CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-932

ADMINISTRATIVE DOCUMENTS

CSO Review of Labeling

NDA 20-932

Drug: Roxicodone (oxycodone hydrochloride) Sustained Release Tablets, 10 mg and 30 mg

Sponsor: Roxane Laboratories, Inc.

Materials Reviewed:
Draft labeling (package insert) submitted with the NDA application on December 29, 1997; an amendment with draft labeling was submitted on April 24, 1998.

Review: The labels are in conformity with labeling regulations (21 CFR 201.1, 201.5, 201.10, 201.15, 201.17, 201.18, 201.50, 201.51, 201.55, and 201.100).

Conclusions: On December 29, 1997, the NDA application was submitted with a draft package insert and draft container labeling. On April 24, 1998 an amendment with an electronic disk of the package insert was submitted. This draft was identical to that submitted on December 29, 1997.

In September, 1998, the package insert was placed on a shared drive for all members of the team to enter proposed changes. Changes by the clinical pharmacology (Doddapaneni), substance abuse (Hayes and Klein), preclinical pharmacology (Geyer), and statistics (Ma) reviewers were made to the discipline specific sections of the label on the shared drive document. Changes by the medical reviewer (Scheinbaum) were later added to the document. There were no changes from the chemistry reviewer.

A labeling meeting was held on October 20, 1998. Since some essential members of the team could not attend, most of the group left the meeting and the medical reviewer made additional changes to the labeling. The division director helped with some of the changes and a draft of the labeling was prepared which showed all changes up to this point with the filename PI1120.doc.

A cleaned up (correction notations deleted) version was further edited by the division and deputy division directors producing the draft with filename PI1021.fin.dot. (Table 1 was removed in error in this version and replaced in subsequent versions.)

A number of changes were made to PI1021.fin.doc and are shown in the marked up draft of 10/22/98. Hand written corrections and a few more minor changes were made to produce the final draft which was issued with the approval letter. The filename of this version is PI1026fin.dot.

/S/ 1/20/98

Bonnie McNeal
Project Manager

/S/

Concur: 1/21/98

Corinne P. Moody
Chief, Project Management Staff

cc:
orig NDA 20-932
Div File
HFD-170/BMcNeal

MEMO

DIVISION OF ANESTHETIC, CRITICAL CARE
AND
ADDICTION DRUG PRODUCTS

AUG 25 1998

ABUSE LIABILITY ASSESSMENT

NDA:	20-932
SPONSOR:	Roxane Laboratories
DRUG:	Roxicodone™ SR (oxycodone Hydrochloride)
CHEMICAL NAME:	4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride
DOSAGE FORM:	Tablets
STRENGTHS:	10 and 30 mg
INDICATION:	Management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days.
DATE SUBMITTED:	December 29, 1997
DATE Rcd. BY REVIEWER:	March 31, 1998
REVIEWER:	BeLinda A. Hayes, Ph.D.
REVIEWER DATE:	July 7, 1998

BACKGROUND.

Oxycodone hydrochloride, 4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride, a semisynthetic derivative of thebaine has been used clinically as a narcotic analgesic since the 1920's for the treatment of moderate to moderately severe pain. Oxycodone is available in the United States, Canada, Colombia, Czechoslovakia, Finland, Germany, Hungary, Japan, New Zealand and Switzerland in oral formulation as the hydrochloride and terephthalate salts either alone or in combination with aspirin or acetaminophen. In Finland, it is commonly used intramuscularly for premedication before anesthesia and severe postoperative pain. As an analgesic, oxycodone is approximately equipotent with morphine in the dose-range of 5-10 mg (every 6 hours).

Currently, Roxicodone is marketed as an immediate-release tablet, as an oral solution, and as a concentrated oral solution (Intensol). The sponsor has developed a sustained-release formulation of Roxicodone (Roxicodone SR) that is indicated for the management of moderate to severe pain when the patients requires an opioid analgesic for more than a few days. Roxicodone™ SR tablets will be available in two strengths, 10 and 30 mg. To manage pain, Roxicodone™ SR will be administered every 12 hours.

Per 21 CFR 314.50(5)(vii) when a NDA is submitted for a drug that has the potential for abuse, the sponsor must submit an abuse liability package along with the NDA submission as part of the approval process. Roxicodone SR meets this criteria. This package must contain a descriptive analysis of studies (i.e., preclinical and clinical studies conducted by the sponsor, data from the published literature), all available information related to abuse of the drug and the sponsor's scheduling proposal for the drug. CFR 314.50(5)(vii) also requires the sponsor to submit a letter stating its intention (i.e., requesting rescheduling or no scheduling change) for its drug product that is currently controlled under the Controlled Substances Act.

ABUSE LIABILITY INFORMATION PROVIDED IN THE SUBMISSION.

The sponsor did not submit an abuse liability package as required by CFR 314.50(5)(vii). The only information that was submitted in the NDA which was relevant to the abuse potential of oxycodone included: 1) The sponsor's proposed label for the Drug Abuse and Dependence and Overdosage sections in the package insert.; 2) A 3 page in the "Safety Summary" section (Item 3.0) titled. "Tolerance, Abuse, Dependence, and Overdosage."

ABUSE POTENTIAL OF OXYCODONE.

All marketed preparations of oxycodone hydrochloride are included under Schedule II of the Controlled Substance Act. A literature review on published data pertinent to the abuse potential of oxycodone only revealed a few published clinical studies and no preclinical studies that have evaluated the reinforcing efficacy, physical dependence and tolerance producing properties of oxycodone hydrochloride. It has been reported that the abuse potential of oxycodone is equivalent to that of morphine (Poyhia *et al.*, J. Pain Symptom Manage., 8(2):63-67, 1993). Parenteral administration of oxycodone hydrochloride to ex-addict prisoner volunteers revealed that its abuse liability was comparable to parenteral morphine in doses that are equianalgesic (Martin, 1966). Furthermore, one would expect its dependence-producing potential to be similar to morphine; i.e., producing morphine-like dependence (i.e., psychic and physical dependencies) and tolerance since oxycodone is a μ agonist and possesses a morphine-like pharmacological profile.

