
Average No. of Doses^c		
N	82	82
Mean	1.640	1.676
S.D.	1.035	0.931

^a Includes patients who did not take rescue medication.

^b For each patient, the number of days rescue medication was taken was divided by the number of days of therapy. Values were adjusted to assume 6 days of therapy for each formulation.

^c For each patient, the total number of doses of rescue medication taken was divided by the number of days of therapy with the indicated double-blind treatment.

8.2247 Integrated Analysis of VAS Scores and Rescue Medication

An integrated analysis of VAS scores and rescue medication use was performed by the sponsor using analysis of variance (ANOVA) to compare treatment groups during both Period 1 and Period 2 of the Double-Blind Treatment Period. All patients who took both formulations (SR and IR) were assigned a rank according to their VAS score. The mean rank of treated patients (SR and IR) was determined as $(n+1)/2$. (For example, if 42 patients received both SR and IR, and all have VAS scores at the time point being analyzed, then the mean rank is $43/2$ or 21.5.) The percent difference of the VAS rank and the rank mean was calculated for each patient: $[(\text{pt. VAS rank} - \text{rank mean})/\text{rank mean}]$. The same procedure was performed for rescue medication use rank. For each patient, the percent differences for the two ranks were added together as the "Summated Percent Difference". Means of this variable (summated percent difference) per formulation were compared using ANOVA. All "intent-to-treat" patients, including those that did not require rescue medication, were included in the analysis. The integrated assessment of VAS scores and rescue medication use over the 6 hours preceding each VAS score (summated percent difference) for Days 1 through 6, is summarized for the intent-to-treat population in Table 31. The treatment group with a negative mean value in the table for 'Summated Percent Difference' indicates lower individual patient ranks compared to the overall mean rank; summated percent difference = (each patient mean rank - overall mean rank), per treatment. Lower patient ranks indicate less pain on the VAS scale, and less rescue medication usage, hence a more efficacious response to oxycodone treatment. Results of the analysis indicate no statistically significant differences in the SR and IR treatment groups with respect to their VAS scores and rescue medication use on any of the study days. For 10 out of the 18 time points (56%), patients receiving the SR formulation had lower ranks compared to the combined mean rank (i.e., negative mean value in the table), indicating better pain control for patients receiving SR; however the difference was not statistically significant.

-- Table 31 Integrated Assessment of VAS Score
and Rescue Medication Use

Days 1 Through 6		Intent-to-Treat Population		
Time point		Summated Percent Difference ^a		p-value ^b
		Oxycodone SR	Oxycodone IR	
Day 1 6:00 am	N	50	51	
	Mean (S.E.)	5.78 (10.368)	-5.67 (9.327)	0.356
	12:00 noon			
	N	63	69	
	Mean (S.E.)	5.37 (9.953)	-4.90 (10.223)	0.479
6:00 pm	N	82	82	
	Mean (S.E.)	5.14 (9.494)	-5.14 (8.736)	0.241
Overall ^c	N	82	82	
	Mean (S.E.)	1.76 (9.976)	-1.76 (9.576)	0.632
Day 2 6:00 am	N	79	82	
	Mean (S.E.)	2.22 (7.843)	-2.14 (8.285)	0.639
	12:00 noon			
	N	79	82	
	Mean (S.E.)	0.44 (9.986)	-0.42 (8.854)	0.845
6:00 pm	N	79	82	
	Mean (S.E.)	-2.20 (9.433)	2.12 (8.199)	0.501
Overall ^c	N	79	82	
	Mean (S.E.)	0.04 (10.508)	-0.04 (9.484)	0.954
Day 3 6:00 am	N	79	81	
	Mean (S.E.)	1.80 (8.604)	-1.76 (7.493)	0.641
	12:00 noon			
	N	79	81	
	Mean (S.E.)	-0.28 (9.653)	0.27 (9.680)	0.856
6:00 pm	N	79	81	
	Mean (S.E.)	-4.53 (8.867)	4.42 (8.930)	0.139
Overall ^c	N	79	81	
	Mean (S.E.)	-0.57 (10.479)	0.55 (10.204)	0.967
Day 4 6:00 am	N	79	81	
	Mean (S.E.)	-3.11 (7.880)	3.03 (7.751)	0.296
	12:00 noon			
	N	79	81	
	Mean (S.E.)	-3.11 (9.627)	3.03 (8.940)	0.425
6:00 pm	N	78	80	
	Mean (S.E.)	1.46 (9.934)	-1.42 (9.043)	0.901
Overall ^c	N	79	81	
	Mean (S.E.)	-2.85 (10.930)	2.78 (9.183)	0.481
Day 5 6:00 am	N	79	81	
	Mean (S.E.)	-1.67 (8.310)	1.63 (8.177)	0.565
	12:00 noon			
	N	79	81	
	Mean (S.E.)	-6.41 (9.857)	6.25 (9.227)	0.130
6:00 pm	N	79	80	
	Mean (S.E.)	-1.35 (9.310)	1.34 (8.967)	0.682
Overall ^c	N	79	81	
	Mean (S.E.)	-6.69 (10.759)	6.53 (9.870)	0.082
Day 6 6:00 am	N	79	79	
	Mean (S.E.)	-3.02 (8.465)	3.02 (8.782)	0.306
	12:00 noon			
	N	79	80	
	Mean (S.E.)	-3.45 (9.785)	3.41 (9.273)	0.412
6:00 pm	N	79	79	
	Mean (S.E.)	3.55 (9.543)	-3.55 (8.827)	0.376
Overall ^c	N	79	80	
	Mean (S.E.)	-3.89 (10.841)	3.84 (10.009)	0.368

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

^b Comparison between oxycodone SR and oxycodone IR based on Analysis of Variance (ANOVA).

^c Overall is based on the average VAS assessment score across all three time points and the number of doses of rescue medication between 12:00 am and 8:00 pm.

Note: Negative mean values for summated % differences indicate lower VAS scores (better pain control) and less rescue medication use than the total rank mean.

8.2248 Reviewer Comparison of Individual Patient Efficacy

The reviewer examined results for the 78 patients for which there was complete Day 6 (or Day 5 or 7- 9, if Day 6 data was unavailable) VAS pain intensity score and total daily dose (including escape medication) crossover data. 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. Otherwise neither treatment was judged to be superior for the patient. On this basis, neither formulation demonstrated meaningfully better efficacy for 53 (68%) patients, 14 (18%) patients did slightly better on IR, and 11 (14%) did slightly better on SR. These results are consistent with those of the sponsor's integrated approach to analyzing VAS pain intensity and escape medication use.

8.225 Study Conclusions

The primary efficacy variable, VAS pain intensity for Day 6, had similar mean values for both formulations. The secondary efficacy parameters (breakthrough pain, VAS scores, integrated analysis of VAS scores and breakthrough pain treatment for Days 1 through 6) were consistent with similar efficacy for both formulations. The reviewer's comparison of individual patient results confirmed this conclusion. 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 cancer patients with chronic pain.

8.3 Study CBI-963

(30-day Open-Label Safety Study)

8.31 Investigators

Eighteen sites enrolled patients:

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8.32 Plan

8.321 Objective

This 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. A secondary objective was to determine effectiveness of oxycodone SR to control pain via a 100-mm global Visual Analog Scale (VAS), and via the number of patients who required rescue medication (oxycodone IR), the mean daily dosage taken, and the average number of rescue doses taken per day. Blood samples for pharmacokinetic analysis were drawn from a subset of the total study population. Objectives were to attempt to correlate oxycodone concentrations with effect, as measured by a separate 100-mm VAS for pain intensity at the time of sampling (i.e., "right now"), and to construct and analyze a population pharmacokinetics model.

8.322 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. Patients were to be over 18 years old with a life expectancy of at least 8 weeks and able to ingest and tolerate oral medications (without emesis). Women of child-bearing potential were to be nonpregnant or lactating and practicing adequate means of birth control. Exclusions included surgery (or radiation therapy) in the month (two weeks) prior to stabilization or scheduled anytime during the trial. History of alcohol or drug abuse or hypersensitive reaction to opioids or opioid-like medications, physical or mental disorder that would prohibit completion of study measures or interfere with the absorption, distribution, metabolism, or excretion of study medications were exclusions. received any investigational drug within 30 days prior to screening.

8.323 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. entry criteria, they entered into the 30-day SR Treatment Period of the study.

8.324 Stabilization Period

The oxycodone SR dose to be taken was calculated by dividing the TDD of oxycodone IR taken during the IR Stabilization Period (including scheduled and rescue doses) by 2, and then rounding up to the nearest multiple of 10. Rescue doses of oxycodone IR (supplied as 5-mg tablets) were used for breakthrough pain. Patients returned to the clinic for evaluations twice during the SR Treatment Period. At the final visit, a global VAS measuring overall effectiveness of oxycodone SR to control pain was completed and blood was drawn for laboratory tests. Patients were required to keep daily records of adverse experiences, as well as rescue and concomitant medications, in a patient diary. Blood samples for pharmacokinetic analysis were drawn at each of the 2 scheduled visits during the 30-day SR Treatment Period. (Visit 3, Day 15; Visit 4, Final Visit). Samples were drawn utilizing a random block design for timing of samples. Efficacy variables included the global VAS score for overall effectiveness obtained at the Final Visit, the number of patients who required rescue medication during the SR Treatment Period, the mean dose of rescue medication taken and the average number of rescue doses taken per day. Efficacy analyses were limited to descriptive statistics.

