CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202245Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review
NDA 202245: Codeine Sulfate Oral Solution 30mg/5mL

NDA	202245	*Submission Date(s)*	September 27, 2010
Brand Name	Codeine Sulfate Oral Solution 30 mg/5mL		
Generic Name	Codeine Sulfate Oral Solution 30 mg/5mL		
Reviewer	Sheetal Agarwal, Ph.D.		
Team Leader	Yun Xu, M.D, Ph.D.		
OCP Division	Division of Clinical Pharmacology-2		
OND Division	Anesthesia, Analgesia and Abuse Products (DAAAP)		
Sponsor	Roxane Laboratories, Inc.		
Submission Type; Code	505 (b) (2)	S	
Reference	Codeine Sulfate Tablets, NDA 22-402		
Formulation; Strength(s)	Oral solution		
Indication	(b) (4) of mild to moderately severe pain		
Proposed Dosing Regimen	15 to 60 mg single doses, not to exceed 360 mg per day. Doses may be repeated up to every 4 hours as needed for pain.		

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1.0 Executive Summary

1.1 Recommendation:

The submission is acceptable from a Clinical Pharmacology perspective provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert; and a DSI audit of the data submitted for the pivotal BE study (S30-T30-PVFS), is deemed acceptable.

1.2 Phase 4 commitments:

From the Clinical Pharmacology perspective, no Phase 4 commitment is applicable to this NDA.

1.3 Summary of important Clinical Pharmacology findings:

The NDA for codeine sulfate oral solution, 30 mg/5mL, was submitted under 505(b)(2) regulations by Roxane Labs. The reference for this NDA is NDA 22-402 (codeine sulfate IR tablets) which were the first single-entity codeine product, approved by the Agency on 07/16/2009, the sponsor for which was also Roxane Labs. NDA 22-402 was also a 505(b)(2) NDA, referencing codeine in Tylenol® with codeine # 3 (ANDA 85-055). Although the sponsor did market codeine sulfate oral solution as an unapproved product previously, at the time of this review, Roxane is not currently marketing the product.

In order to be able to bridge the test product to the reference product, the Sponsor conducted a bioequivalence study linking the codeine sulfate oral solution to the codeine sulfate IR tablets. No other clinical data related to its safety and efficacy, was provided in support of this application. The codeine sulfate oral solution contains about (b) (4) sorbitol in the formulation; sorbitol is considered to interact with food and affect retention time of the drug product leading to a delay in drug absorption. However, a sorbitol concentration of 30% or higher is generally considered significant enough to have a positive interaction with food. Moreover, since the test product is BE to the reference product under fasted conditions, food effect from the codeine tablets can be extrapolated to the codeine solution. The Sponsor is relying on the existing language in the package insert of codeine sulfate IR tablets for all the other general Clinical Pharmacology aspects not specifically acquired for this product.

Study S30-T30-PVFS assessed relative bioavailability of codeine between the test (codeine sulfate oral solution, 5 mL of 30mg/5mL) and reference product (1 of 30 mg codeine sulfate IR tablet) under overnight fasting conditions in healthy volunteers, who were not naltrexone blocked. The test product was BE to the reference product with respect to codeine.

Overall, codeine sulfate oral solution 30mg/5mL is bioequivalent to the reference, codeine sulfate immediate release tablets. There are no Clinical Pharmacology related issues that preclude the approval of this product.

