

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20-932**

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**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**Clinical Pharmacology and Biopharmaceutics Review  
Pharmacometrics Consult**

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<b>NDA:</b>	20-932
<b>Oxycodone HCl 10 and 30 mg Extended-Release Tablets (Roxicodone SR®)</b>	
<b>Original Submission Date:</b>	22 December 1997
<b>Sponsor:</b>	Roxane Labs
<b>Type of Study:</b>	Population PK/PD study
<b>Primary Reviewer:</b>	Suresh Doddapaneni
<b>Medical Division:</b>	Anesthetics, Critical Care, and Drug Addiction Drug Products (HFD-170)
<b>Reviewer:</b>	Michael J. Fossler

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**Study**

The present study titled *Population Pharmacokinetic-Pharmacodynamic Analysis of Oxycodone SR: Analysis of Data from Controlled Clinical Efficacy (Protocols CBI-961/962 and CBI-1252) and Open-Label (Protocol CBI-963) Studies* was performed for Roxane Laboratories by

The present review is written at the request of the primary reviewer, Dr. Suresh Doddapaneni.

**Study Design**

The data used for this analysis came from three clinical efficacy and safety studies submitted to the NDA. In general, each of the studies consisted of a 2-7 day run-in period where each patient was stabilized on an oxycodone dose that satisfactorily controlled the patient's pain. The patient was then randomized to either IR oxycodone (given qid using the total daily dose determined in the run-in period) for seven days or SR oxycodone given twice daily for seven days. Patients were then brought into the clinic for evaluation and blood sampling (see below). For the uncontrolled study (Study 963) patients were put on SR oxycodone immediately after the run-in. Subjects were allowed "rescue" medication when they experienced break-through pain. Rescue medication consisted of 5 mg IR oxycodone taken as needed. The time of all doses of medication were recorded by the patient in a medication diary.

In all three studies blood sampling was performed according to a random-block design. The clinic visits were set up so that 1/3 of subjects would be sampled between 0 and 4 hours post-dose, 1/3 between 4-8 hours, and 1/3 between 8-12 hours. At the time of the blood draw, each patient completed a visual analog scale (VAS) of pain intensity. This consisted of a 100 mm line that the subject marked, indicating pain intensity at the time, with 100 mm being the worst pain imaginable, and 0 being complete relief.

Plasma samples from all studies were analyzed by a validated method. The primary reviewer has indicated that the method is adequate, so little more will be said about the assay.

### **Data Assembly**

Both PK/PD data and covariate information (such as weight, age, etc.) were placed in a format suitable for NONMEM analysis. Missing individual covariate data were replaced with the mean covariate value for the complete data set. Plasma observations which were below the limit of quantitation for the assay were set equal to one half the quantitation limit.

### **PK Analysis**

### Data Summary

A total of 261 subjects (94 males, 167 females) were usable in the analysis. These patients yielded a total of 556 PK and 546 PD samples.

Demographics for the population are summarized in Table 1. A good distribution of most of the parameters was obtained in the study. Exceptions include race (only 14 black and 3 hispanic subjects were enrolled) and LFT status (only 6 patients had liver enzymes over 3 x normal).

The analyst examined the distribution of PK/PD samples taken throughout the study. These data are summarized in Figure 2. As shown in the figure, there were few samples (about 12%) drawn after 8 hours post-dose. The reason for this was not explained by the firm. This is important since a deficit of samples in this part of the dosing interval may affect the estimate of apparent clearance, although to what extent it might have done so is impossible to determine. In the reviewer's opinion, this does not invalidate the study, but should be borne in mind when interpreting the results of the analysis.

**Table 1: Demographics of patients used in the analysis. Values in the table are median (range).**

Demographic	Males (n=94)	Females (n=167)	All Patients (n=261)
Age (yrs)	49 (24-86)	53 (23-94)	52 (23-94)
Weight (kg)	81 (47-132)	69 (40-159)	75 (40-159)
Creatinine Clearance <sup>†</sup> (L/hr)	7.0 (2.1-13.6)	5.0 (0.9-12.2)	5.6 (0.9-13.6)
Race			
Black	5	9	14
White	89	155	244
Hispanic	0	3	3
LFT Status			
Normal	92	163	255
Elevated	2	4	6

<sup>†</sup>by the method of

### Base Model

The mean parameter estimates for the base model (excluding any covariates) along with estimates of inter- and intra-individual (residual) variability are shown in Table 2. The fixed effect parameter estimates for the pharmacokinetic model are reasonably precise, except for V/F. In contrast, estimates for inter-individual effects (eta's) are very imprecise. Notably, the inter-individual error for V/F was not estimable.

Figure 2: Distribution of sampling times for the data used in the analysis.