8.33 Study Conduct/Outcome

8.331 Patient Disposition

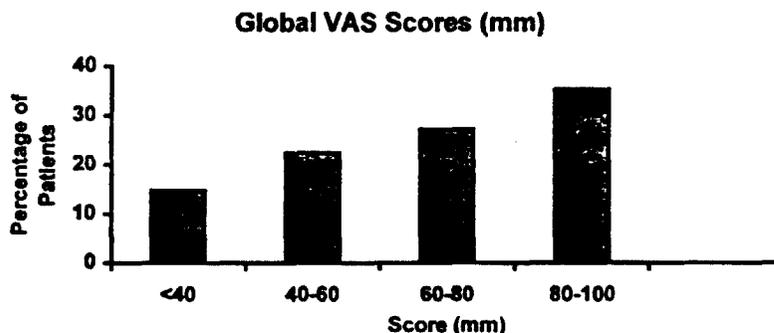
A total of 292 patients entered the IR Stabilization Period, and 238 patients (81.5%) completed this phase of the study. Two hundred thirty-three patients entered the SR Treatment Period, and 188 patients (80.7%) completed this phase of the study. Of the 45 patients who discontinued prior to completion 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.

8.332 Efficacy Results

8.3321 Global Pain Control

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 (Figure 8). Global VAS scores for completers and for patients grouped on the basis of cancer vs. non-cancer pain were generally similar.

Figure 8 Global Pain Control VAS Scores (CBI-963)



8.3322 Escape Medication

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 number of doses of rescue medication decreased within the 2-hour interval following the administration of oxycodone SR and increased during the next 10 hours until study medication was again administered. Use of rescue medication decreased from 6:00 p.m. to 6:00 a.m. The majority of patients (158/233, 67.8%) did not require an adjustment of their oxycodone SR TDD over the course of the study.

8.34 Conclusions Regarding Efficacy from CBI-963

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.

8.4 CBI-964 Ongoing One-Year Study

This was an ongoing (as of the data cutoff date of 31 August 1997), 1-year, open-label, multi-center, compassionate-use study assessing the safety of oxycodone SR tablets administered every 12 hours in patients with chronic pain of malignant or non-malignant origin. The last patient from this study was expected to finish in May 1998. The study population consisted of 232 patients who have completed Studies CBI-961/962, CBI-1252, and CBI-963. Efficacy data were not collected in this study.

8.5 Pharmacokinetic/Pharmacodynamic Analysis

Oxycodone plasma level data from 261 selected patients in the CBI-961/962, CBI-1252 and CBI-963 studies was analyzed using the VAS score as the pharmacodynamic effect by three models described in detail in the Clinical Pharmacology and Biopharmaceutics Review (and Pharmacometrics Consult). Steady state levels of both formulations after chronic dosing were similar, and there was an age-dependent effect on oxycodone clearance. These analyses failed to detect any PK/PD relationship. PK/PD analyses of opioids, usually involving parenteral morphine in single doses, have shown correlations between plasma levels and analgesia (Derendorf & Hochhaus, Handbook of Pharmacokinetic/Pharmacodynamic Correlation, 1995 pp. 146-155). The present oxycodone studies, with inadequately controlled timing of oral dosing, plasma sampling and escape medication, have not provided useful PK/PD information.

8.6 Published Literature

Immediate-release (IR) oxycodone has been used for the management of acute and chronic pain for over 70 years. Oxycodone hydrochloride has been used both orally and parenterally, and the pectinate salt has been used rectally in Europe. Oxycodone, as the hydrochloride or terephthalate salt has often been prescribed in oral combination products containing 5 mg of oxycodone with aspirin, phenacetin, and/or acetaminophen. Single-dose, double-blind studies evaluating the efficacy of oxycodone have demonstrated analgesic efficacy relative to placebo in postoperative dental pain (Cooper SA et al, Oral Surg 1980;50:496-501), in hospitalized postoperative patients (Young RES, J Med 1979;10:417-28) and in patients with cancer pain (Stambaugh JE. et al J Clin Pharmacol 1980; April:261-270). The latter publication also reported greater analgesic efficacy for oxycodone than zomepirac in patients with cancer pain in a double-blind, repeated dose crossover trial. Oxycodone was similar to morphine in the management of cancer pain according to Kalso and Vainio (Curr Ther Res 1980; 27:302-308.)

8.6 Discussion of NDA 20-932 Pivotal Trials

This NDA had two double-blind, double-dummy, active-controlled, crossover trials comparing the effectiveness of individually determined optimal doses of oxycodone sustained release (SR) administered every 12 hours to that of oxycodone IR administered every 6 hours. The patients enrolled in these studies had chronic pain of either cancer (Study CBI-961/962) or non-cancer (Study CBI-1252) etiology that required opioid analgesics for more than a few days. The results of Studies CBI-961/962 and CBI-1252 demonstrate that sustained-release oxycodone tablets (oxycodone SR) administered every 12 hours are as effective an analgesic as immediate-release oxycodone tablets (oxycodone IR) administered every 6 hours in patients with moderate-to-severe chronic pain of cancer or non-cancerous etiology. This conclusion is supported by results of both studies showing comparable VAS scores on Day 6 of treatment for each formulation (the primary efficacy parameter for both studies). Similar efficacy of the formulations is further supported by comparable VAS scores on Days 1 through 6, incidence of breakthrough pain treatment, escape medication use and mean global VAS scores for both treatments. Utilizing an integrated assessment of VAS scores and rescue medication use before a dose (summed percent difference), 17 of 18 integrated values for sustained-release versus immediate-release oxycodone in Study CBI-961/962 indicated no difference in pain control. At only one time point, 12:00 noon on Day 5, was the integrated value for oxycodone SR significantly higher than that for immediate-release oxycodone. None of the integrated values for sustained-release versus immediate-release oxycodone in Study CBI-1252 indicated a statistical difference in pain control. The reviewer's integrated pain intensity and escape medication usage in both studies confirms the similar performance of the two formulations.

8.6 Efficacy Conclusions

Based on the results of the two controlled trials, it may be concluded that oxycodone SR administered every 12 hours 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. The open-label, 30-day, CBI-964 safety study reports efficacy for the SR formulation that is consistent with that found in the pivotal trials.

9.0 Safety Findings

9.01 Exposure

This NDA includes 11 completed human pharmacokinetics and bioavailability studies, two completed efficacy crossover trials with one-week legs comparing IR and SR formulations, a completed open-label study, and an ongoing open-label, compassionate-use study. A total of 393 patients and 193 healthy subjects received oxycodone SR in the 15 completed studies. The numbers of patients or subjects evaluated for safety are tabulated according to study type in Table 32 and according to study in Table 34. There were 1720 patient-days exposure to SR in controlled studies and 6516 patient-days exposure to SR in the uncontrolled study, CBI-963. Total exposure to SR for completed studies was 8236 patient-days. Table 33 tabulates numbers of patients on SR from completed studies according to dose range and duration of treatment range.

Table 32: Number of Subjects/Patients in the Clinical Program

Type of Study	Number of Studies	Oxycodone SR Tablets	Oxycodone IR Tablets	Oxycodone IR Solution	Any Treatment
Human Pharmacokinetics and Bioavailability Studies	11	193	80	179	275
Controlled Clinical Studies	2	160	145	NA	183
Uncontrolled Clinical Study	1	233	292	NA	292
Ongoing Clinical Study	1	232	NA	NA	232
Total	15	586	517	179	750

In the controlled and uncontrolled studies, patients received oxycodone IR or SR during the stabilization period and may also have received oxycodone IR as rescue medication for breakthrough pain during study. These totals do not include patients who may have taken rescue medication.