Consistent with its μ opioid agonist profile, oxycodone SR produces an opioid-like withdrawal syndrome. Abrupt discontinuation of oxycodone SR produces an abstinence syndrome characterized by rhinitis, myalgia, abdominal cramping and occasional diarrhea. If no treatment is administered these symptoms are usually present for 5 to 14 days. A secondary or chronic abstinence syndrome can occur which is characterized by insomnia, irritability and muscular aches and can persist for 2 to 6 months.

There was one reported incidence of a mild withdrawal syndrome in a patient enrolled in the 30-day uncontrolled clinical study. The sponsor reported that this patient experienced three abstinence syndrome episodes. The first episode began on day 1 of the IR stabilization period; the patient displayed intermittent episodes of chills and sweat. This episode lasted for 3 days. Beginning on day 5 of the treatment period, the patient had a recurrence of intermittent chills and sweats which lasted for two days. On day 13 of the study, the patient began to experience sweats and chills again which lasted for 2 days.

LABEL REVIEW.

EVALUATION AND COMMENTS.

Roxicodone SR is an opioid analgesic indicated for the management of pain. Roxicodone SR will be available for oral administration in 2 strengths; 10 mg and 30 mg tablets. Oxycodone has been available clinically for over 70 years and has proven to be an effective analgesic agent for the management of pain associated with cancer, lower back problems, and osteoarthritis. Oxycodone dependence-producing properties are morphine-like. All marketed oxycodone preparations are regulated under Schedule II of the Controlled Substances Act (CSA). Roxicodone SR will also be included under Schedule II of the CSA upon approval

RECOMMENDATIONS.

We have no objections to the approval of this NDA. Minor labeling revisions will be necessary prior to approval.

/S/ July 7, 1998

BeLinda A. Hayes, Ph.D. Date

/S/ Aug. 25, 1998

Concurred by Team Leader:

Michael Klein, Ph.D. Date

CC: Orig NDA# 20-932
HFD-170/Div File
HFD-170/BHayes
HFD-170/Mklein
HFD-170/BMcNeal
F/T by:BHayes/7-7-98

NDA 20-932

No phase 4 commitments were requested of the sponsor for this NDA.

971

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530) NLRC

From: Division of Anesthetic, Critical Care & Drug Abuse Drug Products	HFD- 170
~~Attention:~~ HAROLD BLATT	Phone: (301)443-4250
Date: 2-17-98	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: Roxicodone SR	NDA/ANDA# 20-932
Established name, including dosage form: Oxycodone hydrochloride, sustained release	
Other trademarks by the same firm for companion products: N/A	
Indications for Use (may be a summary if proposed statement is lengthy): Management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days	
Initial Comments from the submitter (concerns, observations, etc.):	

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible. {Rev. August 95}

Food and Drug Administration
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Center for Drug Evaluation and Research
Division of Anesthetics, Critical Care, and Addiction Drug Products

MEMORANDUM

to:	Division File, NDA #20-932
from:	Cynthia McCormick, MD Cynthia McCormick MD Director, Division of Anesthetics, Critical Care and Addiction Drug Products
subject:	Roxycodone™ SR (oxycodone HCl Sustained Release) 10 mg and 30 mg tablets–Action Memo
date:	October 19, 1998

This memo records and explicates for the file the basis for the action to be taken on the Roxycodone™ SR (oxycodone HCl Sustained Release) 10 and 30 mg tablets, NDA 20-932 submitted to the FDA on December 29, 1997. The Sponsor, Roxane laboratories also markets Roxicodone™ Tablets USP (5 mg), Roxicodone™ oral solution USP (5mg/5mL) and Intensol™ (20 mg/mL). The current product intended for q12 hour dosing was developed in an effort to improve compliance as the currently available IR formulation is taken every 4 hours. Submitted in support of this NDA were three clinical studies and a portfolio of eleven pharmacokinetics studies.

This product represents a new formulation (sustained release) of an semisynthetic opiate which has been in use since 1917 as an analgesic agent. There is an extensive experience with the safety and efficacy, abuse potential and toxicology of this product, therefore, as an immediate release formulation, and this application is intended to support the same indication but with q12 hour dosing.

Efficacy

Dr. Scheinbaum and Ma have reviewed the two efficacy studies CBI-961/962 and CBI-1252. These are multicenter, double blind, and active-controlled crossover studies in opiate tolerant patients in one case with chronic cancer pain and the other in chronic nonmalignant pain. The entrance criteria also differ in the severity of pain allowed, with patients with more severe baseline VAS scores in the nonmalignant pain group. On accrual, patients were stabilized on IR

Roxycodone prior to treatment and were placed on a "comparable" total daily dose based on their current maintenance regimen of opiates. They were then randomized to a sequence of SR/IR or IR/SR. In both studies patients' pain intensity (VAS) scores and use of rescue medication (oxycodone IR) were both compared primarily as endpoints while on IR Roxycodone administered q4hours and SR Roxycodone q12 hours.

Dr. Rappaport's supervisory memo provides a thorough but concise summary of the findings of both of these studies and supports the finding of therapeutic equivalence between the two formulations. There were no statistically significant differences between the two treatments either for VAS scores on medication or in the total daily dose or mean number of doses of rescue medication. On a composite score integrating both VAS and rescue medication there was only one observable time point during which there was a statistically significant difference in this composite scale in favor of IR formulation. This is noted in Dr. Rappaport's summary. There is probably little clinical significance of this isolated finding at a single time point and on a scale that has not been validated, without confirmation at other time points and in other studies.

There is adequate assurance based on two clinical trials that Roxycodone™ SR is effective and comparable to Roxycodone IR in the treatment of moderate to severe pain associated with cancer or other chronic nonmalignant painful conditions requiring opiate treatment.

Safety

A safety database of 393 opiate tolerant patients and 193 healthy volunteers for a total of 586 exposures, and 160 for greater than one month provides sufficient assurance of the safety of this new formulation. Analysis of the deaths, serious adverse events and study withdrawals due to adverse events, and common adverse events revealed no new or unexpected findings—and were typical of either the underlying disease or due to the well known CNS effects of opiates—such as abnormal mental status, somnolence, dizziness, nausea and vomiting.