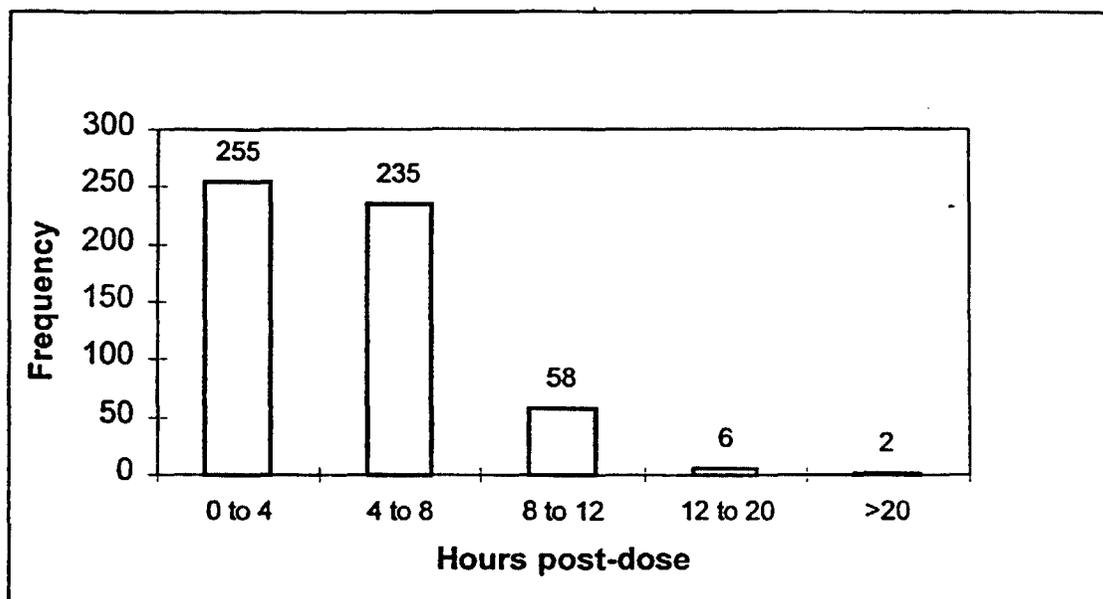


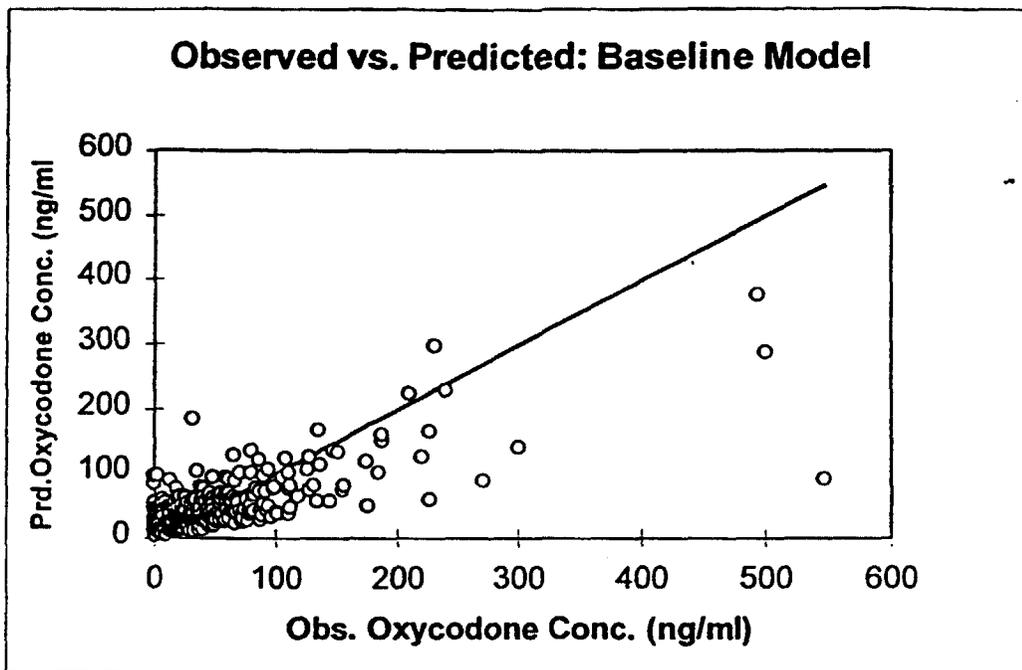
Table 2: Mean parameter estimates for the baseline pharmacokinetic model. Objective function value for this model was 3076.73.

Parameter	Mean Estimate (%SEM)	Random Interindividual Effect %CV (%SEM)
$k_{e,IR}$	5.82 hr <sup>-1</sup> (16.9)	2930 (77.6)
$k_{e,SR}$	0.262 hr <sup>-1</sup> (32.8)	46.3 (481)
CL/F	64.9 L/hr (7.2)	28.7 (70.8)
V/F	608 L (225)	NE
$F_{rel(SR)}$	1.03 (8.7)	47.8 (37.7)
<b>Residual Error</b>		
Additive	0.0625	fixed
Proportional	32.2% CV	14.8

N.E. - not estimable; individual values are equal to the population value

Figure 3 shows the plot of observed vs. predicted concentrations. Oxycodone concentrations higher than about 300 ng/ml are under-predicted by the model. This is not surprising since 95% of the measured concentrations were less than 150 ng/ml, with the majority falling between 0 and 50 ng/ml. Residual plots (not shown) are essentially featureless, indicating minimal bias.

**Figure 3: Observed vs. predicted concentrations for the baseline model.**



#### Final PK Model

The parameters for the final model are shown in Table 3. The estimates of inter-individual random effects are unchanged from the baseline model, indicating that the incorporation of covariate data did little to help reduce inter-individual variability. The precision of these estimates is still poor, although slightly improved over the baseline model. As in the baseline model, the interindividual random effects for V/F could not be estimated. The precision of the fixed effect parameter estimates is reasonably good.

A protocol effect was noted for  $k_{a,IR}$ , indicating that the absorption of the rescue medication in Protocol 963 differs from that in Protocols 961/2 and 1252. It is unclear why this difference exists, and equally unclear whether or not the fact that 963 is the uncontrolled study has anything to do with the difference seen. The precision of the parameter estimates is such that it may simply be due to chance. The author of the study hypothesizes that the difference may be due to sampling differences in this protocol. This is not an unreasonable conjecture.

The only other covariate which was found to affect the pharmacokinetics of oxycodone is age. As shown in Table 4 and Figure 4, age has a significant effect on clearance. While clearly statistically significant, it is unlikely to be clinically significant, since opiates are generally individually titrated based on the patient's pain status.

Goodness-of-fit for the final model is shown in Figure 5. The figure is essentially unchanged from the baseline model, with levels > 200 ng/ml under-predicted by the model. Figure 6 depicts the ability of the final model to predict the test data set. As in the previous plots, high levels are under-predicted by the model. Although not shown, plots of the individual Bayesian predictions and weighted residuals show no pattern, indicating that the model adequately describes the parameter-covariate relationship in the test data set.

Figure 7 is a comparison of the plasma levels resulting from typical dosing regimens of the IR and the SR product. The SR product gives comparable steady-state oxycodone levels as the IR dosage form with half the dosing frequency.

PK/PD Model

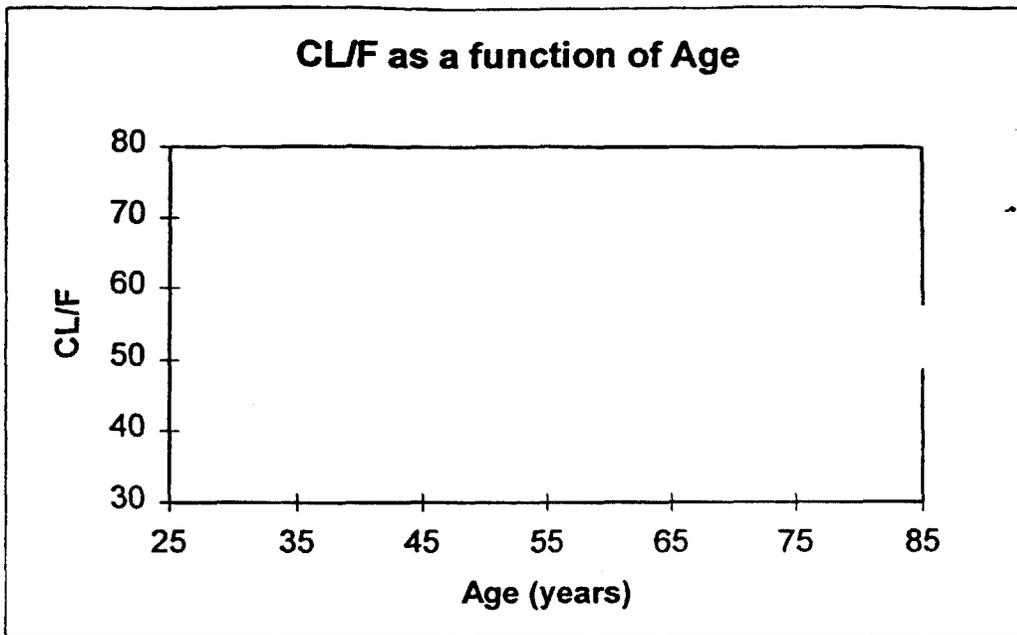
The results of the PK/PD analysis are shown in Table 4. The analysis was not successful, in that satisfactory runs could not be obtained for the two linear models. The intercept-only model did run, but this model provides no information on the relationship between plasma oxycodone levels and pain response.

The failure of the analysis to detect any PK/PD relationship might have been anticipated, given the design of the studies. All of the studies included a run-in period where each patient was titrated to a satisfactory level of pain relief. For the study, each patient was then randomized to receive either IR or SR oxycodone and then crossed over to the opposite dosage form, using the same total daily dose determined in the run-in period. If data had been obtained during the run-in period, the relationship between pain relief and plasma oxycodone might have been better elucidated.