Table 33: Therapy Durations and Daily Dose Exposure of Oxycodone SR

(Combined Clinical Studies -- 961/962, 963 and 1252)

Therapy Duration (days)	0-20 mg/d n(%)	21-40 mg/d n(%)	41-80 mg/d n(%)	81-200 mg/d n(%)	201-400 mg/d n(%)	>400 mg/d n(%)	Total mg/d n(%)
1-7	41 (36%)	37 (26%)	35 (25%)	20 (27%)	7 (54%)	1 (25%)	60 (15%)
8-14	23 (20%)	37 (26%)	27 (19%)	15 (20%)	1 (8%)	3 (75%)	73 (19%)
15-21	13 (11%)	24 (17%)	21 (15%)	6 (8%)	0 (0%)	0 (0%)	60 (15%)
22-28	6 (5%)	10 (7%)	16 (12%)	7 (9%)	1 (8%)	0 (0%)	28 (7%)
29-35	30 (26%)	34 (24%)	36 (26%)	23 (31%)	4 (31%)	0 (0%)	157 (40%)
36-45	1 (1%)	2 (1%)	4 (3%)	3 (4%)	0 (0%)	0 (0%)	13 (3%)

Table 34 Clinical Studies Included in the Safety Summary

Study No.	Type	Number of Subjects/Patients			
		Oxycodone SR Tablets	Oxycodone IR Tablets ^a	Oxycodone IR Solution	Any Treatment ^b
Human Pharmacokinetics and Bioavailability Studies in Normal Volunteers					
<i>Pilot/Background Studies</i>					
315-01	Bioequivalency (Single-Dose, 4-Way Crossover)	28	–	28	28
315-05	Single-Dose Bioavailability, 2-Way Crossover	–	26	26	26
XIR0296	Bioequivalence 3-way Crossover	–	26	26	27
XIR0196	Single-Dose, 3-Way Crossover	–	28	–	28
<i>Bioavailability/Bioequivalence</i>					
315-03	Single-Dose, 3-Way Crossover Bioavailability	30	–	29	30
315-08	Single-Dose, 2-Way Crossover Bioavailability	26	–	–	26
<i>Steady-State Pharmacokinetics</i>					
315-04	Multiple-Dose, 3-Way Crossover Bioequivalence	30	–	30	30
315-09	Bioavailability 2-way crossover	25	–	26	26
<i>Food Effects</i>					
315-10	Single-Dose, 4-Way Crossover, Food Effect Study	14	–	14 ^c	14
315-11	Single-Dose 4-Way Crossover, Time to Food Effect	24	–	–	24
<i>Dose Proportionality</i>					
315-12	S.D., 4-Way Crossover, Dose-Proportionality	16	–	–	16
Human Pharmacokinetics and Bioavailability Studies Subtotal		193	80	179	275
Controlled Clinical Studies					
CBI-961/962	Multicenter Crossover Efficacy Chronic Cancer Pain				
	<i>Stabilization Period</i>	6	63	–	69
	<i>Double-Blind Treatment Period</i>	44	43	–	47 ^c
CBI-961/962 Subtotal		46	63	–	69
CBI-1252	Multi-Site Crossover Chronic Pain				
	<i>Stabilization Period</i>	114	–	–	114
	<i>Double-Blind Treatment Period</i>	82	82	–	85 ^d
CBI-1252 Subtotal		114	82	–	114
Controlled Clinical Studies Subtotal		160	145	–	183
Uncontrolled Clinical Study					
CBI-963	Multicenter 30-Day, Safety, Chronic Pain				
	<i>IR Stabilization Period</i>		292	–	292
	<i>SR Treatment Period</i>	233	–	–	233
Uncontrolled Clinical Study Subtotal		233	292	–	292
Ongoing Clinical Study^e					
CBI-964	One-Year, Multicenter, Compassionate-Use	232	–	–	232
Ongoing Clinical Study Subtotal		232	–	–	232
Grand Total		586	517	179	750

- ^a Patients may have received oxycodone IR as rescue medication for breakthrough pain during any of the study periods in the controlled and uncontrolled clinical studies. The rescue medication dosing is not included in these totals.
- ^b Total number of subjects/patients who received study drug of any formulation.
- ^c Does not include 2 patients (Guthrie/Patient 8 and Tkaczuk/Patient 3) who received double-blind study drug, but did not complete the study medication page in the patient diary.
- ^d Does not include 1 patient (Larijani/Patient 1) who was randomized but did not take double-blind study drug because of adverse experiences that had begun during stabilization.
- ^e This study is comprised of patients who participated in Studies CBI-961/962, -963, and -1252, therefore, these patients are accounted for in previous categories.
- Not applicable.

9.02 Patient Disposition

There were 475 patients who entered the stabilization periods of all studies combined is described in Figure 9. Of these, 375 (79%) completed the stabilization phases, and 100 (21%) discontinued prior to entering the treatment periods. Of the 375 patients completing stabilization, 368 (98%) entered the treatment periods, and 365 (99%) of these actually received study medication, and 303 (83%) completed the studies. The most common reasons why the remaining patients (17%) discontinued from the studies included adverse experiences in 31 patients (8%) and inadequate therapeutic response in 11 patients (3%). The demographic and baseline characteristics of the patients who entered the treatment period of the controlled and uncontrolled studies combined are summarized in Table 35. The mean age of the patients who entered the treatment period was 52.4 years (range; years). Most patients were female (61%), white (92%), and were being treated for non-cancer pain (82%). The mean total daily dose of oxycodone required for stabilization across studies was 68.0 mg (range mg). Most patients (87%) required at least one dose of rescue medication during the stabilization phase. The healthy subjects in the PK studies were mostly male (82%; 224/275) and white (83%, 227/275), ranging in age from years (mean, 30.1 years).

**Table 35 Demographic and Baseline Characteristics
Patients Who Entered the Treatment Period
Combined Clinical Studies
(CBI-961/962, -1252, and -963)**

Characteristic		
Age (yrs)		
	N	368
	Mean (S.D.)	52.4 (14.13)
	Range	
Gender (N [%])		
	Male	143 (38.9)
	Female	225 (61.1)
Race (N [%])		
	White	337 (91.6)
	Black	25 (6.8)
	Hispanic	5 (1.4)
	Other	1 (0.3)
Weight (lb)		
	N	360
	Mean (S.D.)	171.3 (45.45)
	Range	
Etiology of Pain (N [%])		
	Cancer	65 (17.7)
	Non-cancer	303 (82.3)
Stabilization Medication (N [%])		
	Oxycodone IR	278 (75.5)
	Oxycodone SR	90 (24.5)
Patients Requiring Rescue Medication During Stabilization Period (N [%])		320 (86.9%)
Stabilized Total Daily Dose (mg) of Oxycodone		
	N	367
	Mean (S.D.)	68.0 (70.35)
	Range	

Studies pooled: CBI-961/962, -1252, and -963.

9.1 Deaths

There were 12 deaths reported (Table 36). Two deaths occurred in association with Study 961/962 in cancer patients receiving IR oxycodone. One (Kerr) involved sepsis associated with progression of metastatic disease; the other (Thaczuk) involved congestive heart failure and respiratory failure in a patient with both atherosclerotic disease and pulmonary metastases. Two deaths occurred in patients from Study 963 receiving SR oxycodone, one (Allen) from progression of cancer, another (Strauss) as a consequence of a myocardial infarction (MI). The latter patient, a 57-year old woman treated for nonmalignant neck, back and leg pain, had a history of coronary artery disease (including angina) and hypercholesterolemia. The patient was hospitalized with chest pain on Study Day 3 and study medication was discontinued. Cardiac catheterization was performed on Study Day 4 followed by bypass surgery on Study Day 6. The patient suffered an MI Study Day 7, became comatose and died one week later when life support was removed. Eight deaths occurred among the 232 patients on SR oxycodone in the ongoing long-term compassionate Study 964; seven (Allen , Allen , Kerr , Kerr , Kerr , Lefton , and McLaughlin) of these were from cancer progression and one (Birbaum) from myocardial infarction. The latter was a 55-year old woman with neck and back pain and a history of hypertension treated with dyazide, multiple sclerosis treated with Tegretol, and rheumatoid arthritis treated with Imuran, Naprosyn, methotrexate, prednisone and Vicodin. She suffered a fatal myocardial infarction on Study Day 106. None of the deaths were considered related to study drug treatment.

Table 36: Patient Deaths Reported During the Clinical Program

Study #	Inv./Pt.#	Sex	Age	Rx	Day of Death in Relation to Last Dose of Study Drug	Cause of Death	Days on Study Rx
961/2	Kerr	F	46	IR	6 days after d/c for sepsis, hypercalcemia & neutropenia	Progression of breast cancer metastases	5
961/2	Thaczuk	F	48	IR	1 day after dc for dyspnea (CHF) pneumonia and atrial fibrillation.	CHF and respiratory failure in patient with atherosclerosis, cervical CA & lung metastases	31
963	Allen	M	65	SR	16 days after dc for LOE	Progression of bladder CA	24
963	Strauss	F	57	SR	11 days after dc for myocardial infarction	MI in patient with CAD & nonmalignant pain	7
964	Allen	F	52	SR	on study	Breast CA with lung metastasis	75
964	Allen	M	57	SR	31 days after dc	Nasopharyngeal CA progression	60
964	Birbaum	F	55	SR	on study	Myocardial Infarction in patient with RA, MS and hypertension	106
964	Kerr	F	70	SR	on study	Renal cell CA progression	62
964	Kerr	M	42	SR	9 days after dc for hepatic failure	Progression of adenocarcinoma with liver metastases	25
964	Kerr	F	58	SR	5 days after dc for progression	Progression of lung cancer	91
964	Lefton	F	67	SR	on study	Progression of lung cancer	34
964	McLaughlin	M	81	SR	3 days after discontinuing	Prostate cancer progression	47

9.2 Overdosage

There were no overdose experiences that occurred during this NDA program. Overdose was reported for one patient in spontaneous post-marketing reports for the sponsor's oxycodone IR. According to Goodman and Gilman (The pharmacological basis of therapeutics. New York: McGraw Hill, 1990: 551), acute overdosage with an opioid, such as oxycodone SR, 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. Primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation. The narcotic antagonists, naloxone or nalmefene, are specific antidotes for opioid overdose, but should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone SR overdose. They should be administered cautiously to persons who are known, or suspected to be, physically dependent on any opioid agonist including oxycodone. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome, the severity of which will depend on the degree of physical dependence and the dose of the antagonist administered.