Statistical analysis of adverse events by individual adverse events in the controlled trials did not demonstrate any specific adverse event which might have been more prevalent in one treatment group compared to another. When adverse events were pooled across body systems, there appeared to be a statistically significant increase in the adverse events in the SR compared to the IR formulations. Such an increase, however, since it is not accompanied by a specific increase in any individual adverse event, may be only a function of pooling and an artifact of the analysis.

No important signals were found in analysis of laboratory values or vital signs.

There is adequate assurance based on review of the safety data presented with this NDA for approval of this product for patients with moderate to severe pain.

Pharmacokinetics

The majority of studies submitted in support of marketing approval were biopharmaceutical studies. They are summarized, analyzed and discussed in the very thorough review by Dr. Doddapaneni. This included bioavailability, single and multiple dose pharmacokinetics, dose proportionality, effect of food, and population pharmacokinetics and pharmacodynamics.

It has been shown that the pharmacokinetics profile demonstrates the appropriateness of this product for BID dosing.

In vivo bioequivalence between the IR formulation and the SR tablets based on AUC has been demonstrated. Bioequivalence has been demonstrated on AUC and C_{max} between the 10 mg Roxycodone SR and IR oxycodone at steady state.

It has been demonstrated that food significantly increases the rate of absorption of oxycodone from the sustained release formulation with a 57% increase in the C_{max} under fed conditions. Notably, however there was not a significantly different increase in the AUC under fed conditions (10%).

There was an effort to correlate pharmacodynamic endpoints in this study with PK parameters, using a population pharmacokinetics approach (see reviews by Drs. Doddapaneni and Fossler). While this analysis was not successful, it is not considered critical to approval, as the two clinical trials were sufficient to satisfy the efficacy standards for approval.

Other

Chemistry and manufacturing of this product have presented no issues. The preclinical pharmacology review has revealed no new toxicity concerns, however as an older pharmaceutical agent, there has not been a comprehensive carcinogenicity evaluation. This however can be conveyed to the treating physician in the product's package insert. Morphine class labeling will be used to provide similar information to prescribing physicians

Summary

The pharmacokinetics of this new formulation have been adequately studied and there is adequate evidence for safety and effectiveness of Roxycodone SR tablets 10 and 30 mg in this NDA to support approval.

Action

Approval of Roxycodone™ SR 10 and 30 mg for the treatment of moderate to severe pain.

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)443-3741

MEMORANDUM

DATE: October 8, 1998

TO: File, NDA 20-942

FROM: Bob A. Rappaport, M.D.
Deputy Director, DACCADP

RE: Supervisory Review of NDA 20-932 Roxicodone™ SR
(Oxycodone HCl Sustained Release) 10 mg and 30 mg, tablets

BACKGROUND:

NDA 20-932 for Roxicodone™ SR (Oxycodone HCl Sustained Release) 10 mg and 30 mg, tablets, was submitted by Roxane Laboratories, Inc. on December 29, 1998. The sponsor currently markets Roxicodone™ as an immediate release tablet (5 mg) and as oral solutions (5 mg/mL and [Intensol™] 20 mg/mL), indicated for the treatment of moderate to severe pain. Oxycodone is a morphine-like, semisynthetic opioid analgesic which has been in clinical use since 1917. Dosing guidelines for the marketed products state that the usual adult dose is 10 to 30 mg every 4 hours or as directed by a physician. The sponsor has developed the sustained release formulation of oxycodone under IND , and the labeling submitted to this application recommends a dosing schedule of administration every 12 hours.

This application contains complete reports for three clinical and eleven pharmacokinetic studies. An open-label compassionate use study is ongoing. The submission also contains forty-eight published articles relating to the clinical pharmacology, efficacy and safety of oxycodone. The clinical studies of the effectiveness and safety of this new formulation, as well as the literature references, have been reviewed [submitted July 15, 1998] by Monte Scheinbaum, M.D. The application has also been reviewed by Z. Jonathan Ma, Ph.D. (biostatistics), Suresh Doddapaneni, Ph.D. (clinical pharmacology

and biopharmaceutics), Harry Geyer, Ph.D. (pharmacology/toxicology), Pramoda Matūrū, Ph.D. (chemistry), and BeLinda Hayes, Ph.D. (abuse liability). In this memo, I will briefly review the effectiveness and safety data summarized in the primary clinical review, as well as any relevant information found in the primary reviews from the other disciplines, and make appropriate recommendations for action on the NDA.

EFFECTIVENESS:

Evidence of efficacy has been submitted in the clinical studies CBI-961/962 and CBI-1252.

Study CBI-961/962:

Two trials, CBI-961 and CBI-962, were initially begun in patients with cancer pain. However, due to slow patient enrollment for both protocols, the studies were merged into a single, multicenter trial, CBI-961/962. This change received approval from the Division based on submissions (#028 and #034) to this application in May and November of 1996.

This was a randomized, double-blind, crossover, active-controlled, multicenter, multiple dose study comparing the effect of oxycodone SR administered q 12 hours to oxycodone IR [immediate release] administered q 6 hours in patients with chronic pain due to cancer. The study was divided into a Stabilization Period of five days and a Double-blind Treatment Period lasting two weeks.

During the Stabilization Period the patients were treated with either open-label oxycodone IR q 6 hours or open-label SR q 12 hours (6 patients from CBI-962 remained on SR; the remaining 63 patients were started on IR in CBI-961, or switched to IR when the studies were combined [per Dr. Scheinbaum, personal communication 10/6/98]). The initial total daily dose [TDD] was determined by standard conversion to oxycodone equivalence from the patient's previous opioid medication regimen. Dosage adjustments were carried out after pain control assessment during daily telephone calls. Oxycodone IR (5 mg tablets) was used as rescue medication. Patients requiring no more than two doses of rescue medication in a 24 hour period, and who had a pain intensity rating of ≤ 5 (on a verbal scale of 0 [no pain] to 10 [worst pain]) in that same 24 hour period, were brought into the clinic and completed a VAS (Visual Analogue Scale) assessment of pain intensity over the prior 24 hour dosing period. Patients whose score was ≤ 50 mm on the VAS were randomized into the Double-blind Treatment Period.