2. Question Based Review

2.1 General Attributes/Background:

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

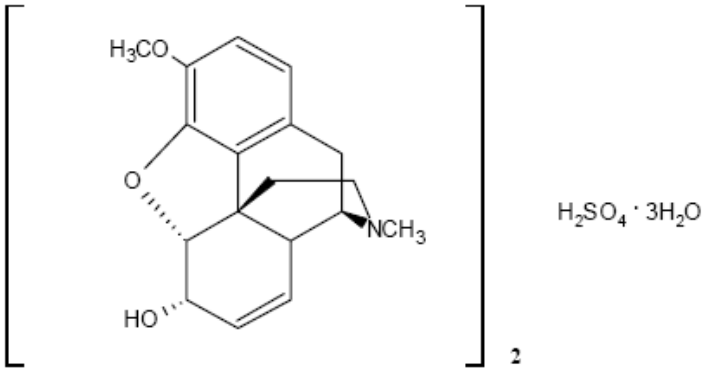
The 505(b) (2) NDA 22-402 for codeine sulfate oral solution, 30mg/5mL was submitted to the Agency on September 27, 2010. Roxane had been marketing this product as well as the now approved codeine sulfate tablet product, since the early 1980s without approved NDAs. However, the sponsor submitted an NDA for codeine sulfate oral tablets which were approved in July of 2009. As of the time of this review, the sponsor is not currently marketing the codeine sulfate oral solution in the US. There was no pre-NDA meeting that was held for this product.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Codeine Sulfate is a trihydrate crystalline powder or crystals. One gram of codeine sulfate dissolves in 30 ml water, 6.5 ml water at 80° or 1300 ml alcohol. Codeine is insoluble in chloroform or ether (Merck Index). The pka of codeine is 8.2 (Casarett & Doull, 1980).

Codeine Sulfate USP active pharmaceutical ingredient has a molecular formula of $(C_{18}H_{21}NO_3)_2 \cdot H_2SO_4 \cdot 3H_2O$ and the chemical name is Morphinan-6-ol, 7, 8-didehydro-4, 5-epoxy-3-methoxy-17-methyl-,(5α, 6α)-, sulfate (2:1) (salt), trihydrate

Chemical Structure:



2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Mechanism of Action:

Codeine sulfate is an opioid analgesic, related to morphine, but with less potent analgesic properties. Codeine is selective for the mu receptor, but with a much weaker affinity than morphine. The analgesic properties of codeine have been speculated to come from its

conversion to morphine, although the exact mechanism of analgesic action remains unknown.

Indications:

Codeine sulfate oral solution, 30mg/5mL, is indicated for the (b) (4) of mild to moderately severe pain.

2.1.4 What are the proposed dosage(s)?

Codeine sulfate oral solution, 30mg/5mL: 15 mg, 30 mg, and 60 mg.

- Usual adult dosage: 15 to 60 mg up to every 4 hours as needed not to exceed 360 mg per day.
- Doses above 60 mg may fail to give commensurate pain relief, and may be associated with an increased incidence of undesirable side effects.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

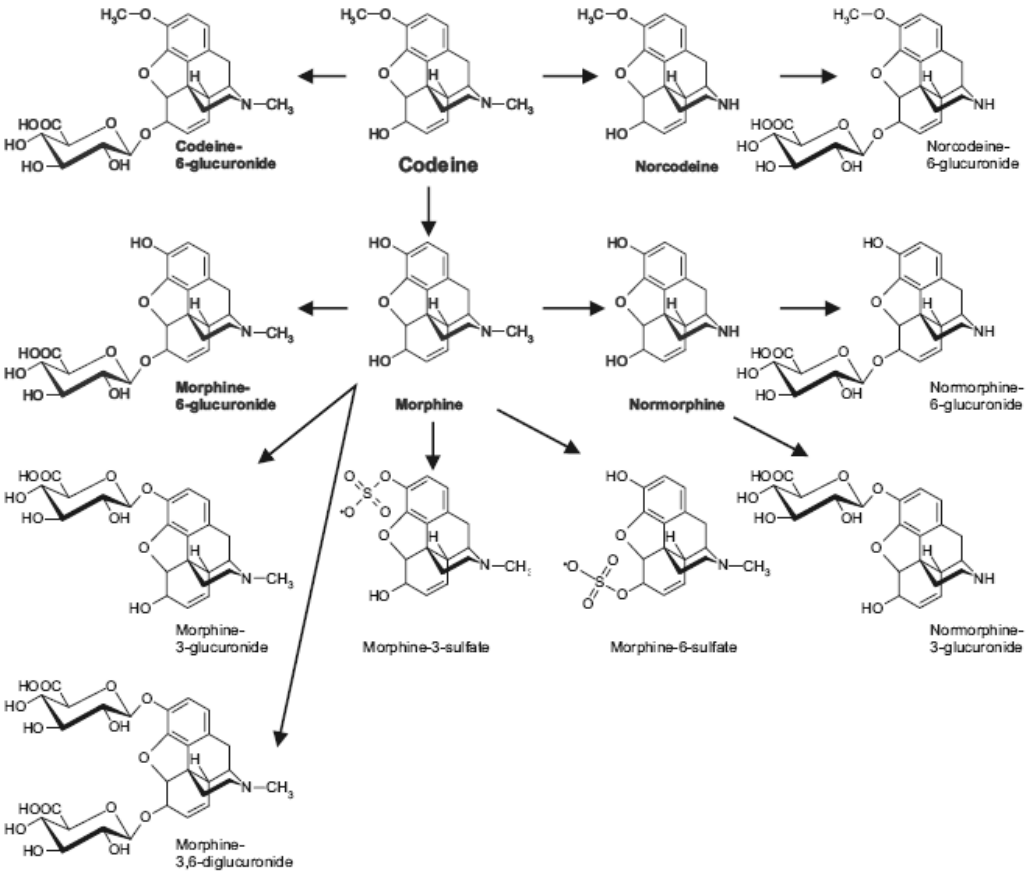
In this NDA, one pivotal BA/BE study (S30-T30-PVFS) that evaluates relative bioavailability of the proposed codeine sulfate oral solution to the approved codeine sulfate immediate release tablets was submitted. Study S30-T30-PVFS was a study designed to assess the comparative bioavailability of codeine sulfate oral solution 30 mg/5mL to codeine sulfate tablets 30 mg under fasting conditions. Thirty-six subjects were enrolled and all subjects completed both periods of the study and comprised the evaluable population for pharmacokinetics. The subjects were not naltrexone blocked.