9.3 Significant Events of at Least Possible Drug Relationship

9.31 Nonfatal Serious Medical Events

There were no deaths or serious adverse events reported among the 275 subjects (193 on SR) in the healthy volunteer studies. There was only one patient (Plezia) in 961/2) in the controlled clinical trials (CBI-961/2 and -1252) with a nonfatal serious adverse experience that was of possible drug relationship. This was a 54 year-old man discontinued from IR on Day 2 of the stabilization period for confusion (disorientation) and increased ascites. Summaries of numbers of patients with different types of adverse experiences, including nonfatal serious adverse events, are found in Table 37 for stabilization period events and Table 38 for double-blind treatment period events. One patient (Tilker) in the open-label study, CBI-963, had altered mental status (abnormal thinking) considered serious and possibly drug-related, but the patient was not discontinued from treatment.

9.32 Adverse Events Leading to Discontinuation:**9.321 Phase I Studies**

There were three subjects (all on IR formulations) who discontinued for adverse events, two of these cases (nausea and rash) may have been drug-related.

9.322 Pivotal Studies Stabilization Period Discontinuations

There were 9 of 63 (14.3%) on IR (study 961/962) and 5 of 120 (4.2%) patients on SR (study 1252) that discontinued because of adverse events during the stabilization period of the pivotal studies (Table 37). Six of the nine IR patients had possible or probable drug-related side effects. Most frequent complaints were nausea and vomiting (4 patients), dizziness (3 patients), and confusion (2 patients). The five SR patients had possible or probable drug-related adverse events. Most frequent complaints leading to discontinuation were nausea (2 patients) and dizziness (2 patients) and abdominal pain (1). None of the drug-related adverse events were considered serious with either formulation.

9.322 Pivotal Studies Double-Blind Period Discontinuations

There were 5 of 125 patients (4%) randomized to IR and 4 of 126 (3.2%) randomized to SR in the pivotal studies who discontinued because of adverse events (Table 38). Four of the five IR dropouts had possibly drug-related events (vomiting, flu syndrome, confusion and fatigue), The four SR dropouts had possibly drug-related problems (headache, vomiting, nausea, somnolence). None of the drug-related adverse events were considered serious with either formulation.

**Table 37: Summary of Adverse Experiences Stabilization Period
Controlled Clinical Studies (CBI-961/962 and -1252)**

Number of Patients:	Number (%) of Patients	
	Oxycodone SR (N=120)	Oxycodone IR (N=63)
With One or More Adverse Experiences	75 (62.5)	39 (61.9)
With Drug-Related Adverse Experiences	54 (45.0)	26 (41.3)
With Serious Adverse Experiences	0	3 (4.8)
With Serious Drug-Related Experiences	0	1 (1.6)
Who Died*	0	1 (1.6)
Who Discontinued Due to Adverse Experiences	5 (4.2)	9 (14.3)

Studies pooled: CBI-961/962 and -1252.

AE's are attributed to the "nominal" treatment during the specified period. Patients may have taken rescue medication (oxycodone IR) throughout the study.

* Does not include one patient (Investigator Tkaczuk, Patient 6) who died during Period 2, but did not complete the Study Medication page of the patient diary.

Table 38 Summary of Adverse Experiences Double-Blind Treatment Period Controlled Clinical Studies (CBI-961/962 and -1252)

Number of Patients:	Number (%) of Patients		
	Oxycodone SR (N=126)	Oxycodone IR (N=125)	Total (N=132)
With One or More Adverse Experiences	65 (51.6)	59 (47.2)	87 (65.9)
With Drug-Related Adverse Experiences	35 (27.8)	33 (26.4)	53 (40.2)
With Serious Adverse Experiences ^a	4 (3.2)	2 (1.6)	6 (4.5)
With Serious Drug-Related Adverse Experiences	0	0	0
Who Died ^a	0	0	0
Who Discontinued Due to Adverse Experiences ^{a,b}	4 (3.2)	4 (3.2)	8 (6.1)

Studies pooled: CBI-961/962 and -1252.

AE's are attributed to the "nominal" treatment during the specified period. Patients may have taken rescue medication (oxycodone IR) throughout the study.

- ^a Does not include one patient (Investigator Tkaczuk, Patient ██████, Protocol CBI-961/962) who died during Period 2. This patient did not complete the study medication diary, thus treatment with study drug could not be verified.
- ^b Does not include one patient (Investigator Larjani, Patient ██████, Protocol CBI-1252) who was randomized but did not take study drug due to adverse experiences that started during stabilization.

Table 39 Summary of Clinical Adverse Experiences During SR Treatment Period of CBI-963

Patients (N=233)	Number (%) of Patients
With One or More Adverse Experiences	164 (70.4)
With Drug-Related Adverse Experiences	101 (43.3)
With Serious Adverse Experiences	7 (3.0)
Who Died	2 (0.9)
With Serious Drug-Related Adverse Experiences	1 (0.4)
Who Discontinued Due to Adverse Experiences	21 (9.0)

9.323 Study CBI-963 and CBI-964

Seventeen patients on IR discontinued for drug-related adverse events during the stabilization period of CBI-963. Nineteen patients on SR discontinued for drug-related adverse events during the double-blind period of CBI-963. Eight patients discontinued for drug-related events in CBI-964.

Adverse events associated with discontinuation were abnormal thinking, asthenia x 2, dizziness x 6, depersonalization, constipation x 5, edema, emotional lability, hallucinations, headache x 2, nausea x 9, pruritis x 3, rash, rhinorrhea, somnolence x 7 and vomiting x 4. Table 40 summarizes total numbers of patients who died, had serious adverse events or discontinued for adverse events.

9.4 Significant Events Considered Not Drug Related

Three patients (Tables 37 and 38) had serious nonfatal, non-drug-related events on IR in the pivotal trials; these include a patient with heart failure and pneumonia, another with fracture and two with sepsis.

Serious nonfatal, non-drug-related events on SR in the pivotal trials (four patients, Tables 37 and 38) and CBI-963 (four patients, Table 39) include CHF, increased ascites, cellulitis, chest pain x 2, dyspnea, fracture, hypoglycemia, lung carcinoma progression x 2, myocardial infarction x 4, pancytopenia, pneumonia, pulmonary edema, sepsis, thrombophlebitis x 2, abdominal pain from hepatic metastases, and renal failure.

There were four patients in the pivotal trials, all on IR, with non-drug-related events leading to discontinuation. There were five patients on SR in CBI-963 with non-drug-related events leading to discontinuation. These include: cough, headache, hyperglycemia, sepsis x 1, urinary tract infection, increased pain for patients on IR and fracture x 2, hypoglycemia, and myocardial infarction for patients on SR.

Serious events on SR (19 patients, Tables 39 and 40) reported in the ongoing CBI-964 study (usually leading to discontinuation) include renal cell carcinoma progression, increasing chest wall ulceration, pneumonia, adenocarcinoma with liver metastasis progression, chest pain x 2, hernia repair, lung carcinoma progression, sepsis, trauma, pathological fracture, hypotension, prostate carcinoma progression, and uterine prolapse.

There was one subject in the Phase I trials who received an IR solution that discontinued prematurely because of a bone fracture (Table 40).

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Table 40: Number (%) of Patients who Died, had Serious AE's, and had AE's Resulting In Discontinuation

	Oxycodone SR Tablets	Oxycodone IR Tablets	Oxycodone IR Solution	All Treatments
Deaths				
Human Pharmacokinetics and Bioavailability Studies	0/193 (0%)	0/80 (0%)	0/179 (0%)	0/275 (0%)
Controlled Clinical Studies				
Stabilization Period	0/120 (0%)	1/63 (1.6%)	—	1/183 (0.6%)
Treatment Period ^a	0/126 (0%)	0/125 (0%)	—	0/132 (0%)
Subtotal ^a	0/160 (0%)	1/145 (0.7%)	0/0 (0%)	1/183 (0.5%)
Uncontrolled Clinical Study				
Stabilization Period	—	0/292 (0%)	—	0/292 (0%)
Treatment Period	2/233 (0.9%)	—	—	2/233 (0.9%)
Ongoing Studies ^b	7/232 (3.0%)	—	—	7/232 (3.0%)
Total^{a,b}	9/586 (1.5%)	1/517 (0.2%)	0/179 (0%)	10/750 (1.3%)
Adverse Experiences That Resulted in Discontinuation				
Human Pharmacokinetics and Bioavailability Studies	0/193 (0%)	1/80 (1.3%)	2/179 (1.1%)	3/275 (1.1%)
Controlled Clinical Studies				
Stabilization Period	5/120 (4.2%)	9/63 (14.3%)	—	14/183 (7.7%)
Treatment Period ^a	4/126 (3.2%)	4/125 (3.2%)	—	8/132 (6.1%)
Subtotal ^a	9/160 (5.6%)	13/145 (9.0%)	—	22/183 (12.0%)
Uncontrolled Clinical Study				
Stabilization Period	—	17/292 (5.8%)	—	17/292 (5.8%)
Treatment Period	21/233 (9.0%)	—	—	21/233 (9.0%)
Ongoing Studies	22/232 (9.5%)	—	—	22/232 (9.5%)
Total^a	52/586 (8.9%)	30/517 (5.8%)	2/179 (1.1%)	84/750 (11.2%)
Serious Adverse Experiences				
Human Pharmacokinetics and Bioavailability Studies	0/193 (0%)	0/80 (0%)	0/179 (0%)	0/275 (0%)
Controlled Clinical Studies				
Stabilization Period	0/120 (0%)	3/63 (4.8%)	—	3/183 (1.6%)
Treatment Period ^a	4/126 (3.2%)	2/125 (1.6%)	—	6/132 (4.5)
Subtotal ^a	4/160 (2.5%)	5/145 (3.4)	—	9/183 (4.9)
Uncontrolled Clinical Study CBI-963				
Stabilization Period	—	0/292 (0%)	—	0/292 (0%)
Treatment Period	7/233 (3.0%)	—	—	7/233 (3.0%)
Ongoing Study CBI-964	19/232 (8.2%)	—	—	19/232 (8.2%)
Total^{a,b}	30/586 (5.1%)	5/517 (1.0)	0/179 (0%)	35/750 (4.7)