**Table 4: Mean parameter estimates for the final pharmacokinetic model. Objective function value for this model was 3054.288**

Parameter	Final Model	Mean Parameter (%SEM)	Random Effects %CV (%SEM)	interindividual
$k_a$ IR	$\theta_1 + \theta_6 \cdot PR$	$\theta_1 = 7.07$ hr <sup>-1</sup> (7.4) $\theta_6 = -2.65$ (41.5)	2886 (63.6)	
$k_a$ SR	$\theta_2$	$\theta_2 = 0.242$ hr <sup>-1</sup> (26.9)	80.3 (178)	
CL/F	$\theta_3 \cdot (AGE/54)^{\theta_7}$	$\theta_3 = 62.8$ L/hr (6.0) $\theta_7 = -0.381$ (58.8)	24.6 (93.7)	
V/F	$\theta_4$	$\theta_4 = 594$ L (21.2)	NE	
$F_{rel(SR)}$	$\theta_5 \cdot F_{rel(SR)}$	$\theta_5 = 1.01$ (7.4)	48.6 (33.8)	
<b>Residual Error</b>	<b>Estimate</b>	<b>%SEM</b>		
Additive	0.0625	fixed		
Proportional	32.5% CV	15.1		

**Figure 4: Effect of age on plasma oxycodone clearance.**



**Figure 5: Observed vs. predicted for the final model.**

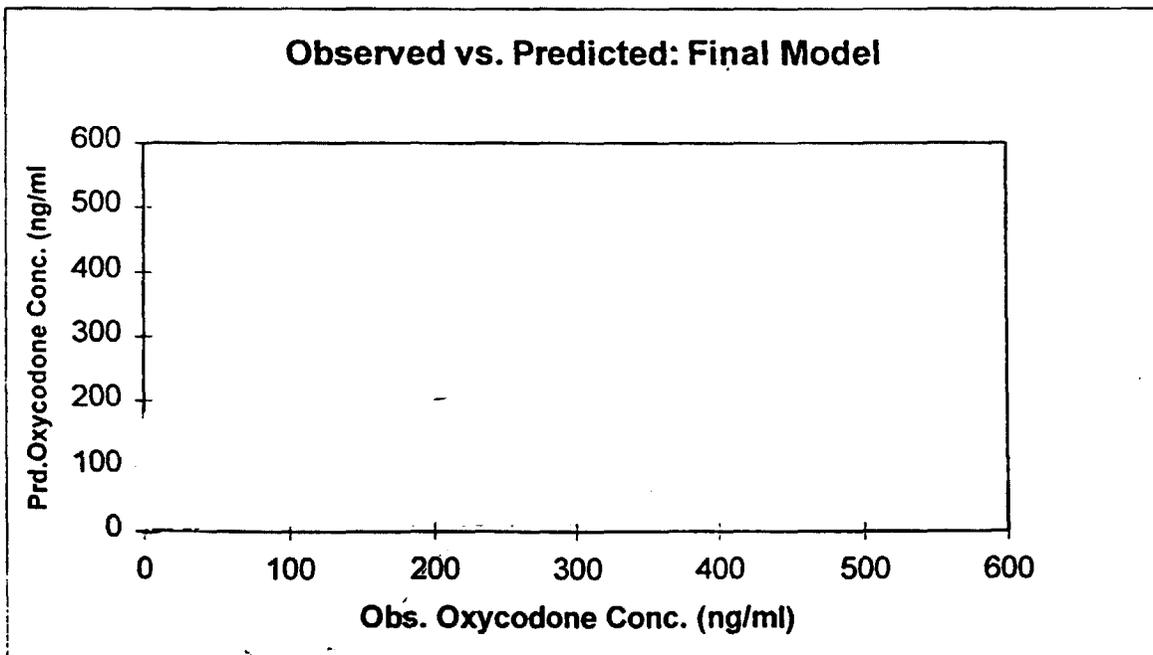


Figure 6: Observed vs. predicted for the final model using the test data set.

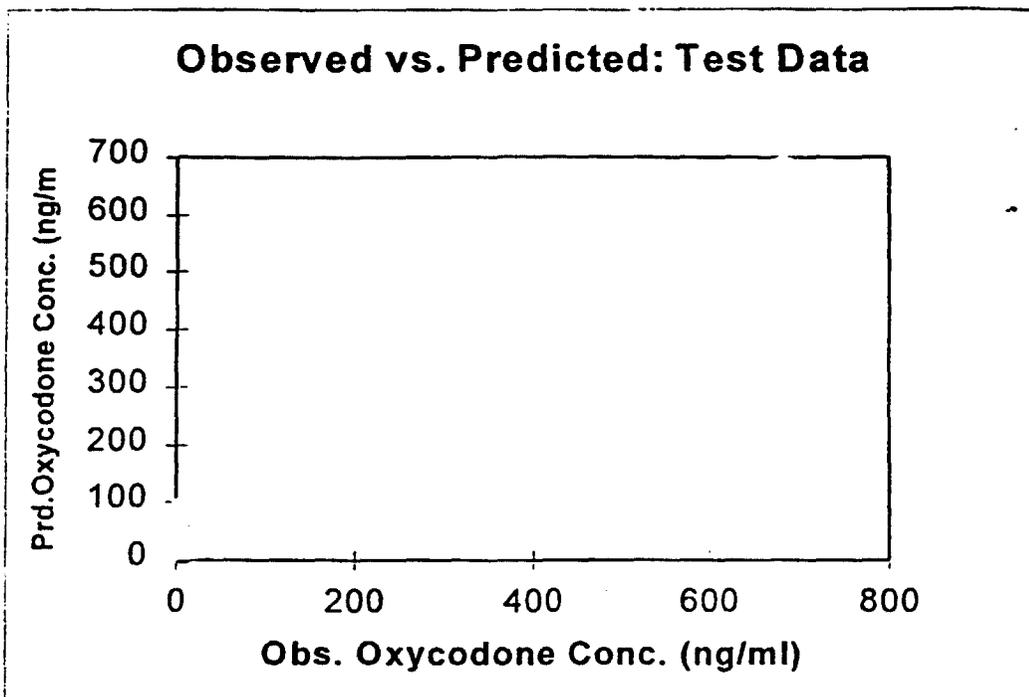
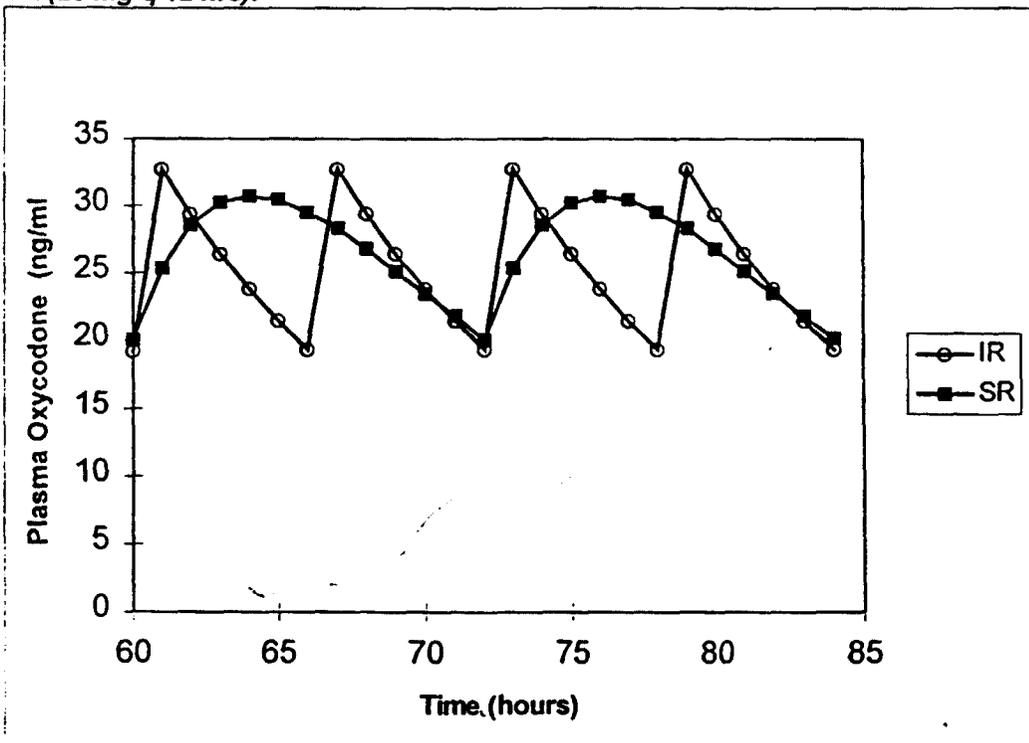


Figure 7: Predicted mean steady state plasma oxycodone levels after IR (10 mg q 6 hrs) or SR (20 mg q 12 hrs).



## Study Author's Conclusions and Reviewer Comments

The sponsor concluded the following from the study. Reviewer comments (if warranted) are below each of the sponsor's comments in italics.