2.2.2 What are the known PK characteristics of codeine and its metabolites?

Cytochrome P-450 2D6 is the major enzyme mediating O-demethylation of codeine to morphine. Approximately 90% of the total dose of codeine is excreted through the kidneys, of which approximately 10% is unchanged codeine. Codeine has been reported to have an apparent volume of distribution of approximately 3-6 L/kg, indicating extensive distribution of the drug into tissues. About 7-25% of codeine, reportedly, is bound to plasma proteins.

From the studies submitted in this NDA, maximum plasma concentrations of codeine are observed at about ~1 h and the half-life of codeine in plasma is about 2-4 h. Based on Clinical Pharmacology review of NDA 22-402 (Codeine Sulfate Tablets), dose proportionality was demonstrated among the three tablet strengths (15, 30 and 60 mg) under fasted condition with respect to codeine.

Codeine is metabolized by Phase 1 UGT, CYP2D6 and CYP3A4 enzymes to a variety of metabolites (Shown in schematic below).



The major metabolites of codeine are: codeine-6-glucuronide (a UGT metabolite-approximately 70-80% of administered dose), morphine (a CYP2D6 metabolite-approximately 5-10% of administered dose) and norcodeine (a CYP3A4 metabolite-approximately 10% of administered dose). Morphine is further metabolized by conjugation with glucuronic acid to morphine-3ß -glucuronide (M3G) and morphine-6ß -glucuronide (M6G).

2.3 Intrinsic factors

2.3.1 Does age, weight, race, or disease state affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

No formal studies were conducted in special populations in this NDA.

Regarding the sponsor's proposed plan to study this product in the pediatric population, Roxane Labs has requested a deferral of pediatric studies until after approval has been granted for codeine sulfate products in adult patients in accordance with 21 CFR 314.55(b) *Deferred Submission*. This pediatric deferral is requested for the following pediatric populations: infants (≥ 1 month to < 2 years), children (≥ 2 years to < 12 years) and adolescent (≥ 12 years to < 16 years). The sponsor requests deferral of all pediatric ages until after the approval has been granted for codeine sulfate oral solution, after

which, the sponsor proposes to study safety and PK of codeine sulfate in the pediatric population ≥ 2 years to < 17 years and safety, efficacy and PK in the pediatric population ≥ 1 month to < 2 years. A similar pediatric plan proposed for the earlier approved codeine sulfate tablets was reviewed and approved by the PeRC committee, based on that, the sponsor's current plan for codeine sulfate oral solution, is also expected to be acceptable.

2.5 General Biopharmaceutics

2.5.1 Is the proposed test product bioequivalent to the reference immediate release codeine sulfate tablet following single dose administration in fasting conditions?