Patients may be counted in more than one category.

^a Does not include one patient who died during Period 2 of the treatment period; however, the patient did not complete a patient diary so treatment with study drug could not be verified.

^b Does not include one patient who died 31 days after discontinuing from the ongoing study.

9.5 Other Safety Findings

9.51 ADR Incidence Tables

9.511 Adverse Events in Phase I Studies

Table 41 lists adverse drug reactions frequently reported in the healthy volunteer studies. Most frequent were dizziness and nausea.

Table 41: Adverse Experiences That Occurred in $\geq 5\%$ of Volunteers Human Pharmacokinetics and Bioavailability Studies

Adverse Experience	Oxycodone SR Tablets (N=193)	Oxycodone IR Tablets (N=80)	Oxycodone IR Solution (N=179)	Any Treatment (N=275)
Dizziness	36 (18.7)	48 (60.0)	69 (38.5)	123 (44.7)
Nausea	36 (18.7)	37 (46.3)	36 (20.1)	93 (33.8)
Headache	58 (30.1)	11 (13.8)	34 (19.0)	87 (31.6)
Asthenia	54 (28.0)	6 (7.5)	24 (13.4)	74 (26.9)
Somnolence	35 (18.1)	11 (13.8)	34 (19.0)	70 (25.5)
Vomit	18 (9.3)	27 (33.8)	16 (8.9)	53 (19.3)
Pruritus	20 (10.4)	20 (25.0)	22 (12.3)	51 (18.5)
Euphoria	9 (4.7)	8 (10.0)	7 (3.9)	23 (8.4)
Hiccup	7 (3.6)	10 (12.5)	5 (2.8)	21 (7.6)
Vasodilation	6 (3.1)	10 (12.5)	4 (2.2)	19 (6.9)
Fatigue	0	14 (17.5)	7 (3.9)	16 (5.8)
Dyspepsia	5 (2.6)	4 (5.0)	2 (1.1)	10 (3.6)
Paresthesia	2 (1.0)	5 (6.3)	1 (0.6)	8 (2.9)
Any AE	129 (66.8)	63 (78.8)	139 (77.7)	232 (84.4)

Studies pooled: 315-01, -03, -04, -05, -08, -09, -10, -11, -12, XIR0196, and XIR0296.

9.512 Adverse Event Comparisons

Table 42 compares common adverse events in SR and IR reported by patients during the double-blind periods of CBI-961/2 and CBI-1252. There were no significant differences between overall incidences of adverse events (52% for SR vs. 47% for IR) or incidences of events when classified by body systems. There were 27.8% of patients on SR and 26.4% on IR who reported adverse events thought to be at least possibly drug-related. The most frequent events were nausea (14%), vomiting (13%), headache (11%), diarrhea (7%), constipation (6%), dizziness (6%), somnolence (6%), pruritus (5%), dyspepsia (5%).

9.5121 Nausea, Vomiting and Dyspepsia

The incidences of nausea (8% for SR vs. 7% for IR), vomiting (8% for SR vs. 6% for IR), and dyspepsia (2% for SR vs. 3% for IR) were very similar for the two formulations in the double-blind periods.

9.5124 Constipation and Diarrhea

Constipation (4% for SR vs. 2% for IR) seemed more frequent with SR in the pivotal trial double-blind periods. The incidences of constipation for SR was 9% in the CBI-1252 stabilization period (compared to 14% for IR in the CBI-961/962 stabilization period. There was a 16% incidence of constipation for SR in the CBI-963 trial. Diarrhea (6% for SR vs. 1% for IR) appeared to be more frequent with SR in the double-blind periods. However, the incidences of diarrhea for SR were 4% in the CBI-963 study and only 2% in the stabilization period of CBI-1252, while IR had an incidence of over 3% diarrhea in the stabilization period of CBI-961/962.

9.5125 Pruritis

While pruritis appeared more frequent with IR (2% for SR vs. 4% for IR). The incidence for SR was 13% in the CBI-963 study. Pruritis had the same incidences (14%) for SR and IR in the stabilization periods for the pivotal studies; its incidence was 6% for SR in the CBI-963 trial.

9.5126 Dizziness and Somnolence

The incidences of dizziness (4% for SR vs. 3% for IR) and somnolence (3% for SR vs. 3% for IR) reported in the double-blind periods of the pivotal trials were very similar.

9.5127 Headache

Headache (9.5% for SR vs. 4% for IR) appeared more prevalent with SR in the in the double-blind periods. There was a 23% incidence of headache with SR in the stabilization period of CBI-1252 and an 11% incidence for IR in the stabilization period of CBI-961/962. Generally, the incidences of adverse events were similar for both formulations except for headache, which seemed more prevalent with the SR formulation; however, headache is often a frequent complaint among subjects taking placebo in double-blind trials.

**Table 42: Patients with Most Common ($\geq 5\%$) Adverse Experiences (AE's)
(by Body System and COSTART Term)
Controlled Clinical Studies (CBI-961/962 and -1252) Double-Blind Treatment Period**

Body System COSTART Term	Number (%) of Patients				Total (N=132)	p-value
	Oxycodone SR (N=126)		Oxycodone IR (N=125)			
	All AE's	Drug- Related AE's	All AE's	Drug- Related AE's		
Any Adverse Experience	65 (51.6)	35 (27.8)	59 (47.2)	33 (26.4)	87 (65.9)	0.217
Body As A Whole	27 (21.4)	13 (10.3)	20 (16.0)	8 (6.4)	39 (29.5)	0.248
Headache	12 (9.5)	10 (7.9)	5 (4.0)	3 (2.4)	14 (10.6)	
Cardiovascular System	4 (3.2)	1 (0.8)	4 (3.2)	1 (0.8)	7 (5.3)	1.000
Digestive System	34 (27.0)	18 (14.3)	22 (17.6)	15 (12.0)	48 (36.4)	0.117
Constipation	5 (4.0)	4 (3.2)	3 (2.4)	3 (2.4)	8 (6.1)	
Diarrhea	8 (6.3)	3 (2.4)	1 (0.8)	0	9 (6.8)	
Dyspepsia	3 (2.4)	0	4 (3.2)	3 (2.4)	7 (5.3)	
Nausea	10 (7.9)	7 (5.6)	9 (7.2)	8 (6.4)	18 (13.6)	
Vomiting	10 (7.9)	6 (4.8)	8 (6.4)	4 (3.2)	17 (12.9)	
Hemic/Lymphatic System	3 (2.4)	0	1 (0.8)	0	4 (3.0)	0.314
Metabolic /Nutritional	6 (4.8)	1 (0.8)	4 (3.2)	1 (0.8)	10 (7.6)	0.309
Musculoskeletal System	8 (6.3)	0	6 (4.8)	0	12 (9.1)	0.393
Nervous System	18 (14.3)	12 (9.5)	15 (12.0)	8 (6.4)	26 (19.7)	0.697
Dizziness	5 (4.0)	3 (2.4)	4 (3.2)	2 (1.6)	8 (6.1)	
Nervousness	4 (3.2)	2 (1.6)	0	0	4 (3.0)	
Somnolence	4 (3.2)	4 (3.2)	4 (3.2)	3 (2.4)	8 (6.1)	
Respiratory System	5 (4.0)	1 (0.8)	5 (4.0)	1 (0.8)	9 (6.8)	0.735
Skin & Appendages	6 (4.8)	3 (2.4)	7 (5.6)	5 (4.0)	12 (9.1)	0.776
Pruritus	3 (2.4)	3 (2.4)	5 (4.0)	5 (4.0)	7 (5.3)	
Special Senses	1 (0.8)	0	0	0	1 (0.8)	0.317
Urogenital System	4 (3.2)	1 (0.8)	1 (0.8)	0	4 (3.0)	0.176

Studies pooled: CBI-961/962 and -1252.