- 1) The population pharmacokinetic and pharmacokinetic-pharmacodynamic models and simulation results help to explain and lend support to the efficacy analysis results.

*Reviewer Comment: This statement is a bit too conclusive. Nowhere in the report does the study author attempt to relate the results obtained in this analysis to the clinical efficacy results. The PK results support the finding of similar clinical efficacy in that similar steady-state plasma concentrations are obtained with either dosage form (see Figure 7). However, since the PK/PD modeling portion of the analysis was not successful, no conclusions may be drawn from those results.*

- 2) In these studies, there is no relationship between plasma oxycodone concentration and VAS measurement.

*Reviewer Comment: Again this is a bit too conclusive. The reviewer would argue that the proper conclusion is that no PK/PD relationship was found in the present analysis, not that it does not exist. The distinction is important, since, as written, the statement implies that the analysis was completely successful and that the conclusive result is that there is no PK/PD relationship. In actuality, the data were not sufficient to permit an analysis, and the study author (in the body of the report) acknowledges this.*

- 3) The population pharmacokinetic modeling results describe oxycodone pharmacokinetics in patients and support the results of Phase I pharmacokinetics studies.
- 4) The steady-state oxycodone plasma levels after chronic oral administration of IR and SR oxycodone are similar.
- 5) There is a statistically significant effect of age on oxycodone clearance which is not predicted by creatinine clearance. The clinical relevance of this finding is limited due to the fact that dosing of oxycodone is titrated to response.
- 6) Protocol-dependent differences in the absorption rate of IR oxycodone are minimal and are probably due to differences in data sampling.
- 7) No gender differences in oxycodone PK were identified.
- 8) No racial differences in the PK of oxycodone could be identified; however, the number of non-Caucasians in these studies were insufficient to determine racial effects if they existed.
- 9) No effect of poor liver function (as defined by elevated liver enzymes) on oxycodone PK was identified; however, the number of such individuals with decreased hepatic function in these studies was insufficient.

*Reviewer Comment: The reviewer agrees with the statement, but the application of elevated liver enzymes as a surrogate for liver function has been applied somewhat naively by the study author. There is no established relationship between the level of liver enzymes and liver function. Elevated liver enzymes indicate an insult to the liver has occurred, but do not necessarily indicate loss of function, due to the liver's enormous excess metabolic capacity.*

**Recommendations**

- 1) Overall, the population analysis was conducted appropriately.
- 2) The findings of the pharmacokinetics portion of the analysis ( age-dependent effect on oxycodone clearance, equivalent bioavailability of IR and SR dosage forms, and prediction of steady state levels after IR or SR dosing) are reliable enough to use in labeling as needed.
- 3) Due to design problems, the PK/PD portion of the analysis did not contribute much useful information.

**/S/**

7/13/98

Michael J. Fossler, Pharm.D., Ph.D.

Pharmacometrics Node  
Division of Pharmaceutical Evaluation II  
Office of Clinical Pharmacology and Biopharmaceutics  
Version: Final

CC: HFD-850(Lesko, Ray Miller), HFD-870(M.Chen, Uppoor, Doddapaneni, Fossler,)

SEP 16 1998

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW**

<b>NDA: 20-932</b>	<b>CODE: 3S</b>
<b>NAME: Roxycodone™ SR Tablets 10 and 30 mg</b>	
<b>SPONSOR: Roxane Laboratories, Inc., P.O.Box 16532, Columbus, OH</b>	
<b>SUBMISSION TYPE: Original NDA</b>	<b>SUBMISSION DATE: December 29, 1997</b>
<b>PRIMARY REVIEWER: Suresh Doddapaneni, Ph.D.</b>	
<b>PHARMACOMETRICS CONSULT: Michael J. Fossler, Pharm.D., Ph.D.</b>	

**SYNOPSIS**

Currently, Roxane Laboratories markets Roxycodone™ Tablets USP (5 mg), Roxycodone™ oral solution USP (5mg/5mL), and Intenso™ (20 mg/mL) for the relief of moderate to moderately severe pain. Current dosing guidelines for these products state that the usual adult dose is 10 to 30 mg taken every 4 hours or as directed by the physician. To improve patient compliance, the sponsor developed oxycodone sustained release tablets (10 and 30 mg strengths) to be administered every 12 hours. The single dose and multiple dose performance of the product has been investigated. Food effect has been studied on the to-be-marketed formulation. Attempt to develop pharmacokinetic and pharmacodynamic relationship through population analysis using data collected in patients was not successful. Population pharmacokinetic analysis supported the results of Phase I pharmacokinetic studies. The overall conclusion from the pharmacokinetic studies and population pharmacokinetic analysis is that the sustained release products exhibit desirable properties for once every 12 hours dosing relative to the currently marketed oxycodone oral solution. The sponsor has also submitted data from (two controlled and one uncontrolled) clinical trials on the safety and effectiveness of this product.

**RECOMMENDATION**

From the viewpoint of the Office of Clinical Pharmacology and Biopharmaceutics NDA 20-932 can be approved. However, the dissolution method and specifications proposed by the sponsor can be approved only on an interim basis and sponsor should give assurance to the Agency that dissolution method and specifications more reflective of the *in vivo* delivery of the product would be developed and submitted to the Agency in a timely fashion.

1S/

9/16/98

Suresh Doddapaneni, Ph.D.  
Clinical Pharmacologist  
Division of Pharmaceutical Evaluation II

RD initialed by Ramana Uppoor, Ph.D.

FT initialed by Ramana Uppoor, Ph.D.

CC:

NDA 20-932, HFD-170 (Division files, McNeal, McCormick, Rappaport, Scheinbaum, Geyer, Maturu, Ma, Hayes), HFD-850 (Lesko), HFD-870 (Doddapaneni, Mei-Ling Chen, Uppoor), HFD-340 (Viswanathan), Barbara Murphy (CDR).

9/16/98

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## 1.0. INTRODUCTION

--Oxycodone hydrochloride is a semisynthetic opioid analgesic agent that has been in use since 1917. Currently, Roxane laboratories markets Roxicodone™ Tablets USP (5 mg), Roxicodone™ oral solution USP (5mg/5mL), and Intenso™ (20 mg/mL) for the relief of moderate to moderately severe pain. Current dosing guidelines for these products state that the usual adult dose is 10 to 30 mg taken every 4 hours or as directed by the physician. To improve patient compliance, the sponsor is undertaking the development of sustained release oxycodone tablets (10 and 30 mg strengths) to be administered every 12 hours. It should be pointed out that a sustained release oxycodone product (Oxycontin® - NDA 20-553) was already approved for marketing by the Agency in December of 1995. Currently, Oxycontin® is marketed in strengths of 10, 20, 40, and 80 mg to be used for the management of moderate to severe pain where use of an opioid for more than a few days is appropriate.

Oxycodone has been in clinical use since 1917 and as such the sponsor conducted pharmacokinetic studies characterizing the dosage form only and did not conduct any studies characterizing the general pharmacokinetic properties (including metabolism) of the drug substance.

This submission consists of seven (7) traditional pharmacokinetic studies (pharmacodynamic measurements were not made in any of the studies) conducted in about 193 male and female, healthy volunteers. All seven studies included the 10-mg tablet and two of the studies included the 30-mg tablet. In addition, NONMEM analysis to explore PK/PD relationship was conducted on 556 plasma samples and corresponding pain intensity scores obtained from 261 patients from clinical trials CBI-961/962 and -1252. The to-be-marketed formulation was used in the pivotal clinical trials. Currently, this product is neither approved nor applications are pending in any other country.

## 2.0. FORMULATION

Two different formulations-formulation A and formulation B were investigated in this NDA. Based on the *in vivo* sustained release performance (studies 315-03 and 315-04) of formulation B relative to the immediate release solution, formulation B was retained for clinical testing.