These patients were randomized to one of two crossover treatment sequences, IR/SR or SR/IR. Individual treatments consisted of either oxycodone SR administered q 12 hours with IR placebo administered q 6 hours, or oxycodone IR administered q 6 hours with SR placebo administered q 12 hours. The actual doses were calculated by dividing the final total daily dose from the Stabilization Period (including scheduled and rescue

doses) by two, rounding up to the nearest multiple of ten, and dividing the final quantity into either two or four equal doses. After seven days on the first treatment sequence, patients were crossed over to the alternate treatment sequence for another seven days. An additional two days were allowed per sequence period in order to adjust for intervening weekends or difficulty scheduling visits. Oxycodone IR (5 mg tablets) was used as the rescue medication for both treatment sequence periods.

The primary efficacy parameter was pain intensity measured by VAS score at 6:00 a.m., 12:00 noon, and 6:00 p.m., and overall (average of all available scores) on Day 6 of each treatment sequence period. Data from the intent-to-treat [ITT] population (i.e., all patients randomized, receiving at least on dose of double-blind study drug, and recording at least one VAS score or took at least one dose of rescue medication) were analyzed employing ANOVA models. Treatment comparisons for mean VAS scores were carried out for the above noted time points and the overall score. The ratio of mean VAS assessment scores obtained for each of the two formulations and the 95% confidence interval of the difference were calculated.

The following secondary efficacy endpoints were recorded and analyzed:

1. VAS score at 6:00 a.m., 12:00 noon, and 6:00 p.m., and overall, on Days 1 through 5, and the last measurement after Study Day 3, i.e., after patients were stabilized on the new drug
2. The number and percent of patients who required rescue medication
3. The average daily dose of rescue medication
4. The average number of doses of rescue medication
5. Integrated assessment of VAS scores and rescue medications on Days 1 through 6
6. Global VAS scores for overall effectiveness of study drug

Results:

A total of 69 patients were enrolled. Fifty of these patients completed the Stabilization Period. One patient withdrew consent prior to randomization. A total of 49 patients were randomized to the Double-blind Treatment Period. Twenty-two patients received the SR/IR sequence and 25 received the IR/SR sequence. (Two of the patients who had been randomized to the SR/IR sequence did not complete the study medication page of the patient diary and, therefore, did not provide any dosing information.) Ten patients discontinued during the Double-blind Treatment Period due to: adverse events (3 IR, 2 SR), inadequate therapeutic response (1 IR, 2 SR), or withdrawal of consent (1 IR, 1 SR). A total of 47 patients were available for the ITT analysis.

Treatment groups appeared to be generally matched on relevant measures at baseline.

The total daily dose of oxycodone used during the Double-blind Treatment Period is summarized in the following table, based on Dr. Scheinbaum's Table 8, p. 25 of his review:

Table 1.

		Oxycodone SR (N=44)	Oxycodone IR (N=43)
Double-blind study medication (TDD in mg)	Mean	108.2 (16.26)	107.4 (16.63)
	Median	60.0	60.0
	Range		
Rescue medication (TDD in mg)	Mean	15.8 (5.52)	16.3 (5.76)
	Median	5.0	3.6
	Range		

Primary Efficacy Analyses:

The mean VAS scores, the least squares mean difference of the scores, and the 95% confidence intervals are summarized for the ITT in the following table based on Dr. Scheinbaum's Table 9, p. 27 of his review:

Table 2. Mean Day 6 VAS Score (mm)

Time point		Formulation		Least Squares Mean Difference			Mean Ratio	
		Oxy SR	Oxy IR	SR-IR	95% CI	p-value	SR/IR	95% CI
6:00 a.m.	N	39	38					
	Mean	25.15	24.05	0.478	(-4.99,5.95)	0.865	1.019	(0.80,1.23)
	S.E.	3.401	3.663	2.792				
12:00 noon	N	36	37					
	Mean	23.00	22.35	-1.086	(-5.55,3.38)	0.637	0.955	(0.77,1.14)
	S.E.	3.266	3.332	2.278				
6:00 p.m.	N	36	37					
	Mean	22.94	26.00	-5.343	(-10.44,-0.24)	0.049	0.808	(0.62,0.99)
	S.E.	3.477	3.688	2.602				
Overall	N	39	38					
	Mean	25.25	24.55	-1.326	(-5.51,2.85)	0.539	0.950	(0.79,1.11)
	S.E.	3.302	3.007	2.132				

Although there was a statistically significant difference in VAS scores at the 6:00 p.m. time point (difference = 5.3, $p = 0.049$), the sponsor did not consider this difference as clinically meaningful based on their defined clinically meaningful difference of 8 mm.

The sponsor also analyzed the mean change from baseline in VAS score on Day 6. There were no statistically significant differences between the formulations ($0.51 \leq p \leq 0.87$).

Secondary Efficacy Measures:

VAS Scores Days 1 Through 5:

The IR formulation was associated with 4.7 to 6.8 mm less VAS pain intensity at four time points on Day 1 and at 12:00 noon on Day 5. The differences were statistically significant on Day 1 at 6 a.m., 12:00 noon, and overall (p values: 0.04, 0.02 and 0.02, respectively), and on Day 5 ($p = 0.01$). The sponsor considered these VAS differences to be not clinically significant.

The sponsor also analyzed the mean change from baseline in VAS scores for Days 1 through 5. Only the overall VAS score on Day 5 showed a statistically significant difference ($p=0.047$) between the formulations.

VAS Score at Endpoint:

There were no differences between treatments for mean VAS scores at endpoint (i.e., last score after Study Day 3). The mean changes from baseline in VAS scores at endpoint were also not statistically significant.

Number and Percent of Patients Requiring Rescue Medication:

There were no statistically significant differences between the two formulations for the number or percentage of patients requiring rescue medication for Days 1-3, Days 4-6, and Days 1-6. The pattern of usage for the two formulations was similar. Both the percentage of patients taking rescue medication and the number of doses taken decreased during the first two hours after administration of either formulation and increased during the next four hours until study drug was again administered.