Drug Related = Possibly, Probably, or Highly Probably Related.

AE's are attributed to the "nominal" treatment during the specified period. Patients may have taken rescue medication (oxycodone IR) throughout the study.

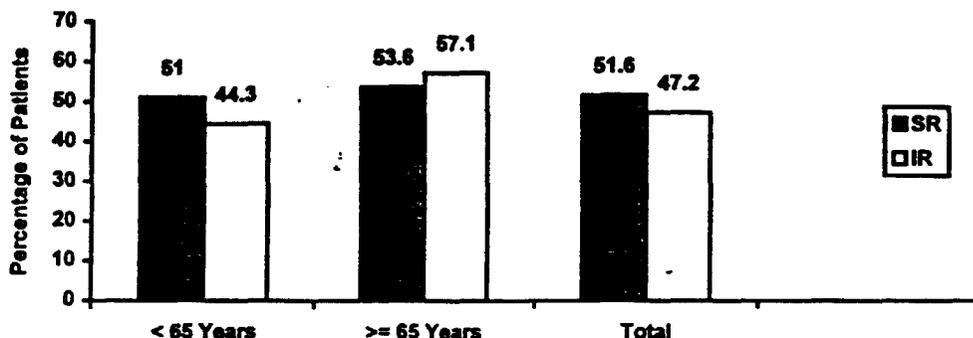
P-value based on McNemar's test and includes patients who took at least one dose of both oxycodone SR and oxycodone IR. Comparison is between "All AE's" for oxycodone SR and oxycodone IR.

9.513 Results of Subgroup Analyses of Adverse Events

9.5131 Effects of Age

The sponsor analyzed the incidence of adverse experiences was by age (< 65, \geq 65). The percentage of patients with adverse experiences in the controlled studies is presented by formulation and age subgroup in Figure 9. As might be expected, older patients appear more likely to report adverse events; this seemed to be exaggerated in the case of the IR formulation.

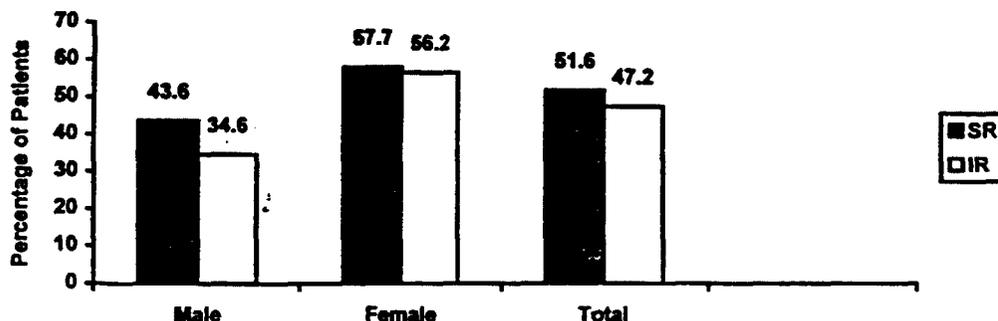
Figure 9: Percentage of Patients with AE's By Formulation and Age Controlled Clinical Studies (CBI-961/962 and -1252)



9.5132 Effects of Gender

Of the 126 patients who received oxycodone SR, 56.3% were female, and of 125 patients receiving IR, 58.4% were female. Overall, more females reported adverse experiences (57.7%) on SR than did males (43.6%). The most commonly reported adverse experience was headache, which was reported in 11.3% of the females and 7.3% of the males. The greatest difference between the sexes was seen for nausea and vomiting, each of which were reported by 11.3% of the females and 3.6% of the males. Females had a higher incidence of adverse experiences of the nervous system than did males (19.7% vs. 7.3%). Dizziness was reported by 7.0% of females compared to 0% of males. Other common adverse experiences that were reported by more females than males were abdominal pain, (5.6% vs. 1.8%), asthenia (4.2% vs. 0%), and pruritus (4.2% vs. 0%). These findings may be due to differences in body weight and/or plasma concentrations. Constipation and diarrhea were reported by more males (5.5% and 9.1%, respectively) than females (2.8% and 4.2%, respectively). The incidence of the other frequently reported adverse experiences was generally similar between males and females. The gender difference was most pronounced for patients on the IR formulation (Figure 10); 56.2% of females vs. 34.6% of males reported adverse experiences. The greatest difference between sexes was seen for vomiting, which was reported by 9.6% of the females compared to 1.9% of the males. Asthenia, dizziness, and dyspepsia, which were each reported by 5.5% of the females, but were not reported by any males.

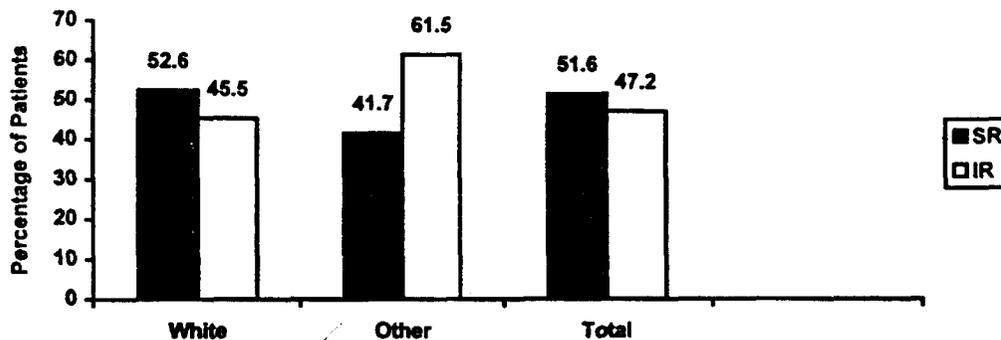
**Figure 10: Percentage of Patients with AE's By Formulation and Gender
Controlled Clinical Studies (CBI-961/962 and -1252)**



9.5133 Effects of Race

The incidence of the most common adverse experiences for white patients, who constituted 90.5% of the 126 patients who received oxycodone SR and 89.6% of the 125 patients who received IR, was similar to that of the overall incidence (Figure 11). Nausea, which is a known opioid effect, was the most commonly reported adverse experience for patients of other races and was reported by 25.0% of these patients on SR and 15.4% on IR. Although there appears to be better tolerability of SR than IR for non-white patients, the numbers of these patients are too small to draw conclusions.

**Figure 11: Percentage of Patients with AE's By Formulation and Race
Controlled Clinical Studies (CBI-961/962 and -1252)**



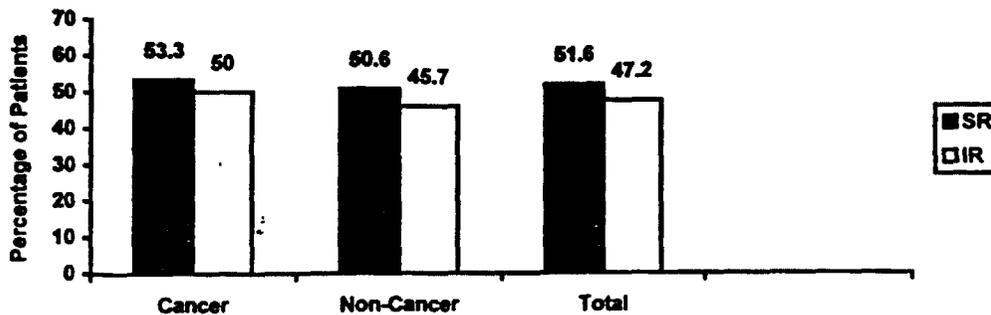
9.5134 Effects of Pain Etiology

The incidence of adverse experiences in the controlled studies was graphed by pain etiology (cancer pain vs. nonmalignant pain) in Figure 12. There appears to be no differences meaningful differences in results from this analysis. Adverse experiences with SR that were reported by a higher percentage of patients with cancer pain than by patients with non-cancer pain were asthenia (6.7% vs. 0%) and nausea (13.3% vs. 4.9%). Patients on SR with non-cancer pain had a higher incidence of headache and diarrhea (12.3% and 9.9% respectively) than did patients with cancer-related pain (4.4% and 0%, respectively).

Adverse experiences that were reported by a notably higher percentage of patients on IR with cancer pain than by patients with non-cancer pain were vomiting (9.1% vs. 4.9%) and dizziness (6.8% vs. 1.2%). Somnolence and dyspepsia were reported by 4.9% of the patients on IR with non-cancer pain, but were not reported by any of the patients on IR with cancer pain.