The proportions of some of the critical inactive ingredients for the 30 mg strength relative to the 10 mg strength are different (Table 1). Lactose (diluent) comprised about 25.8% at 10 mg strength while at the 30 mg strength it comprised 12.2% of the total tablet weight. Similarly, sodium polystyrene sulfonate (probably a disintegrant) comprised 7% at the 10 mg strength while at the 30 mg strength, it comprised 10% of the total tablet weight. However, proportion of the major critical component hydroxy propyl methylcellulose (retardant) has not been changed and bioequivalence between the 10 and 30 mg strengths (at equivalent doses of 30 mg) was demonstrated in study 315-08.

**Table 1. List of ingredients and their amounts (mg) in oxycodone 10 and 30 mg SR tablets. Values in parenthesis indicate the relative occurrence (%) of that particular ingredient with respect to the total tablet weight.**

10 mg Tablet	30 mg Tablet
Oxycodone HCL	Oxycodone HCL
Lactose	Lactose
Sodium Polystyrene Sulfonate	Sodium Polystyrene Sulfonate
Hydroxypropyl Methylcellulose	Hydroxypropyl Methylcellulose
Stearic Acid	Stearic Acid
Total Tablet Weight	D&C Yellow No.10
	D&C Yellow
	Total Tablet Weight

### 3.0. METABOLISM

Roxane Laboratories Inc., did not conduct any specific oxycodone metabolism studies. However, from published literature it is known that oxycodone is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The formation of oxymorphone, but not noroxycodone, is mediated by cytochrome P450 2D6 (CYP2D6). The major circulating metabolite is noroxycodone with a systemic exposure of 0.6-0.8 relative to that of oxycodone. Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The analgesic activity profile of other metabolites is not known. *In vitro* plasma protein binding studies showed that oxycodone is 45% bound, predominantly to albumin.

### 4.0. BIOAVAILABILITY/BIOEQUIVALENCE STUDIES

#### 4.1. Bioavailability of Single Doses of Two Formulations of SR Oxycodone Relative to oxycodone Solution

This was a **single-dose**, randomized, three treatment, three-way cross-over study in thirty (30) healthy volunteers that compared the relative bioavailability of two formulations of sustained release oxycodone HCL under development to the marketed IntensoI™ solution (protocol 315-03). Two tablets each of formulation A and formulation B (corresponding to a total dose of 20 mg each) were compared with a 20 mg dose equivalent of IntensoI™ solution.

Figure 1 and Table 1 show mean oxycodone plasma concentration-time profiles and pharmacokinetic parameters respectively. The two sustained release formulations seemed to exhibit similar profiles with formulation B displaying slightly lower  $C_{max}$ . ANOVA analysis indicated statistically significant differences between formulation A and IntensoI solution as well

as formulation B and Intensol solution with respect to  $C_{max}$ ,  $t_{max}$ ,  $AUC_{\infty}$ ,  $K_{el}$ , and  $t_{1/2}$ . The 90% confidence intervals were within the bioequivalence criteria with respect to the  $AUC_{\infty}$  when the two formulations were separately compared to the Intensol™ solution. Between the two sustained release formulations, there were statistically significant differences with respect to  $t_{max}$  and  $t_{1/2}$ . However, the confidence intervals for the log transformed  $C_{max}$  and  $AUC_{\infty}$  were within the bioequivalence limits when formulation A and formulation B were compared to each other. The sponsor concluded that formulation B might provide better sustained-release properties in view of the lesser  $C_{max}$  but with comparable extent of absorption when compared to formulation A.

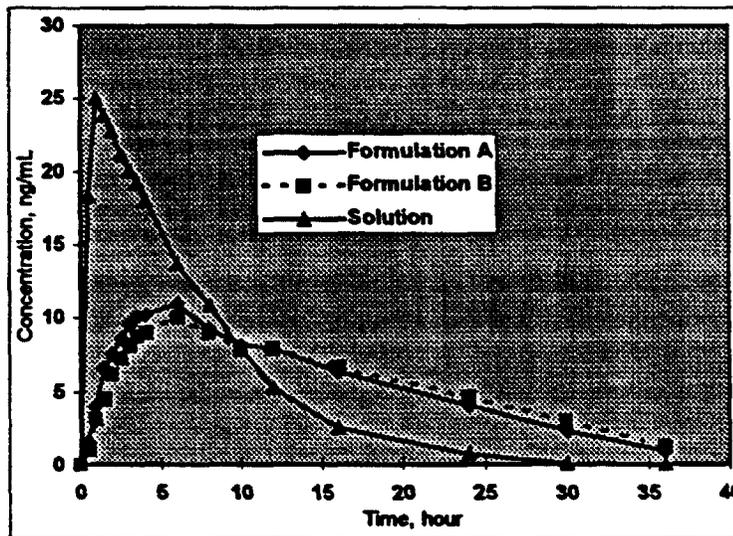


Figure 1. Mean plasma concentration Vs time profiles of oxycodone when administered 20 mg equivalent doses of oxycodone solution and oxycodone 10 mg SR tablets (formulations A and B).

**Table 1. Oxycodone pharmacokinetic parameters when administered as oxycodone SR tablets (formulations A and B) and Intenso<sup>TM</sup> solution in equivalent doses of 20 mg (mean (%CV)).**

Pharmacokinetic Parameter	Formulation A	Formulation B	Solution
$C_{max}$ , ng/mL	11.65 (25)	10.64 (21)	27.5 (27)
$t_{max}$ , hour	5.2 (26)	6.4 (40)	1.4 (74)
AUC <sub>0-∞</sub> , ng hour/mL	219.0 (34)	228.7 (32)	207.0 (27)
$t_{1/2}$ , hour	8.8 (33)	10.1 (32)	4.1 (16)

#### 4.2. Bioequivalence At Steady State of Two Formulations of Oxycodone SR Tablets

This was a multiple dose, randomized, three-period, three-way cross-over study in thirty (30) adult male subjects (protocol 315-04). The objective of this study was to evaluate the bioequivalence at steady state of formulation A and Formulation B of oxycodone sustained release tablets in development and compare these results to an equivalent dose of Roxicodone<sup>TM</sup> solution. This study differs from the previous study (protocol 315-03) in that this is a steady state evaluation at an equivalent dose of 10 mg. The solution was administered in doses of 3.33 mg every 4 hours for 21 doses up to 80 hours. The 10 mg SR tablets were administered every 12 hours for 7 doses up to 72 hours. Pharmacokinetic parameters were evaluated during last dosing interval (72-84 hours).

Figure 2 and Table 2 show mean oxycodone plasma concentration-time profiles and pharmacokinetic parameters respectively. Steady state analysis revealed that trough concentrations in the morning at 24, 48, and 72 hours were higher than those in the evening at 36, 60, and 84 hours. The sponsor attributed this to possible circadian effects (literature survey did not yield any information on this aspect). Separate assessment of steady state in the morning and evening yielded trough concentrations slopes which were significantly different from zero. However, based on the small values for these slopes, the sponsor concluded that steady state was achieved.

Both formulation A and formulation B when compared to the oral solution separately, and formulation A and formulation B between each other, were bioequivalent with respect to logarithmically transformed  $C_{max}$  and AUC<sub>72-84</sub>. Between both formulations, ANOVA analysis indicated statistically significant differences between the treatment means for  $C_{min}$  and the fluctuation indices. The fluctuation index values were smaller and the  $C_{min}$  was higher for both formulations over those of oral solution. The fluctuation index values were about 76% and 63% for formulation A and formulation B, respectively, of that of the oral solution. The  $C_{min}$  values were about 108% and 118% for formulation A and formulation B, respectively, of that of the oral solution. From these data it is also clear that formulation B has better sustained release performance characteristics over formulation A.

The conclusions from this study were that both sustained release formulations exhibit similar sustained-release properties over the multiple dosing regimen and were bioequivalent to the oral solution in terms of the extent of absorption. Based on the results from studies 315-03 and 315-04, formulation B was retained for further development and used in all subsequent pharmacokinetic and clinical studies (315-09, 315-10, 315-11, 315-12, CBI-961/962, and CBI-1252).