Average Daily Dose of Rescue Medication:

The mean total daily dose of rescue medication was slightly higher for the IR formulation. However, this difference was not statistically significant ($p = 0.9453$).

Average Number of Doses of Rescue Medication:

The mean number of doses of rescue medication taken were similar at 0.815 and 0.884 for the SR and IR formulations, respectively. The difference between these results was not statistically significant.

Integrated Assessment of VAS Scores and Rescue Medication:

In response to a request by the Division, the sponsor performed a statistical evaluation which integrated both the VAS scores and rescue medication consumption. Dr. Scheinbaum provides a description of this analysis on page 34 of his review. The only statistically significant difference between the two formulations was observed at 12:00 noon on Day 5 (p=0.034), with a result which favored the IR formulation.

Global VAS Scores for Overall Effectiveness of Study Drug:

This score was recorded in order to measure the overall effectiveness of study drug over each of the seven day double-blind treatment periods. There were no statistically significant differences between the treatments for the mean global VAS scores (p=0.760).

Study CBI-1252:

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

During the Stabilization Period the patients were treated with open-label oxycodone SR q 12 hours. The initial total daily dose [TDD] was determined by standard conversion to oxycodone equivalence from the patient's previous opioid medication regimen. Dosage adjustments were carried out after pain control assessment during daily telephone calls. Oxycodone IR (5 mg tablets) was used as rescue medication. Patients requiring no more than two doses of rescue medication in a 24 hour period, and who had a pain intensity rating of < 7 (on a verbal scale of 0 [no pain] to 10 [worst pain]) in that same 24 hour period, were brought into the clinic and completed a VAS (Visual Analogue Scale) assessment of pain intensity over the prior 24 hour dosing period. Patients whose score was < 70 mm on the VAS were randomized into the Double-blind Treatment Period.

These patients were randomized to one of two crossover treatment sequences, IR/SR or SR/IR. Individual treatments consisted of either oxycodone SR administered q 12 hours with IR placebo administered q 6 hours, or oxycodone IR administered q 6 hours with SR placebo administered q 12 hours. The actual doses were calculated by dividing the final total daily dose from the Stabilization Period (including scheduled and rescue doses) by two, rounding up to the nearest multiple of ten, and dividing the final quantity into either two or four equal doses. Of note, investigators were given the option of altering the patients' stabilized dose at the beginning of the double-blind treatment period. After seven days on the first treatment sequence, patients were crossed over to the alternate treatment sequence for another seven days. An additional two days were

allowed per sequence period in order to adjust for intervening weekends or difficulty scheduling visits. Oxycodone IR (5 mg tablets) was used as the rescue medication for both treatment sequence periods.

The primary efficacy parameter was pain intensity measured by VAS score at 6:00 a.m., 12:00 noon, and 6:00 p.m., and overall (average of all available scores) on Day 6 of each treatment sequence period. Data from the intent-to-treat [ITT] population (i.e., all patients randomized, receiving at least on dose of double-blind study drug, and recording at least one VAS score or took at least one dose of rescue medication) were analyzed employing ANOVA models. Treatment comparisons for mean VAS scores were carried out for the above noted time points and the overall score. The ratio of mean VAS assessment scores obtained for each of the two formulations and the 95% confidence interval of the difference were calculated.

The following secondary efficacy endpoints were recorded and analyzed:

1. VAS score at 6:00 a.m., 12:00 noon, and 6:00 p.m., and overall, on Days 1 through 5, and the last measurement after Study Day 3, i.e., after patients were stabilized on the new drug
2. The number and percent of patients who required rescue medication
3. The average daily dose of rescue medication
4. The average number of doses of rescue medication
5. Integrated assessment of VAS scores and rescue medications on Days 1 through 6
6. Global VAS scores for overall effectiveness of study drug

Results:

A total of 114 patients were enrolled. Eighty-seven of these patients completed the Stabilization Period. One patient withdrew consent prior to randomization. A total of 86 patients were randomized to the Double-blind Treatment Period. Forty-two patients were randomized to the SR/IR sequence and 44 to the IR/SR sequence. One patient randomized to the IR/SR sequence withdrew due to an adverse event which occurred prior to taking double-blind study medication. Eighty-two patients took IR and 82 took SR. Seventy-eight patients completed the double-blind phase of the study. Seven patients discontinued during the Double-blind Treatment Period due to: adverse events (1 IR, 2 SR), protocol violation (1 SR), withdrawal of consent (1 IR, 1 SR), or lost to follow-up (1 IR). A total of 85 patients were available for the ITT analysis.

Treatment groups appeared to be generally matched on relevant measures at baseline.

The total daily dose of oxycodone used during the Double-blind Treatment Period is summarized in the following table, based on Dr. Scheinbaum's Table 21, p. 43 of his review:

Table 3.

		Oxycodone SR (N=82)	Oxycodone IR (N=82)
Double-blind study medication (TDD in mg)	Mean (S.E.)	65.4 (11.09)	58.5 (8.92)
	Median	40.0	40.0
	Range		
Rescue medication (TDD in mg)	Mean	13.8 (1.60)	13.8 (1.47)
	Median	9.4	9.3
	Range		

While some potential for bias appears to be implicit in a study design which allows investigators to adjust a variable (i.e. baseline dose oxycodone) that is being measured as a primary endpoint (i.e. quantity of oxycodone used as rescue medication), Dr. Scheinbaum reviewed the changes which actually occurred during the Double-blind Period. Dosing increases occurred only on Day one and then remained stable throughout the Period. (A similar investigation into Study CBI-961/962 revealed the same results.)

Primary Efficacy Analyses:

The mean VAS scores, the least squares mean difference of the scores, and the 95% confidence intervals are summarized for the ITT in the following table based on Dr. Scheinbaum's Table 23, p. 45 of his review:

Table 4. Mean Day 6 VAS Score (mm)

Time point		Formulation		Least Squares Mean Difference			Mean Ratio	
		Oxy SR	Oxy IR	SR-IR	95% CI	p-value	SR/IR	95% CI
6:00 a.m.	N	79	79					
	Mean	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	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 p.m.	N	79	79					
	Mean	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	N	79	80					
	Mean	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				

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 sponsor also analyzed the mean change from baseline in VAS score on Day 6. There were no statistically significant differences between the formulations ($0.156 \leq p \leq 0.890$).