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**Figure 12: Percentage of Patients with AE's By Formulation and Pain Etiology
Controlled Clinical Studies (CBI-961/962 and -1252)**

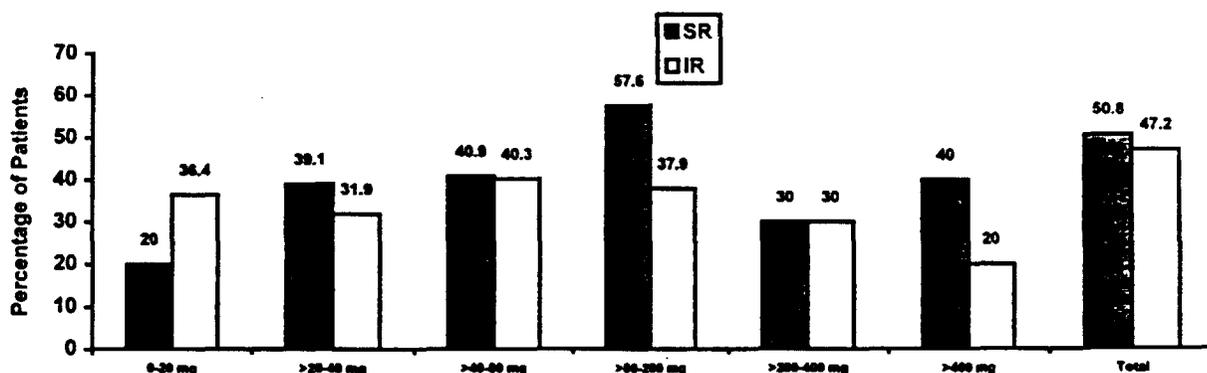


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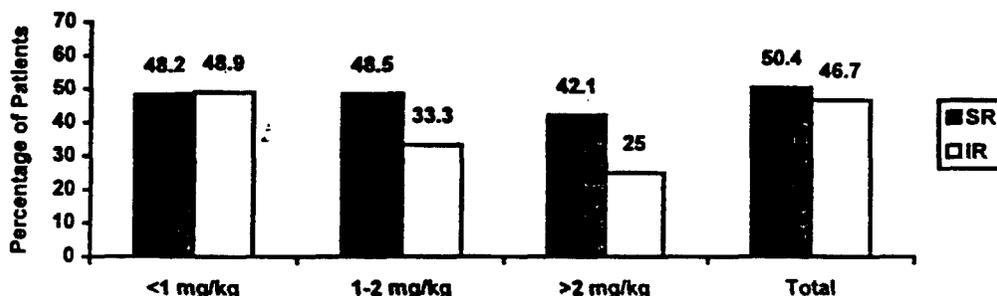
9.5135 Effects of Dose

Most of the 126 patients on SR received a total daily dose in the range of mg. More than half (52.4%) received a total daily in the range of mg, 36.5% in the range of mg, and 26.2% in the range of mg. The incidence of diarrhea on SR appeared to increase as the total daily dose increased; however, differences in sample sizes interfere with comparisons between doses. Most of the 125 patients on IR received a total daily dose in the range of mg, more than half (53.6%) received a total daily in the range of mg, 37.6% in the range of mg. The incidences of nausea and vomiting appeared to increase as the total daily dose increased. The incidence of adverse experiences was plotted by dose in relation to body weight (mg per kg) in Figure 14. Most patients (69.1% on SR and 72.1% on IR) received a dose of less than 1 mg per kg of body weight (26.8% on SR and 27% on IR received 1 to 2 mg per kg, and 15.4% on SR and 13.1% on IR received > 2 mg per kg. There was no apparent dose-related increase in the incidence of adverse experiences either formulation, probably because of differences in selected range sizes.

Figure 13: % Patients with AE's By Formulation and Total Daily Dose
Controlled Clinical Studies (CBI-961/962 and -1252)



**Figure 14: % Patients with AE's by Formulation and Dose by Weight
Controlled Clinical Studies (CBI-961/962 and -1252)**



9.514 Safety Update on Long-term Study CBI-964

A 4-month safety report sent 5/4/98 (received 5/11/98) listed three significant adverse events. Two events involve cancer patients and were not considered drug-related. A 56 yo woman (Plezia) with a nonhealing chest wound died from disease progression; a 55 yo woman (Plezia) had seizures and sepsis requiring hospitalization and allergic rash (possibly secondary to porta-cath insertion or antibiotics), all of which resolved without discontinuation from the trial. A possibly drug-related event, headache, resulted in discontinuation of a 26-yo man (Rauck).

9.52 Laboratory Findings

Blood samples were collected during the screening and the final visits for laboratory tests and analyzed by

Blood samples were also drawn at the time the patient discontinued prematurely from the study. Urine pregnancy tests were performed either in the clinic or at a local lab at the screening visit. Comparisons between formulations could not be made since patients had usually received both treatments. Mean final values in laboratory parameters for patients who entered CBI-963 or the double-blind portions of the pivotal trials showed no remarkable differences from screening values. Generally, the numbers of values below normal limits were similar to those above normal for each laboratory test. Another way of evaluating laboratory parameters is a count of how many patients with normal values at screening had final values that were markedly abnormal (Table 43). None of these abnormalities are likely to be drug related.

**Table 43 Patients Markedly Abnormal Posttreatment Laboratory Values
(and with Normal Screening Values CBI-961/962, -1252, and -963)**

Parameter	#Patients	Patient ID's
Low WBC	2	Saltzman, Bricker
High WBC	2	Bricker, Kerr
Low Lymphocytes	2	Kovalic, Kern
High Lymphocytes	1	Bricker
Eosinophilia	2	Birnbaum, Rauck
High Neutrophils	2	Katz/2, Rauck
Low Hematocrit	3	Bricker, Lipton, Lipton
High BUN & Creatinine	1	Birnbaum
High Glucose	1	Birnbaum
Low Potassium	1	Tkaczuk

9.53 Vital Signs and ECG

The mean changes in vital signs for patients who entered the open-label or double-blind treatment periods for the combined studies are tabulated in Table 44. Mean heart and respiratory rates were unchanged. There were small mean reductions of 3.2 mm in systolic and 2.1 mm in diastolic blood pressures, not considered of clinical significance. EKG's were recorded at screening and at the end of treatment in five of the Phase I studies (315-10, 315-11, 315-12, XIR0196, and XIR0296). There were no clinically significant changes from screening reported in any of these studies.

**Table 44: Vital Signs
Combined Clinical Studies (CBI-961/962, -1252, and -963)**

	Parameter	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)	Respiration Rate (/min)
Screening Visit	N	366	366	362	355
	Mean	129.5	78.7	77.0	17.3
	S.E.	0.99	0.55	0.61	0.17
	Median	130.0	80.0	78.0	16.0
Final Visit	N	333	333	332	324
	Mean	126.3	76.7	76.8	17.2
	S.E.	0.92	0.57	0.66	0.16
	Median	124.0	78.0	76.0	16.0
Change	N	333	333	331	322
	Screening	129.5	78.8	76.9	17.3
	Mean	-3.2	-2.1	-0.0	-0.1
	S.E.	0.84	0.53	0.58	0.17
Outside Reference Criteria*	Median	-2.0	-2.0	0.0	0.0
	n Above	33	27	31	5
	n Below	60	52	28	2

Studies pooled: CBI-961/962, -1252, and -963.

* Reference criteria are as follows: (Final Visit vs. Screening Visit) increase/decrease >15 mmHg in systolic blood pressure; increase/decrease >10 mmHg in diastolic blood pressure; increase/decrease >15 bpm in heart rate; increase/decrease >8/min in respiration rate

9.54 Drug-Demographic Interactions

Effects of age, gender and race on adverse events are discussed in sections 9.5131, 9.5132 and 9.5133. The only firm conclusion was that women were more likely to report adverse events than men.

9.55 Drug-Disease Interactions

9.551 Renal

Only 3 of the 126 patients who received oxycodone SR and 3 of the 125 patients who received oxycodone IR in the controlled clinical studies were considered renal-impaired (creatinine clearance < 60 ml/min.). This sample was too small for comparisons to be made. 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 are higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

9.552 Biliary and Hepatic

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level. Although amylase levels were not measured in the clinical trials with patients, there were no adverse events or physical findings reported suggestive of treatment-emergent pancreatic or biliary disease. In studies conducted previously in patients with hepatic impairment, the plasma concentrations of oxycodone are greater than those in patients with normal liver function. The initiation of therapy at $\frac{1}{3}$ to $\frac{1}{2}$ of the usual doses and careful titration is warranted.

9.553 Cancer

Section 9.5134 examined effects of cancer versus nonmalignant etiologies of pain on adverse events, but identified no clear differences between formulations.

9.554 Head Trauma

There were no patients with head injury and resultant exaggerated respiratory depressant effects. in these clinical trials. However, it should be noted that 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. Oxycodone produces effects on pupillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

9.555 Respiratory Depression

Respiratory depression is the chief hazard from all opioid agonist preparations. Respiratory depression occurs most frequently in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration. Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose. Nine (6.8%) of the 132 patients who received oxycodone during the treatment period of the controlled studies reported events involving the respiratory system, with five patients (4.0%; 5/125) reporting events for each formulation. Dyspnea was reported by three patients (2.4%; 3/126) receiving SR, but was not reported by any of the patients while receiving IR. No other event of the respiratory system was reported by more than one patient while receiving either treatment. There were 29 of 233 patients (12.4%) receiving SR in CBI-963 study reporting respiratory events; most frequent was rhinitis (4.7%; 11/233). Five patients (2.1%) reported episodes of dyspnea. One patient discontinued for severe dyspnea secondary to heart failure; the relationship to study drug was considered unlikely. For two of the patients (0.9%), the episodes of dyspnea were considered possibly related to oxycodone SR. There were no reports of respiratory depression while taking oxycodone SR in this clinical program, even at high doses (360 mg bid). This is probably reflective of the trial conditions (the drug was titrated to effect in patients who were opioid-tolerant). One patient had a mild episode of hypoventilation on Day 6 of the IR stabilization period. Two patients had a decrease of > 8 respirations per minute from screening values; however, the respiration rate remained within normal limits for both patients. A cancer patient (Tkaczuk) was hospitalized for apnea and died from respiratory failure during the IR treatment period. These events were not considered related to the study drug.