When administered as a 30 mg dose (5 mL of 30mg/5mL, Lot # 4000060A) in the fasted state, the codeine plasma concentration-time profiles for test codeine sulfate oral solution and the reference codeine sulfate IR tablet are similar (Figure 1). The statistical analysis results for the assessment of bioequivalence between the two are presented in Table 1. Results showed that the ratio of the geometric means for log transformed Cmax and AUC values as well as its corresponding 90% confidence intervals fell within the range of 80% to 125%. PK Parameters for codeine are presented in Table 2. The Tmax values for both test and reference are similar. PK parameters and corresponding statistical analysis for the 3 metabolites that were measured, i.e morphine, M3G and M6G, were reviewed and used as supportive data only. Results showed that the ratio of the geometric means for log transformed Cmax and AUC values as well as its corresponding confidence intervals fell within the range of 80% to 125% for all the 3 metabolites (Tables 3 and 4 for morphine, 5 and 6 for M3G and 7 and 8 for M6G, respectively). It is concluded that the test codeine sulfate oral solution (30mg/5mL) is bioequivalent to the reference codeine sulfate IR tablets under fasting conditions.

Figure 1: Mean Plasma Concentrations (ng/mL) of Codeine in Fasted Healthy Volunteers (N=36) in Study S30-T30-PVFS

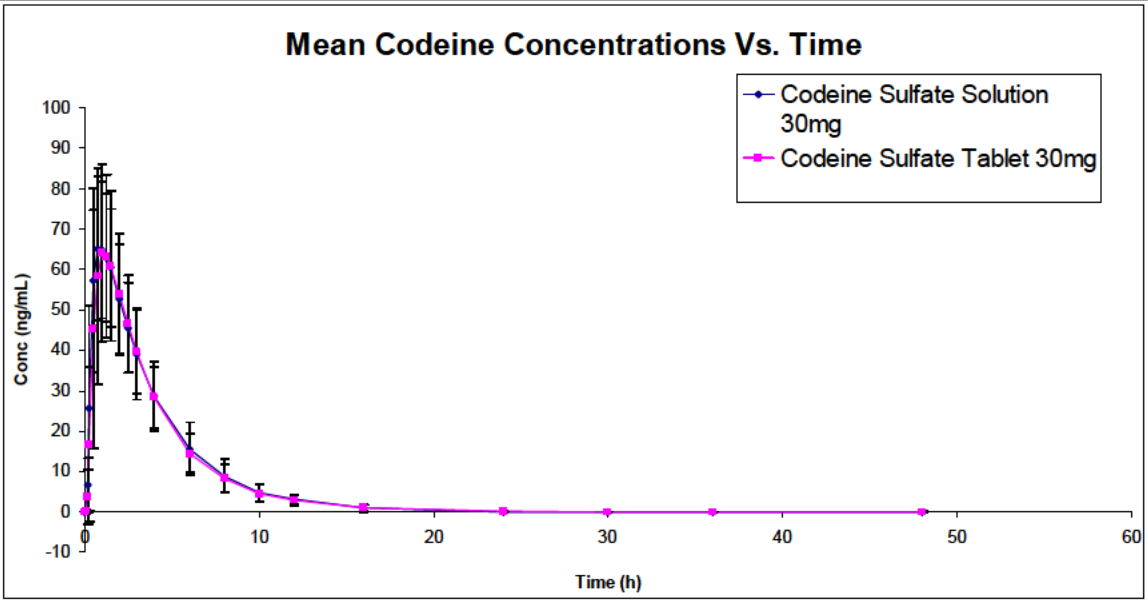


Table 1: **PK Parameters for Codeine in Study S30-T30-PVFS (N = 36)**

Parameter*	Solution 30 mg	Tablet 30 mg
Cmax (ng/mL)	74.4 ± 18.8 (36)	71.4 ± 21.2 (36)
Tmax (h)	1.00 (36) [0.25 – 2.50]	1.00 (36) [0.50 – 2.50]
AUC(0-t) (h×ng/mL)	279 ± 76.9 (36)	270 ± 76.6 (36)
AUC(inf) (h×ng/mL)	285 ± 77.1 (36)	274 ± 77.5 (35)
λz (h^{-1})	0.2826 ± 0.0343 (36)	0.2929 ± 0.0422 (35)
t½ (h)	2.49 ± 0.33 (36)	2.42 ± 0.39 (35)
Ln(Cmax)	4.28 ± 0.26 (36)	4.22 ± 0.33 (36)
Ln[AUC(0-t)]	5.60 ± 0.26 (36)	5.56 ± 0.29 (36)
Ln[AUC(inf)]	5.62 ± 0.26 (36)	5.57 ± 0.29 (35)

*Arithmetic mean ± standard deviation (N) except Tmax for which the median (N) [Range] is reported.