Secondary Efficacy Measures:

VAS Scores Days 1 Through 5:

There were no statistically significant differences between the treatments at any time point or overall on any of the five days ($0.137 \leq p \leq 0.981$).

The sponsor also analyzed the mean change from baseline in VAS scores for Days 1 through 5. There were no significant differences between the treatment groups for this measure.

VAS Score at Endpoint:

There were no differences between treatments for mean VAS scores at endpoint (i.e., last score after Study Day 3). The mean changes from baseline in VAS scores at endpoint were also not statistically significant.

Number and Percent of Patients Requiring Rescue Medication:

There were no statistically significant differences between the two formulations for the number or percentage of patients requiring rescue medication for Days 1-3, Days 4-6, and Days 1-6. The pattern of usage for the two formulations was similar. Both the percentage of patients taking rescue medication and the number of doses taken decreased during the first two hours after administration of either formulation and increased during the next four hours until study drug was again administered.

Average Daily Dose of Rescue Medication:

The mean total daily dose of rescue medication for both treatments was approximately 14 mg. ($p=0.999$).

Average Number of Doses of Rescue Medication:

The mean number of doses of rescue medication taken were similar at 1.640 and 1.676 for the SR and IR formulations, respectively. The difference between these results was not statistically significant.

Integrated Assessment of VAS Scores and Rescue Medication:

In response to a request by the Division, the sponsor performed a statistical evaluation which integrated both the VAS scores and rescue medication consumption. Dr. Scheinbaum provides a description of this analysis on page 51 of his review. Their were no statistically significant differences between the treatment groups on any day.

Global VAS Scores for Overall Effectiveness of Study Drug:

This score was recorded in order to measure the overall effectiveness of study drug over each of the seven day double-blind treatment periods. There were no statistically significant differences between the treatments for the mean global VAS scores ($p=0.361$).

Pharmacokinetic/Pharmacodynamic [PK/PD] Evidence of Efficacy:

Data from the two controlled clinical trials described above, and from an uncontrolled clinical safety study (CBI-963), were used to perform these analyses. A total of 556 plasma oxycodone levels and 546 pain intensity measurements obtained from 261 subjects were used in the analyses. Dr. Doddapaneni provides a full description of the analysis plan and results on page 13 of his review. While a statistically significant age effect on oxycodone clearance was noted, the population PK/PD analysis was not successful.

SAFETY:

A total of 393 patients and 193 healthy subjects received oxycodone SR in the sponsor's clinical program. Dose by duration data for the patients is displayed in Dr. Scheinbaum's Table 33 on page 59 of his review. There were 1720 patient-days exposure to SR in controlled studies and 6516 patient-days exposure in the uncontrolled study. Approximately 160 patients received study drug for greater than one month. The vast majority of these patients, and the patients who received study drug for less than one month, took ≤ 200 mg of study drug per day. Only 13 patients received between 200 and 400 mg per day; and only 4 received > 400 mg per day.

Deaths:

Twelve deaths were reported from the clinical studies (see Dr. Scheinbaum's Table 36, page 62 of his review). Two of the deaths occurred in cancer patients receiving IR oxycodone in Study CBI-961/962. The first of these occurred six days after study medication was discontinued because of sepsis, hypercalcemia and neutropenia; the cause of death attributed to progression of the metastatic cancer. The second death occurred one day after discontinuation of study drug because of dyspnea due to CHF, pneumonia

and atrial fibrillation; the cause of death attributed to CHF and respiratory failure in a patient with atherosclerosis, cervical CA and lung metastases.

Two deaths occurred in patients receiving SR oxycodone in Study CBI-963. The first occurred 16 days after study medication was discontinued because of lack of efficacy; the cause of death attributed to progression of bladder cancer. The second occurred 11 days after study medication was discontinued because of an MI; the cause of death attributed to the CAD.

Eight deaths occurred in the 232 patients on SR oxycodone in the ongoing long-term compassionate use Study CBI-964. Seven of those deaths were attributed to progression of cancer. One death was attributed to an MI. The deaths occurred on study (4 patients) or on days 3, 5, 9 or 31 (1 patient each) after discontinuation of study drug. The patient whose death was attributed to an MI suffered this fatal myocardial infarction on Study Day 106.

Discontinuations:

Dr. Scheinbaum reports that three subjects, all on the IR formulation, discontinued due to adverse events in the Phase I studies. Two of the cases, nausea and rash, may have been drug related.

During the Stabilization Period of the controlled studies, Dr. Scheinbaum reports, 9/63 (14.3%) patients on IR formulation (in CBI-961/962) and 5/120 (4.2%) patients on SR formulation (in CBI-1252) discontinued due to adverse events. The most frequent complaints for the IR patients were nausea and vomiting (4 patients), dizziness (3 patients), and confusion (2 patients). The most frequent complaints for the SR patients were nausea (2 patients), dizziness (2 patients) and abdominal pain (1 patient).

During the Double-blind Period of the controlled studies 5/124 (4%) patients on IR formulation and 4/126 (3.2%) patients on SR formulation discontinued due to adverse events. Events that were considered possibly drug related included: nausea, vomiting, flu syndrome, confusion, fatigue, headache, and somnolence.

Seventeen patient on the IR formulation (Stabilization Period) and nineteen patients on the SR formulation (Treatment Period) discontinued for drug related adverse events in Study CBI-964. These events included: abnormal thinking , asthenia, dizziness, depersonalization, constipation, edema, emotional lability, hallucinations, headache, nausea, pruritis, rash, rhinorrhea, somnolence, and vomiting.

Serious Adverse Events:

Dr. Scheinbaum reports that only one patient in the controlled trials experienced a serious, non-fatal, adverse event considered to be related to study drug. This patient was

discontinued from IR oxycodone on Day 2 of the Stabilization Period due to disorientation and increased ascites.

In the open-label study, one patient experienced an altered mental status with abnormal thinking which was considered both serious and possibly drug related. However, this patient was not discontinued from treatment.