Table 2. Oxycodone pharmacokinetic parameters (mean (%CV)) when administered as 10 mg equivalent multiple doses of oxycodone solution (3.33 mg every 4 hours) and oxycodone 10 mg SR tablet (every 12 hours)- formulation A and formulation B.

Pharmacokinetic Parameter	Formulation A	Formulation B	Solution
$C_{max}$ , ng/mL	12.68 (26)	12.78 (27)	12.9 (24)
$C_{min}$ , ng/mL	7.77 (28)	8.44 (30)	7.15 (32)
$t_{max}$ , hour	3.7 (41)	4.3 (42)	1.04 (27)
AUC <sub>0-24</sub> , ng hour/mL	106.41 (26)	108.26 (28)	99.02 (25)
Fluctuation Index *	0.649 (26)	0.537 (34)	0.857 (26)

\*Fluctuation Index =  $(C_{max} - C_{min}) / C_{min}$

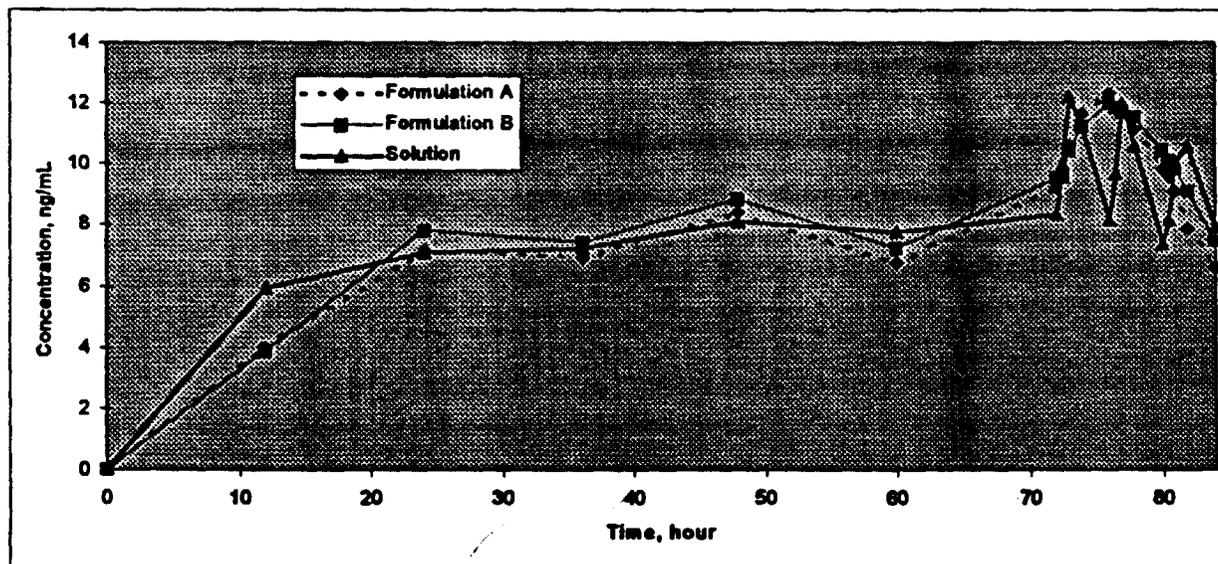


Figure 2. Mean plasma concentration Vs time profiles of oxycodone when administered as 10 mg equivalent multiple doses of oxycodone solution (3.33 mg every 4 hours) and oxycodone 10 mg SR tablet (every 12 hours)- formulation A and formulation B.

### 4.3. Relative Bioavailability of the Oxycodone 10 mg SR Tablet with 10 mg of Roxycodone™ solution

This was an open label, randomized, multiple dose, two-way cross-over study conducted in twenty six (26) adult male subjects with at least one week washout period between the two treatments (protocol 315-09). The oxycodone 10 mg SR tablet was given every 12 hours for seven doses while the solution (5 mg dose) was given every six hours for 14 doses (in study 315-04, the 3.33 mg dose of the solution was given every 4 hours). Linear regression of the trough oxycodone concentrations at 48, 60, 72, and 84 hours indicated mean slopes for both treatments not significantly different from zero indicating the attainment of steady state by the final dosing period. Unlike in study 315-04, where both morning and evening trough concentrations were obtained, only morning trough concentrations were obtained in the current study. As such, the pattern of relatively high morning and relatively low evening trough concentrations attributed to the circadian rhythm could not be confirmed in this study. Figure 3 shows the mean oxycodone plasma concentration-time profiles. Oxycodone 10 mg SR tablet administered every 12 hours seems to exhibit adequate sustained release properties as a substitute for 10 mg oxycodone solution administered every six hours. Analysis of variance indicated statistically significant differences between the treatments for all of the pharmacokinetic parameters evaluated. The 90% confidence intervals for both untransformed and log transformed  $C_{max}$ ,  $C_{av}$  and  $AUC_{72-84}$  were within the FDA recommended bioequivalence limits. Based on comparison of the  $AUC_{72-84}$  values, the 10 mg sustained release tablet had a relative bioavailability of 108% compared to 10 mg of the oral solution.

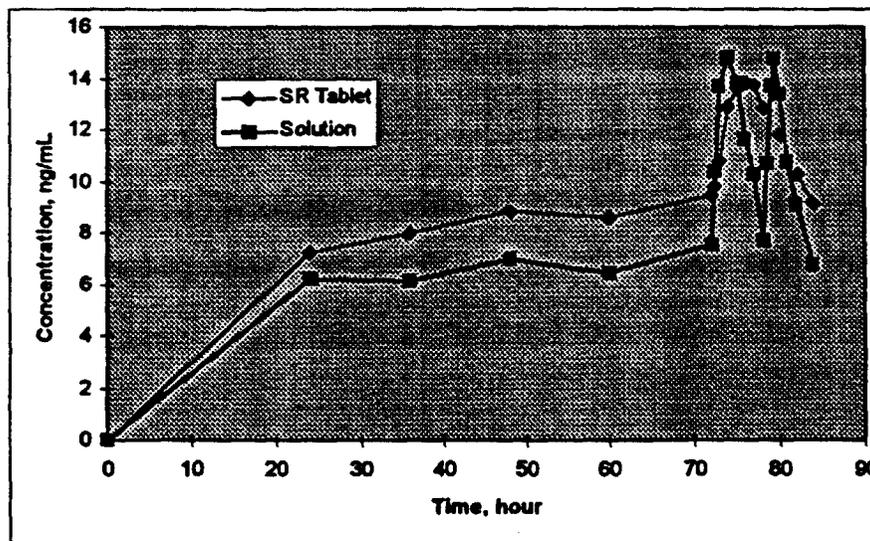


Figure 3. Mean plasma concentration Vs time profiles of oxycodone when administered 10 mg equivalent multiple doses of oxycodone solution (5 mg every 6 hours) and oxycodone 10 mg SR tablet (every 12 hours).

#### 4.4. Bioequivalence of Oxycodone 30 mg and 10 mg SR Tablets

This was a single-dose, randomized two period, two-way cross-over study conducted in 26 adult male volunteers after a 10 hour overnight fast (protocol 315-08). The objective of this study was to evaluate the dose equivalence of one 30 mg SR tablet with three 10 mg SR tablets, following single dose administration.

Analysis of variance indicated no statistically significant differences between the treatments for any of the pharmacokinetic parameters. The percentage differences between the treatments were less than 8% for all parameters. The 90% confidence intervals were within the bioequivalence limits for all parameters except  $t_{max}$  (Table 3).

Table 3. Pharmacokinetic parameters of oxycodone after the administration of one oxycodone 30 mg SR tablet and three oxycodone 10 mg SR tablets (mean (%CV)).