Table 2: **Summary of Statistical Analysis for Codeine in Study S30-T30-PVFS (N = 36)**

Parameter	Geometric Mean Ratio (%)*	
	Estimate	90% Confidence Interval
Cmax	105.98	99.29 → 113.13
AUC(0-t)	104.06	99.26 → 109.09
AUC(inf)	104.27	99.51 → 109.26

Table 3: **PK Parameters for Morphine in Study S30-T30-PVFS (N = 36)**

Parameter*	Solution 30 mg	Tablet 30 mg
Cmax (ng/mL)	2.39 ± 1.19 (34)	2.39 ± 1.57 (34)
Tmax (h)	0.50 (34) [0.25 – 3.00]	0.68 (34) [0.25 – 1.53]
AUC(0-t) (h×ng/mL)	9.37 ± 8.17 (34)	8.84 ± 6.65 (34)
AUC(inf) (h×ng/mL)	8.34 ± 6.60 (19)	8.44 ± 7.38 (18)
λz (h^{-1})	0.2375 ± 0.0974 (19)	0.2394 ± 0.0990 (18)
t½ (h)	4.12 ± 3.59 (19)	4.93 ± 6.34 (18)
Ln(Cmax)	0.74 ± 0.55 (34)	0.67 ± 0.67 (34)
Ln[AUC(0-t)]	1.92 ± 0.85 (34)	1.88 ± 0.85 (34)
Ln[AUC(inf)]	1.88 ± 0.70 (19)	1.85 ± 0.75 (18)

*Arithmetic mean ± standard deviation (N) except Tmax for which the median (N) [Range] is reported.

Table 4: **Summary of Statistical Analysis for Morphine in Study S30-T30-PVFS (N = 36)**

	Geometric Mean Ratio (%)*	
Parameter	Estimate	90% Confidence Interval
Cmax	106.77	96.27 → 118.43
AUC(0-t)	104.30	93.76 → 116.02
AUC(inf)	96.37	89.40 → 103.88

Table 5: **PK Parameters for M3G in Study S30-T30-PVFS (N = 36)**

Parameter*	Solution 30 mg	Tablet 30 mg
Cmax (ng/mL)	59.5 ± 27.8 (34)	62.5 ± 29.5 (34)
Tmax (h)	1.25 (34) [0.75 – 2.47]	1.28 (34) [0.50 – 2.00]
AUC(0-t) (h×ng/mL)	397 ± 215 (34)	404 ± 200 (34)
AUC(inf) (h×ng/mL)	455 ± 245 (26)	504 ± 204 (25)
λz (h^{-1})	0.0823 ± 0.0505 (26)	0.0703 ± 0.0307 (25)
t½ (h)	10.3 ± 3.87 (26)	11.3 ± 3.92 (25)
Ln(Cmax)	3.98 ± 0.49 (34)	4.02 ± 0.50 (34)
Ln[AUC(0-t)]	5.83 ± 0.60 (34)	5.87 ± 0.56 (34)
Ln[AUC(inf)]	5.96 ± 0.64 (26)	6.13 ± 0.45 (25)

*Arithmetic mean ± standard deviation (N) except Tmax for which the median (N) [Range] is reported.