Other Adverse Events:

The most common adverse events in the healthy volunteers treated with the SR formulation were dizziness (36/193, 18.7%), nausea (36/193, 18.7%), headache (58/193, 30.1%), asthenia (54/193, 28.0%), somnolence (35/193, 18.1%), vomiting (18/193, 9.3%), and pruritis (20/193, 10.4%). Dizziness, nausea, vomiting and pruritis occurred in a greater percentage of volunteers treated with the IR formulation (48/80, 60.0%; 37/80, 46.3%; 27/80, 33.8%; and, 20/80, 25.0%, respectively).

Dr. Scheinbaum's Table 42 on page 70 of his review summarizes the overall incidences of adverse events occurring in IR and SR treated patients during the double-blind periods of trials CBI-961/962 and CBI-1252. The profiles are similar for the two groups, with the most frequent (≥ 5%) adverse events being: nausea (14%), vomiting (13%), headache (11%), diarrhea (7%), constipation (6%), dizziness (6%), somnolence (6%), pruritis (5%), and dyspepsia (5%).

The following table summarizes the incidences of the above adverse events occurring during treatment with the IR and SR formulations in trials CBI-961/962 and CBI-1252:

Table 5.

Adverse Event	Number (%) of Patients			
	Oxycodone SR (N=126)		Oxycodone IR (N=125)	
	All AE's	Drug Related AE's	All AE's	Drug Related AE's
Nausea	10 (7.9)	7 (5.6)	9 (7.2)	8 (6.4)
Vomiting	10 (7.9)	6 (4.8)	8 (6.4)	4 (3.2)
Headache	12 (9.5)	10 (7.9)	5 (4.0)	3 (2.4)
Diarrhea	8 (6.3)	3 (2.4)	1 (0.8)	0
Constipation	5 (4.0)	4 (3.2)	3 (2.4)	3 (2.4)
Dizziness	5 (4.0)	3 (2.4)	4 (3.2)	2 (1.6)
Somnolence	4 (3.2)	4 (3.2)	4 (3.2)	3 (2.4)
Pruritis	3 (2.4)	3 (2.4)	5 (4.0)	5 (4.0)
Dyspepsia	3 (2.4)	0	4 (3.2)	3 (2.4)

[based on Dr. Scheinbaum's Table 42, p. 70 of his review]

While Dr. Scheinbaum's analysis appears to support generally equivalent adverse event profiles for the SR and IR formulations, Dr. Ma performed a separate set of analyses

which paint a somewhat different picture. Dr. Ma's analyses focus on the adverse events occurring only during the double-blind treatment periods, in order to provide valid statistical results. These analyses were performed using data from the overall incidences of adverse events and/or adverse events by Body System/COSTART term rather than individual adverse events due to the small sample sizes. While the incidence of adverse events in the combined data from the double-blind periods of Studies CBI-961/962 and CBI-1252 appeared to be higher for the SR formulation than for the IR formulation, the difference was not statistically significant ($p=0.22$). However, when Dr. Ma analyzed the incidences of adverse events occurring for individual Body Systems, a notable difference was apparent. The incidence of adverse events appeared to be generally higher for the SR formulation; with the difference between the two formulations more prominent for Body Systems with relatively higher adverse event rates.

The sponsor did not directly compare the frequency of adverse events between the two formulations. Dr. Ma performed his own analyses on the data and reports his results in Tables 4.4 and 4.5 (for Studies CBI-961/962 and CBI-1252, respectively) on page 17 of his review. For Study CBI-961/962, the percentage increase in adverse event frequency from IR to SR formulation was 51%. For Study CBI-1252, the percentage increase in adverse event frequency from IR to SR formulation was 17%. For the combined data from both studies, the percentage increase in adverse event frequency from IR to SR formulation was 31%. Based on the sponsor's analysis of the incidences of adverse events occurring at different mg per kg daily doses, Dr. Ma has calculated the relative hazards of adverse events under SR vs. IR as 1.0, 1.5 and 1.7 for dose levels < 1 mg/kg, 1-2 mg/kg, and > 2 mg/kg, respectively. Dr. Ma concludes that the oxycodone SR formulation may cause an increase in incidences of common adverse events, and that this increase is more pronounced in patients already experiencing an adverse event on the IR formulation. He also concludes that the increase seen with the SR formulation may be dose related. (Of note, Dr. Scheinbaum concludes, based on the sponsor's analyses, that there was no apparent dose related increase in the incidence of adverse events with either formulation.)

Dr. Scheinbaum discusses subgroup analyses of adverse events in the controlled studies and concludes that older patients (≥ 65) and women appear more likely to report adverse events (for either formulation) than younger patients (< 65) and men, respectively. Individual adverse events are difficult to assess due to the small numbers involved. Overall, the effect of pain etiology (cancer vs. non-cancer) did not appear to result in a difference in the incidence of adverse events in either formulation. The effect of race could not be assessed due to the small numbers of non-white subjects.

Laboratory Values:

Comparisons between formulations could not be made as most patients had received both treatments prior to blood sampling. However, no significant abnormal trends were noted.

Vital Signs and ECG:

No clinically significant changes occurred in the open-label or double-blind treatment periods.

COMMENTS:

The sponsor has submitted the results of two adequate and well-controlled clinical trials. Based on these results, oxycodone SR appears to be effective in controlling chronic, moderate to severe pain. This effectiveness appears to be similar or comparable to that of oxycodone IR.

While the sponsor's evaluation of the safety data obtained during the clinical trials would indicate no difference in safety profile between the SR and IR formulations of oxycodone, the results of Dr. Ma's analyses are suggestive of an increased incidence of common adverse events in patients taking the SR formulation. This increased incidence appeared to occur predominantly in patients who had previously experienced an adverse event while on the IR formulation. The increased incidence also appeared to be dose related.

RECOMMENDATIONS:

I recommend that the NDA be approved with appropriate labeling.

Bob A. Rappaport, M.D.