Pharmacokinetic Parameter	30 mg SR Tablet	10 mg SR Tablet	90% confidence Intervals
$C_{max}$ , ng/mL	14.69 (22)	15.44 (27)	89.0-101.1
$t_{max}$ , hour	5.62 (62)	5.89 (52)	73.8-117.1
$AUC_{0-48}$ , ng hour/mL	286.94 (24)	309.28 (27)	86.5-99.1
$AUC_{0-\infty}$ , ng hour/mL	301.70 (25)	324.08 (27)	87.1-99.1
$t_{1/2}$ , hour	9.84 (36)	9.59 (32)	88.5-116.9

#### 5.0. FOOD EFFECT

Two studies were conducted on the oxycodone 10 mg SR tablet to determine; (1) Effect of food and (2) Effect of food as a function of time of administration of the SR tablet with respect to time of consumption of meal.

##### 5.1. Food Effect

This was a single-dose, four-way cross-over, food effect study of oxycodone 10 mg SR tablets with oxycodone immediate-release oral solution as a comparator in thirty (30) male, healthy volunteers (protocol 315-10). The four treatments involved; (1) One 10 mg SR tablet administered under fasting conditions after a 10-hour overnight fast (2) One 10 mg SR tablet administered following the consumption of an FDA high-fat meal (3) 10 mg of a 5 mg/ 5mL oral solution administered under fasting conditions after a 10-hour overnight fast (4) 10 mg of a 5 mg/ 5mL oral solution administered following the consumption of an FDA high-fat meal.

Food significantly increased the rate of absorption of oxycodone from the sustained release tablet (Table 4). There was a 57% increase in the  $C_{max}$  under fed conditions.

However, the extent of absorption was not significantly different between the fed and fasting conditions. There was only a 10% increase in the  $AUC_{0-\infty}$  under fed conditions. The sustained release tablet was bioequivalent (two one sided t-test procedures) under the two conditions with respect to  $AUC_{0-\infty}$  but not for  $C_{max}$ . For the oral solution, food had no significant effect on the rate of absorption of oxycodone in terms of the  $C_{max}$ . However, there was a significant increase in the extent of absorption under fed conditions with about 26% increase in the  $AUC_{0-\infty}$ . The oral solution was bioequivalent under the fed and fasted conditions with respect to the  $C_{max}$  but not for  $AUC_{0-\infty}$ .

Between the sustained release tablet and the oral solution, bioequivalency was achieved with respect to the extent of absorption ( $AUC_{0-\infty}$ ) but not for  $C_{max}$  under both fed and fasting conditions.

**Table 4.** Pharmacokinetic characteristics of oxycodone SR tablet and solution under both fed and fasting conditions (mean (% CV)).

Pharmacokinetic Parameter	SR Tablet		Solution	
	Fasted	Fed	Fasted	Fed
$C_{max}$ , ng/mL	5.74 (16)	8.92 (27)	19.0 (19)	17.7 (17)
$T_{max}$ , hours	5.64 (27)	4.79 (38)	1.25 (41)	2.54 (47)
$AUC_{0-\infty}$ , ng hour/mL	119 (17)	130 (29)	105 (15)	133 (19)
$T_{1/2}$ , hours	12.5 (60)	9.13 (86)	2.93 (12)	3.26 (15)

## 5.2. Time to Food Effect

This was a single dose, four-way cross-over, time to food effect study of oxycodone 10 mg SR tablets in twenty four (24) normal, healthy male and female volunteers (protocol 315-11). The four treatments involved administering one 10 mg sustained release tablet (1) Under fasting conditions after a 10-hour overnight fast (2) One hour before the consumption of an FDA high-fat meal (3) One hour after the consumption of an FDA high-fat meal and (4) Two hours after the consumption of an FDA high-fat meal.

Dosing the oxycodone 10 mg SR tablet under fasting conditions, one hour before meal, one hour after meal, and two hours after meal showed that dosing after meal significantly increased the rate of absorption relative to dosing under fasting conditions (Table 5). Dosing the SR tablet one hour before meals did not significantly increase the  $C_{max}$ . The food effect was relatively more pronounced when the sustained release tablets were administered two hours after meal. There was a 24% and 36% increase in  $C_{max}$  when the tablets were administered one and two hours after the meal respectively (relative to fasting conditions). On the other hand, the extent of absorption in terms of  $AUC_{0-\infty}$  was not significantly different between the four treatments.

Comparing these results with the results obtained with the previous food effect study (protocol 315-10), about 57% increase in  $C_{max}$  was seen in the previous study when the tablets were administered within 5 minutes after consumption of the meal. This is considerably higher than the 24-36% increase seen in the present study. Presumably, food effect is maximum when these sustained release tablets are administered immediately after the consumption of the meal and decreases with time.

The sponsor in studies conducted subsequently indicated in the protocols that the study medication should be taken on an empty stomach, one hour before eating to avoid any effect of food.

Table 5. Pharmacokinetic characteristics of oxycodone SR tablet following both fasting and at different times before and following a meal (mean (% CV)).

Pharmacokinetic Parameter	Fasted	1 hour before meal	1 hour after meal	2 hours after meal
$C_{max}$ , ng/mL	7.35 (26)	7.96 (37)	8.74 (25)	9.72 (24)
$t_{max}$ , hours	5.61 (29)	4.04 (56)	6.57 (52)	5.74 (28)
AUC <sub>0-∞</sub> , ng hour/mL	137 (20)	145 (25)	141 (30)	142 (24)
$t_{1/2}$ , hours	12.0 (55)	9.22 (38)	8.33 (67)	8.38 (42)

The proportions of some of the critical inactive ingredients for the 30 mg strength relative to the 10 mg strength have been changed in amounts that could make prediction of food effect at this higher strength difficult (Table 3). Lactose (diluent) comprised about 25.8% at 10 mg strength while at the 30 mg strength it comprised 12.2% of the total tablet weight. Similarly, Sodium polystyrene sulfonate (probably a disintegrant) comprised 7% at the 10 mg strength while at the 30 mg strength, it comprised 10% of the total tablet weight. However, equivalency between the 10 and 30 mg strengths (equivalent doses of 30 mg) was shown in study 315-08. Although, this does not substitute for a food effect study at the 30 mg strength, the fact that (i) the two strengths were found to be dose equivalent *in vivo* and (ii) since the proportion of the major critical component hydroxy propyl methylcellulose (retardant) has not been changed, probably food effect at the 30 mg strength will be similar to that seen at 10 mg strength.

## 6.0. DOSE-PROPORTIONALITY

This was a four treatment, four-way cross-over, single dose study conducted in sixteen (16) healthy male and female subjects with a one week washout period between each treatment (protocol 315-12). The four treatments that were tested were single doses of 10, 30, 60, and 100 mg total doses of oxycodone SR tablet with the objective of determining the dose-proportionality.

Table 7 lists the pharmacokinetic parameters at the four administered doses 10, 30, 60, and 100 mg oxycodone. In general, as the dose was increased both  $C_{max}$  and AUC increased. However, this increase was not proportional to the dose. Largest deviation from dose-proportionality occurred when the dose was increased from 60 to 100 mg. It is uncertain, if this deviation from dose-proportionality is due to the drug or the formulation.

Statistical analysis with the ANOVA, pairwise comparison, and power model approaches indicated that  $C_{max}$  was not dose-proportional. The power model used indicated that doubling the dose results in a 1.86 fold increase in  $C_{max}$  (95% confidence of 1.78 to 1.95).

$AUC_{0-\infty}$  showed dose-proportionality using ANOVA and pairwise comparison approaches. However, it failed to show dose-proportionality with the power model approach. The power model indicated that doubling the dose resulted in a 1.82 fold increase in  $AUC_{0-\infty}$  (confidence interval of 1.68 to 1.97).

The clinical implications of these results from an efficacy standpoint is uncertain as no efficacy measurements could be made in this study. However from a safety standpoint, it is comforting that lack of dose-proportionality is resulting in less than proportional exposure to the drug rather than the other way where lack of dose-proportionality could result in more than proportional increase in exposure to the drug. Since, gross deviations from dose-proportionality were not seen (about 1.8 fold increase in  $C_{max}$  and  $AUC_{0-\infty}$  with doubling the dose) and since the patients are titrated to effect at the higher doses of oxycodone employed in this study, clinically the less than proportional increases seen in  $C_{max}$  and  $AUC_{0-\infty}$  may not be critical.