Table 6: **Summary of Statistical Analysis for M3G in Study S30-T30-PVFS (N = 36)**

Parameter	Geometric Mean Ratio (%)*	
	Estimate	90% Confidence Interval
Cmax	95.66	90.67 → 100.92
AUC(0-t)	96.21	91.08 → 101.63
AUC(inf)	93.67	86.47 → 101.48

Table 7: **PK Parameters for M6G in Study S30-T30-PVFS (N = 36)**

Parameter*	Solution 30 mg	Tablet 30 mg
Cmax (ng/mL)	12.0 ± 5.03 (34)	12.7 ± 5.71 (34)
Tmax (h)	1.25 (34) [0.75 – 2.50]	1.28 (34) [0.75 – 2.00]
AUC(0-t) (h×ng/mL)	67.8 ± 34.2 (34)	66.7 ± 33.6 (34)
AUC(inf) (h×ng/mL)	79.0 ± 41.9 (19)	71.2 ± 32.3 (20)
λz (h^{-1})	0.1049 ± 0.0932 (19)	0.1104 ± 0.0914 (20)
t½ (h)	10.0 ± 5.34 (19)	9.75 ± 6.59 (20)
Ln(Cmax)	2.39 ± 0.47 (34)	2.44 ± 0.47 (34)
Ln[AUC(0-t)]	4.06 ± 0.62 (34)	4.06 ± 0.58 (34)
Ln[AUC(inf)]	4.18 ± 0.70 (19)	4.13 ± 0.61 (20)

*Arithmetic mean ± standard deviation (N) except Tmax for which the median (N) [Range] is reported.

Table 8: **Summary of Statistical Analysis for M6G in Study S30-T30-PVFS (N = 36)**

Parameter	Geometric Mean Ratio (%)*	
	Estimate	90% Confidence Interval
Cmax	95.73	90.64 → 101.11
AUC(0-t)	100.60	95.41 → 106.08
AUC(inf)	105.05	95.85 → 115.13

2.6 Analytical Section

Plasma concentrations of codeine, morphine, morphine-3ß -glucuronide (M3G), and morphine-6ß -glucuronide (M6G) were measured using an LC/MS/MS method validated under Project QJV and protocol # CODE-S30-T30-PVFS-1 by (b) (4) The method is applicable for the quantitation of codeine within the nominal range of 1.00 to 100 ng/mL, morphine within the nominal range of 0.200 to 20.0 ng/mL, morphine-3ß-glucuronide (M3G) within the nominal range of 2.00 to 200 ng/mL, and morphine- 6ß-glucuronide (M6G) within the nominal range of 0.500 to 50.0 ng/mL from a 250-µL human plasma aliquot, containing sodium heparin. Overall, the assay validation data are satisfactory. A DSI consult for inspection of the data submitted for the pivotal BE study (S30-T30-PVFS) was requested on December 13, 2010 and the result is still pending.

Table 9: **Inter- and Intra- Assay Precision and Accuracy**

Analyte	Inter-Assay		Intra-Assay	
	Precision (% CV)	**Accuracy (% diff from theoretical)**	**Precision (%)**	**Accuracy (%)**
Codeine	2.14-2.53	-0.684-0.694	0.828-4.92	-2.59-2.68
Morphine	1.96-13	-0.999-1.70	1.18-12.8	-9.23-3.29
Morphine-3ß-glucuronide	2.45-5.39	0.368-2.74	1.40-8.43	-5.16-2.31
Morphine-6ß-glucuronide	3.58-5.78	0.267-2.79	1.50-10.7	-4.60-5.88

15 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2 Individual Study Reviews:

4.2.1. Synopsis: Study CODE-S30-T30-PVFS-1

Name of Sponsor/Company: Roxane Laboratories, Inc. Name of Finished Product: Codeine sulfate Name of Active Ingredient: Codeine sulfate	Individual Study Table Referring to Part of the Dossier: Volume: Page:	*(For National Authority Use Only)*
Title of Study:	A Single Dose, Two-Period, Two-Treatment, Two-Way Crossover Comparative Bioavailability Study of Codeine Sulfate Oral Solution and Tablets Under Fasted Conditions	
Investigators:	Mark T. Leibowitz, M.D.; Majin Miguel Castillo, M.D., MBA, Cynthia A. Zamora, M.D., Steven Hinitt, M.D., MPH, MPA; Nancy K. Hinitt, M.D.; Joe H. Juren, M.D., Mary C. Clarke, MSN, FNP-BC	
Study Center(s):	CEDRA Clinical Research, LLC, 2455 N.E. Loop 410, Suite 150, San Antonio, Texas 78217	
Publication:	None	
Study Period (days): 9	Phase of Development: I	
Objectives: The objective of this pivotal study was to assess the comparative bioavailability of Roxane Laboratories' codeine sulfate 30 mg/5mL oral solution to codeine sulfate 30 mg tablets under fasted conditions.		
Study Methodology: This was an open-label, randomized, 2-treatment, 2-period, 2-sequence crossover study to evaluate the bioequivalence of Roxane Laboratories' codeine sulfate 30 mg/5mL oral solution to codeine sulfate 30 mg tablets.		
Number of Subjects Planned: 36	Enrolled: 36	Analyzed: To be completed by (b) (4)
Diagnosis and Criteria for Inclusion: Healthy adult male or female volunteers, 18-45 years of age (inclusive), Body Mass Index (BMI) between 18 and 30 kg/m² (inclusive)		
Test Product, Dose and Mode of Administration, Lot Number: Codeine sulfate (1 x 30 mg/5 mL oral solution) Lot: 4000060A		
Duration of Treatment: Two single-dose treatments were administered with a 7-day washout period between doses.		

Name of Sponsor/Company: Roxane Laboratories, Inc. Name of Finished Product: Codeine sulfate Name of Active Ingredient: Codeine sulfate	Individual Study Table Referring to Part of the Dossier: Volume: Page:	*(For National Authority Use Only)*
Reference Product, Dose, and Mode of Administration, Lot Number: Codeine sulfate (1 x 30 mg tablet) Lot: 957856A		
Criteria for Evaluation: Efficacy: No efficacy evaluations were performed in this study. Safety: The Investigator assessed safety using the following parameters: physical examinations, vital signs, clinical laboratory evaluations, ECGs, and reported or observed adverse events.		
Statistical Methods: The following was excerpted from Section 10.3 of the protocol: Comparison of the pharmacokinetic parameters C_{max}, $AUC_{(0-t)}$ and $AUC_{(inf)}$ for codeine, morphine, M3G, and M6G with respect to the test (oral solution) and reference (tablet) will be done using an analysis of variance (ANOVA) model with sequence, subject within sequence, treatment, and period as the classification variables, using the natural logarithms of the data. Confidence intervals (90%) will be constructed for the treatment ratios (test to reference) of all three parameters using the log-transformed data and the two one-sided t-tests procedure. The point estimates and confidence limits will be exponentiated back to the original scale.		

Name of Sponsor/Company: Roxane Laboratories, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Codeine sulfate		
Name of Active Ingredient: Codeine sulfate		

SUMMARY - CONCLUSIONS

SAFETY RESULTS:

A total of 34 AEs were reported by 16 of the 36 subjects over the course of the study. All 34 were reported following dose administration; there were no AEs reported prior to dose administration.

Twenty-six (26) of the 34 AEs were mild and 8 were moderate. Twelve (12) of the AEs were probably related, 11 were possibly related, and the remaining 11 were unrelated to the study treatment.

The most commonly reported AEs were headache (n=5; 2 following Treatment A and 3 following Treatment B), nausea (n=5; 2 following Treatment A and 3 following Treatment B), dizziness (n=4; 2 following Treatment A and 2 following Treatment B), and somnolence (n=4; 2 following Treatment A and 2 following Treatment B).

In total, 16 AEs were reported following Treatment A and 18 following Treatment B. None of AEs were related to abnormal laboratory evaluations. Subject 105 had a clinically significant AE of mild hypotension after Treatment B in Period 2, which was assessed as possibly associated with the study drug. There were no other clinically significant abnormalities in vital signs. Subject 106 had a clinically significant AE of a mild bruise on left arm at the discharge physical examination, which was assessed as unrelated to the study drug. No other clinically significant abnormalities in physical exams were observed.

Please refer to Table 14.3.1 for more detailed data regarding the relationships between observed AEs and the relative study treatment.

PHARMACOKINETIC RESULTS:

To be completed by [redacted] (b) (4)

CONCLUSIONS:

A total of 36 subjects participated in the study with all 36 completing both study periods.

There were no unusual or unexpected adverse events related to the study medication. Study exit clinical laboratory and ECG evaluations were completed with no clinically significant findings. Subject 106 had a clinically significant AE of a mild bruise on left arm at the discharge physical examination, which was assessed as unrelated to the study drug. No other clinically significant abnormalities in physical exams were observed.