October 8, 1998

Cc: Original NDA 20-932
HFD-170: Division File
HFD-170:
McCormick
Rappaport
Scheinbaum
Ma
Doddapaneni
Geyer
Maturu
McNeal

13.0 Patent Information

Reference is made to the subject NDA for oxycodone hydrochloride USP, sustained-release (Roxicodone SR™), for the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days and the requirements of 505(b)(1) of the Federal Food, Drug as Cosmetic act as amended and 21 CFR 314.50(h).

Section 355(b)(1) of the Pure Food and Drug Act requires that "The applicant shall file with the [New Drug] application the patent number and expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use or sale of the drug."

To the best of our knowledge at the time of this filing and upon information and belief, there are no patents which claim the drug or the drug product or which claim a method of using the drug product and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of Roxicodone SR™, the product that is the subject of this application and for which approval is being sought.

14.0 Patent Certification

Reference is made to the subject NDA for Roxicodone SR™ (oxycodone hydrochloride USP, sustained-release) for the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days and the requirements of 505(b)(1) of the Federal Food, Drug and Cosmetic Act as amended.

The requirements of 505(b)(1) do not mandate that Roxane Laboratories, Inc. submit a Patent Certification for Roxicodone SR™ (oxycodone hydrochloride USP, sustained-release).

EXCLUSIVITY SUMMARY for NDA # 20-932 SUPPL # NA

Trade Name: Roxicodone SR Tablets **Generic Name: oxycodone hydrochloride**

Applicant Name: Roxane Laboratories, Inc. **HFD- 170**

Approval Date: October 26, 1998

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /_X_/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_X_/

   If yes, what type? (SE1, SE2, etc.) ____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /_X_/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /_X_/ NO /__/

If yes, NDA # 20-553 Drug Name OxyContin

Note: This drug is very similar except the dosage strengths are 20, 40, and 80 mg.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-553 OxyContin (oxycodone hydrochloride) Controlled Release Tablets

NDA # 7-337 Percodan (aspirin;oxycodone hydrochloride; oxycodone terephthalate)

ANDA # 87-743 Roxiprin (aspirin;oxycodone hydrochloride; oxycodone terephthalate)

ANDA # 87-464 Codoxy (aspirin;oxycodone hydrochloride; oxycodone terephthalate)

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

NA YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # CBI-961/962

Investigation #2, Study # CBI-1252

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /_ _/	NO /_X_/
Investigation #2	YES /_ _/	NO /_X_/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA #_____ Study #_____
NDA #_____ Study #_____
NDA #_____ Study #_____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA #_____ Study #_____
NDA #_____ Study #_____
NDA #_____ Study #_____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # CBI 961/962

Investigation #2, Study # CBI-1252

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES /_X_/ NO /___/ Explain: ____

_____

Investigation #2

IND # YES /_X_/ NO /___/ Explain: ____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 NA

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

_____

/S/ Sept. 30, 1998

Signature Date

Title: Project Manager

/S/ 10/31/98

Signature of Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

16.0 Debarment Certification

A Debarment Certification as specified by the Generic Drug Enforcement Act of 1992 is provided.

Certification of Compliance with the Generic Drug Enforcement Act

In compliance with the Generic Drug Enforcement Act of 1992, Roxane Laboratories, Inc. hereby certifies that we did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [Section 306(a) or (b)] in connection with this application.

Kirk V. Shepard, M.D.
Senior Vice-President,
Marketing, Medical Affairs and Product Development

22 December 1997
Date

CERTIFICATION STATEMENT

as requested by the
Generic Drug Enforcement Act of 1992

On behalf of Covance Inc., acting as agent for Roxane Laboratories, Inc., I hereby certify that Covance did not and will not use in any capacity the services of any individual, partnership, corporation, or association debarred under subsections (a) or (b) of Section 306 of the Federal Food, Drug, and Cosmetic Act as published by the Department of Health and Human Services 19 June 1996 Debarment List in connection with New Drug Application for Roxicodone SR™ (oxycodone hydrochloride, sustained-release).

To the best of my knowledge, I am not aware of any relevant convictions of any affiliated persons responsible for the development or submission of the application.

Harris Koffer, Pharm. D.
Corporate Vice President
and General Manager,
North America

12/22/97
Date

000010A

TEAM MEETINGS FOR NDA 20-932

Meeting Dates: May 15, 1998 at 1:00PM
July 1, 1998 at 10:00AM

Location: 9B-45

Drug Name: Roxicodone SR

Sponsor: Roxane Laboratories, Inc.

Two informal meetings were held to update the team members with the progress of the application review. There were no substantial issues discussed as the reviews were going smoothly and no new information was needed from the Sponsor. The division director did not attend.

NDA 20-932
Div. Files
HFD-170/McNeal

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/ # 20-932 Supplement # NA Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-170 Trade and generic names/dosage form: Roxicodone (oxycodone hydrochloride) Sustained Release Tablets, 10mg and 30mg Action: AP

Applicant Roxane Laboratories, Inc. Therapeutic Class 3/S

Indication(s) previously approved NA
Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application: for the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

_X_ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply**, attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ Project Manager — Sept. 30, 1998

Signature of Preparer and Title — Date

cc: Orig NDA/PLA/PMA # 20-932
HFD-170/Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 9/30/98)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-932

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memo

Food and Drug Administration
Rockville MD 20857

NDA 20-932

Roxane Laboratories, Inc.
1809 Wilson Road
Columbus Ohio 43228

AUG 28 1998

Attention: Sean Alan Reade, M.A.
Director, Regulatory Affairs

Dear Mr. Reade:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Roxicodone (oxycodone hydrochloride) Sustained Release Tablets, 10mg and 30mg

Therapeutic Classification: Standard (S)

Date of Application: December 22, 1997

Date of Receipt: December 29, 1997

Our Reference Number: 20-932

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 27, 1998 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 29, 1998.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

If you have any questions, contact Bonnie McNeal, Project Manager, at (301) 443-3741.

Sincerely,

Corinne Moody
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and Addiction
Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20-932
HFD-170/Div. Files
HFD-170/B.McNeal/C.Moody
DISTRICT OFFICE

Drafted by: Bmc/August 5, 1998
Initialed by: C.Moody 8/7/98
final: B.McNeal 8/25/98
filename: N20932.ACK

ACKNOWLEDGEMENT (AC)