9.56 Drug-Drug Interactions

No specific studies examined the interaction of other agents and oxycodone SR. Among the patients who took drugs that effect the cardiovascular system in the controlled clinical studies, 12% (16/132) took calcium channel blockers, 9% (12/132) took beta blockers, and 9% (12/132) took converting enzyme blockers without any clinically significant effects. Among the patients who took anti-depressants in the controlled clinical studies; 20% of the patients (27/132) took bicyclic derivatives and 23% (30/132) took tricyclic derivatives concomitantly with oxycodone SR without any clinically significant effects. Opioid analgesics, including oxycodone SR, may enhance the neuromuscular-blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. Oxycodone is metabolized in part to oxymorphone via CYP2D6. While this pathway may be blocked by a variety of drugs, (e.g., certain cardiovascular drugs and anti-depressants), such blockade has not yet been shown to be of clinical significance with this agent. Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system (CNS) depression, leading to respiratory depression, hypotension, and profound sedation or coma. Oxycodone, like all opioid analgesics, should be started at one third to one half of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers or alcohol. No patient took monoamine oxidase inhibitors concomitantly with oxycodone SR during the double-blind period of these trials. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate. Among the patients in the controlled clinical studies who took drugs that could have CNS depressant effects, 24% (32/132) took benzodiazepine derivatives, 12% (16/132) took carbamic acid esters, and 11% (14/132) took phenothiazine with piperazine without any clinically significant effects. Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients. In this clinical development program, no patient took mixed agonist/antagonist opioid analgesics concomitantly with oxycodone SR during the double-blind period. The intake of food has been shown to significantly (but moderately) increase the rate, but not the extent, of oxycodone absorption from the sustained-release tablets. The clinical relevance of the increased rate of absorption of this magnitude is questionable for a drug intended for chronic usage at individualized dosages. There is no evidence from the clinical trials with patients that efficacy or safety were affected by concomitant administration of oxycodone SR with food.

9.6 Abuse/Dependence Liability

9.61 Abuse Potential

Oxycodone SR is a schedule II narcotic under the United States Controlled Substance Act (21 U.S.C. 801-886). Oxycodone SR can produce drug dependence of morphine-type, and therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of this drug, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, this drug is subject to the Federal Controlled Substance Act. Oxycodone SR is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia. Since oxycodone SR is an opioid agonist drug, it may be subject to misuse, abuse, and addiction. Addiction to opioids prescribed for pain management is rare, but request for opioids from patients addicted to opioids are common and physicians should take appropriate care in prescribing this controlled substance.

9.62 Dependence

Opioid analgesics may cause psychological and physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug. These symptoms may be precipitated through the administration of drugs with antagonistic activity, e.g., naloxone or mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol or nalbuphine) in dependent patients. Physical dependence usually does not occur, to a clinically significant degree, until several weeks of continued opioid usage. Physical dependence, per se, is not ordinarily a concern when one is dealing with a patient in pain, and fear of tolerance should not deter using adequate doses to adequately relieve pain.

9.63 Tolerance

Tolerance, in which increasingly larger doses are required to produce the same degree of analgesia, is initially manifested by a shortened duration of a analgesic effect and, subsequently, by decreases in the intensity of analgesia. In chronic pain patients, and in opioid-tolerant cancer patients, the administration of oxycodone SR should be guided by the degree of tolerance manifested. It should be noted that progression of disease leading to increased pain severity and increased analgesic need can be misdiagnosed as tolerance.

9.64 Withdrawal

If oxycodone SR is abruptly discontinued, an abstinence syndrome may occur. This is usually mild and is characterized by rhinitis, myalgia, abdominal cramping and occasional diarrhea. Most observable symptoms disappear in 5 to 14 days without treatment; however, there may be a phase of secondary or chronic abstinence which may last for 2 to 6 months characterized by insomnia, irritability and muscular aches. If treatment of physical dependence of patients taking oxycodone SR is necessary, the patient may be detoxified by gradual reduction of the dose. Gastrointestinal disturbances or dehydration should be treated with supportive care. Withdrawal syndrome was reported for one patient (0.4%) who was receiving SR in the 30-day uncontrolled study. The patient had three episodes of this event. The first began on Day 1 of the IR stabilization period, when the patient began having intermittent chills and sweats considered consistent with medication withdrawal. The episode lasted for 3 days. The patient had a recurrence of intermittent chills and sweats, beginning on Day 5 of the treatment period and lasting for two days. The patient had a another episode of intermittent chills and sweats on Day 13. The episode was also mild and intermittent over two days.

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9.7 Human Reproduction Data

9.71 Pregnancy and Labor

Oxycodone is classified as Category C, i.e., of unknown teratogenicity. No animal reproductive studies have been carried out with Roxicodone SR. It may be administered to pregnant woman only if clearly needed. Neonates may experience withdrawal effects or respiratory depression. The latter can be treated with naloxone. It is not recommended for use in women immediately prior to labor since opioids such as oxycodone can result in prolongation of labor by reducing the strength, duration and frequency of uterine contractions and can cause respiratory depression in neonates.

9.72 Nursing

Nursing should ordinarily be avoided in patients receiving Roxicodone SR since low concentrations have been detected in breast milk. Withdrawal symptoms can occur in the infant when nursing is stopped.

9.73 Pediatric Exposure

Labeling for Roxicodone (immediate-release tablets, Oral Solution and Intensol concentrated oral solution bottles with calibrated droppers) simply states that "This drug should not be administered to children". Roxicodone SR has not been studied in patients under 18 years old. Labeling for OxyContin controlled-release oxycodone hydrochloride and proposed labeling for Roxicodone SR state that oxycodone has been used extensively in children in other dosage forms and that no specific increased risk is expected in children old enough to safely take oral tablets if dosage is adjusted for weight. The major concern is that tablets cannot be crushed or divided for administration; otherwise the sustained-release properties can be lost, and overdosage can occur from rapid release of drug.

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ON ORIGINAL**

9.8 Conclusions Regarding Safety

The overall incidence of adverse events was not significantly different between the two formulations. When adverse events that were considered not or unlikely to be drug-related were excluded, there were 28% of patients on SR reporting such events, compared with 26% of patients on IR. The most frequent events were nausea, vomiting, headache, diarrhea, constipation, dizziness, somnolence, pruritis and dyspepsia. Dyspnea was reported by 8 patients (6%) on SR. There was one patient on SR who experienced withdrawal symptoms on discontinuation of drug. Serious events, including deaths, were generally thought to be unrelated to oxycodone therapy in these trials. Women were more likely than men to complain of adverse events on either formulation. Age, race, disease and dose effects on adverse event frequency were not established; however, results of population pharmacokinetics did suggest age effects on plasma levels. Laboratory results were unremarkable. Vital sign data revealed a small hypotensive effect of oxycodone treatment, but no differences between formulations are apparent. No patients became pregnant during the trials, none overdosed, and all patients were over 18.

10.0 Labeling Review

The draft labeling submitted with the NDA was reviewed. Two adjustments of clinical nature are addressed below.

10.1 Clinical Studies Section

The following sentence should be inserted after the second sentence ending with "...were dosed every 12 hours.": "Escape medication for breakthrough pain was provided as immediate release oxycodone 5 mg tablets." This change emphasizes that supplementation with immediate release medication may be needed in ordinary use.

10.2 Adverse Reactions Section

The beginning of the first sentence of the third paragraph should be altered from "The less severe adverse events seen on initiation" to "Other drug-related events seen on initiation". This change removes confusion between the terms "severe" and "serious" and clarifies the drug-related character of the AE's listed.

11.0 Conclusions

Roxicodone SR tablets (10 and 30 mg) when given every twelve hours and supplemented with escape medication (oxycodone IR) as needed was essentially equivalent in efficacy to immediate release oxycodone (5 mg) tablets given every six hours and supplemented in the same way. The sustained release formulation was similar to the immediate release formulation with respect to safety. Neither objective advantages or disadvantages of one formulation over the other could be clearly defined in terms of safety or efficacy.

12.0 Recommendations

12.1 Approvability

Roxicodone SR is approvable for the treatment of moderate to severe chronic pain in patients who need opioid analgesia.

12.2 Phase IV

Studies should be carried out in populations of patients younger than 18 to define appropriate pediatric usage.

12.3 Comparative Claims

Aside from the implied advantage of improved convenience for the sustained release formulation, no other advantages relative to immediate release oxycodone have been demonstrated, and no claims of enhanced efficacy or safety should be made.

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The safety update was reviewed. However, no separate review was done.
See information in the clinical review.