Date of Report: 29 April 2010

Amendment Date: 05 May 2010

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHEETAL S AGARWAL
06/02/2011

YUN XU
06/02/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 870)** **Tracking/Action Sheet for Formal/Informal Consults**

From: Zhihong Li, Ph.D.			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: 12/02/2010	IND No.: Serial No.:	NDA No. **202245**	DATE OF DOCUMENT 9/27/2010	
NAME OF DRUG **Codeine Sulfate Oral Solution**	PRIORITY CONSIDERATION **Standard**		Date of informal/Formal Consult: 9/27/2010	

NAME OF THE SPONSOR: **[** Roxane Laboratories, Inc. **]**

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☒ OTHER *(SPECIFY BELOW):* [Filing Meeting]
☐ PHASE IV RELATED		

REVIEW ACTION

☒ NAI (No action indicated)	☐ Oral communication with Name: [ ]	☐ Formal Review/Memo (attached)
☐ E-mail comments to:	☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☐ See comments below
☐Medical ☐Chemist ☐Pharm-Tox ☐Micro ☐Pharmacometrics ☐Others (Check as appropriate and attach e-mail)		☐ See submission cover letter
		☐ OTHER *(SPECIFY BELOW)*:

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

RECOMMENDATIONS:

This NDA application is fileable from a clinical pharmacology perspective.

BACKGROUND:

In accordance with 21 CFR 3 14.50, Roxane Laboratories, Inc. submitted a 505(b)(2) New Drug Application (NDA) for Codeine Sulfate Oral Solution 30mg/5mL. The intended indication is mild to moderately severe pain. The Reference Listed Drug is Codeine Sulfate Tablets (NDA 22-402) from the same sponsor, which was approved on July 16, 2009. One pivotal bioequivalence study to bridge the oral solution formulation and the codeine sulfate tablets was submitted.

The Clinical/Clinical Pharmacology database contains a single pivotal BE study (CODE-S30-T30-PVFS-1). The sponsor requests deferral of pediatric studies for the age groups of Infant (1 month to 2 years), Children (2 to 12 years) and Adolescent (12 years to < 16 years). Data from study CODE-S30-T30-PVFS-1 meets the regulatory requirements

for filing and as such this application is fileable from a clinical pharmacology perspective. Since study CODE-S30-T30-PVFS-1 is a pivotal BE study, this study will be inspected by DSI. Filing meeting was held on 11/09/10. From a Clinical Pharmacology, mid cycle deliverables will consist of the BE assessment of study CODE-S30-T30-PVFS-1. The Clinical Pharmacology filing check list is attached on page 3 of this document.	
SIGNATURE OF REVIEWER: Zhihong Li, Ph.D. **SIGNATURE OF TEAM LEADER: Suresh Doddapaneni, Ph.D.**	Date: 12/02/2010 Date: 12/02/2010
CC.: HFD # [ ]; TL: [ ]	**Project Manager: Date:**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**NDA 202245**	**Brand Name**	**NA**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Codeine sulfate oral solution**
Medical Division	**DAAP**	**Drug Class**	**Opiate**
OCP Reviewer	**Zhihong Li**	**Indication(s)**	**Mild to moderately severe pain**
OCP Team Leader	**Suresh Doddapaneni**	**Dosage Form**	**Oral solution**
Pharmacometrics Reviewer	**N/A**	**Dosing Regimen**	**Titration**
Date of Submission	**9/27/2010**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**3/27/2010**	**Sponsor**	**Roxane Laboratories, Inc**
Medical Division Due Date		**Priority Classification**	**Standard**
PDUFA Due Date	**7/27/2011**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				

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Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	**X**	**1**		
traditional design; single / multi dose:		**1**		
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan		**1**		
Literature References				
Total Number of Studies		**2**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the			X	

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	appropriate format?				
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

Zhihong Li, Ph.D. 12/02/2010
Reviewing Clinical Pharmacologist Date

Suresh Doddapaneni, Ph.D. 12/02/2009
Team Leader/Supervisor Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZHIHONG LI
12/06/2010

SURESH DODDAPANENI
12/06/2010