Table 7. Summary of mean oxycodone pharmacokinetic parameters (mean (%CV)).

Pharmacokinetic Parameter	10 mg	30 mg	60 mg	100 mg
$C_{max}$ , ng/mL	7.26 (26)	20.4 (29)	38.3 (16)	55.8 (27)
$C_{max}$ normalized to 10 mg dose	1	2.81	5.28	7.69
$t_{max}$ , hour	4.93 (21)	4.8 (43)	4.87 (43)	4.47 (47)
$AUC_{0-t}$ , ng hour/mL	106 (30)	327 (23)	616 (30)	900 (39)
$AUC_{0-t}$ normalized to 10 mg dose	1	3.08	5.81	8.49
$AUC_{0-\infty}$ , ng hour/mL	120 (26)	353 (21)	635 (30)	951 (39)
$AUC_{0-\infty}$ , normalized to 10 mg dose	1	2.94	5.29	7.93
$t_{1/2}$ , hour	7.94 (20)	10.0 (49)	6.89 (49)	8.80 (56)

## **7.0. POPULATION PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS**

Dr. Michael Fossler reviewed the population pharmacokinetic and pharmacodynamic analysis at the request of this reviewer. A copy of his review on this analysis is attached in the Appendix on page 40.

The data used in this analysis was obtained from a subset of patients with chronic cancer pain participating in the two controlled (CBI-961/962 and -1252) and one uncontrolled (CBI-963) clinical studies conducted with this product. A total of 556 blood samples and 546 pain intensity measurements were obtained from 261 subjects. In addition, blood samples obtained from subjects in Phase I studies were also used to anchor the models. The general study design of the two controlled studies consisted of a 2-7 day titration period where each patient was stabilized on a stable dose of oxycodone. Patients were then randomized to either immediate release oxycodone (total daily dose administered q6 hours) or sustained release oxycodone (total daily dose administered q12 hours) for seven days. They were then crossed over to the other treatment for another period of seven days. In the uncontrolled study, patients were administered sustained release oxycodone after the titration period. Patients were allowed rescue medication (immediate release oxycodone) to treat breakthrough pain. Patients recorded history of rescue medication intake in a diary.

Blood draws were done in a random-block design fashion. The visits to the clinic were scheduled such that one-third of the patients would be sampled between 0-4 hours post-dose, one-third between 4-8 hours, and 1/3 between 8-12 hours. At the time of blood draw, patients completed a Visual Analog Score (VAS) of pain intensity.

The analysis was conducted using the Pharmacokinetic/Pharmacodynamic analysis was conducted using three models; a linear model relating pain intensity measurements to oxycodone concentration in the central compartment, the same model using oxycodone concentration in a hypothetical effect compartment, and an intercept only model. No reason was provided for the choice of these models. **The population PK/PD analysis was not successful in that satisfactory runs could not be obtained for the two linear models while the intercept-only model did run, it provided no information on the relationship between plasma oxycodone levels and pain intensity.** Dr. Fossler felt that if the data had been obtained during the titration period, the relationship between pain relief and plasma oxycodone might have been better elucidated.

The population pharmacokinetic analysis was conducted appropriately in describing the oxycodone pharmacokinetics in patients and supporting the results of Phase I pharmacokinetic studies. Several covariates were examined in this analysis (see special populations below). A statistically significant effect of age on oxycodone clearance was found. No gender differences were identified. Poor liver function (as defined by elevated liver enzymes) and racial differences were also examined. However, due to limited number of individuals, reliable information was not obtained on these two effects.

## **8.0. SPECIAL POPULATIONS**

-- No specific special population studies were conducted by the sponsor investigating the pharmacokinetics of oxycodone in elderly or hepatic and renal failure patients. A survey of the literature yielded one published article in end-stage renal failure patients which is briefly discussed below.

### **8.1. Renal failure**

Elimination of oxycodone was impaired in end-stage renal failure. Mean elimination half-life was prolonged in uremic patients due to increased volume of distribution and reduced clearance.

(Reference- Kirvela M; Lindgren L; Seppala T; Olkkola KT. The pharmacokinetics of oxycodone in uremic patients undergoing renal transplantation. *J. Clin. Anesth.*, 8(1): 13-18 (1996)).

### **8.2. Hepatic failure**

Oxycodone pharmacokinetics were not studied in hepatic failure patients. However, since oxycodone elimination is mostly metabolic, clearance may decrease in hepatic failure patients. Sponsor attempted to tease out the hepatic failure effect from the population pharmacokinetic analysis conducted on data from patients. However, Dr. Mike Fossler comments that patients with elevated liver enzymes (which by itself is not a total indicator of hepatic failure anyway) were too few in this analysis to yield any meaningful conclusions.

### **8.3. Elderly**

From the population pharmacokinetic analysis conducted on data from patients, age was found to have a statistically significant effect on clearance (about 30% decrease in oral clearance at the age of 85 years compared to the value at the age of 30 years). However, as Dr. Mike Fossler points out, this product will be titrated to response in every patient and as such the age effect on clearance found in this analysis may not be clinically relevant with respect to dosage adjustment.

### **8.4. Gender**

Population pharmacokinetic analysis revealed no gender differences in oxycodone pharmacokinetics.

### **8.5. Racial differences**

From the population pharmacokinetic analysis, no racial differences could be found; however, the number of non-Caucasians in these studies were insufficient to determine racial effects if they existed.

## 9.0. DISSOLUTION TESTING

--Dissolution testing was conducted using USP Apparatus I at a rotation speed of 100 rpm and sampling times of 1, 2, 6, and 12 hours. The media consisted of deaerated Simulated Gastric Fluid without enzymes for 1 hour followed by deaerated Simulated Intestinal Fluid without enzymes for an additional 11 hours. The volume used was 900 mL. The following dissolution specifications are proposed for the 10 mg and 30 mg tablets;

1/2%  
1%  
2%  
10%

These specifications were based on data obtained from dissolution testing on four lots each of the 10 mg and 30 mg strengths of the product. These data are presented in detail in the Appendix on page 39. Close examination of the specifications shows that at 12 hours, the low end of the proposed range is 1/2%. Clearly, it is not acceptable to allow 1/2% released *in vitro* at the end of 12 hours. Furthermore, data on the pH dependence and effect of dissolution media and agitation speed were not provided. The dissolution method and specifications proposed can only be approved on an interim basis. Specifications more reflective of the *in vivo* delivery of the product should be developed and submitted to the Agency in a timely fashion. Dissolution should be carried out until complete or at least 10% of drug is dissolved.

## 10.0. ANALYTICAL METHODOLOGY

### 11.0. CONCLUSIONS

1. The sponsor has demonstrated the *in vivo* bioequivalence of equivalent single doses of Roxycodone SR tablets relative to an immediate release solution of oxycodone with respect to AUC.
2. The sponsor has demonstrated the bioequivalency of Roxycodone 10 mg SR tablets relative to immediate release oxycodone following steady state dosing with respect to both  $C_{max}$  and AUC
3. The effect of a high fat meal on a single dose of Roxycodone 10 mg SR tablet has been investigated.

4. Dosage form bioequivalency was demonstrated between Roxycodone 10 mg and 30 mg SR tablets.
5. Dose-proportionality in the dose range of                      mg has been investigated.
5. Population pharmacokinetic and pharmacodynamic analysis was not successful.
6. Population pharmacokinetic analysis supported the results of Phase I studies.
7. The proposed *in vitro* dissolution method and dissolution specifications are not acceptable to the Agency. The dissolution method used and the specifications proposed can be approved only on an interim basis.

## 12.0. PROPOSED PACKAGE INSERT

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