

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-402

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

Clinical Pharmacology Review

<i>NDA</i>	22-402	<i>Submission Date(s)</i>	July 2, 2008
<i>Brand Name</i>	Codeine Sulfate Tablets, USP		
<i>Generic Name</i>	Codeine Sulfate Tablets		
<i>Reviewer</i>	Sheetal Agarwal, Ph.D.		
<i>Team Leader</i>	Suresh Doddapaneni, Ph.D.		
<i>OCP Division</i>	Division of Clinical Pharmacology-2		
<i>OND Division</i>	Anesthesia, Analgesia, and Rheumatology Products		
<i>Sponsor</i>	Roxane Laboratories, Inc.		
<i>Submission Type; Code</i>	505 (b) (2)		S
<i>Formulation; Strength(s)</i>	Immediate-release oral tablets, 15 mg, 30 mg and 60 mg		
<i>Indication</i>	Relief of mild to moderately severe pain		
<i>Proposed Dosing Regimen</i>	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 and Biopharmaceutics perspective provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

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 tablets (15, 30 and 60 mg) immediate release tablets was submitted under 505(b)(2) regulations. These tablets have been marketed as unapproved products by the sponsor since 1980s under the brand name Codeine Sulfate (Immediate Release) Tablets.

Through the 505 (b) (2) route, the sponsor is relying on Agency's previous findings of safety and efficacy of codeine in Tylenol® with codeine # 3 (ANDA 85-055) containing 30 mg of codeine phosphate. Sponsor conducted a bioequivalence study linking the codeine sulfate tablets and codeine in Tylenol® with codeine # 3. In addition, data from four other Clinical Pharmacology studies assessing dose proportionality, dosage form proportionality, steady state pharmacokinetics and food effect were submitted. Several related published articles were also submitted. No new information related to special populations such as hepatic and renal impairment was submitted by the sponsor. Instead, sponsor is relying on the existing language in the package insert of Tylenol® with codeine # 3 for all other Clinical Pharmacology aspects not specifically acquired for this product.

No new Clinical safety and efficacy studies were conducted in support of this NDA. However, to support the efficacy of their product, the sponsor has extracted data from published randomized, controlled clinical trials during the time period of 1960-2007. The clinical review team identified six published articles from a total of 159 articles submitted as specifically supportive of efficacy of codeine sulfate tablets for the proposed indication. These include three major clinical trials, Study #20 (30 mg codeine, single-dose), Study #69 (60 mg codeine, single-dose) and Study #56 (60 mg codeine, multiple-dose) and three supportive clinical trials Study #78 (30 mg codeine [single-dose] and 60 mg codeine [multiple-dose]), Study #24 (60 mg codeine, multiple-dose) and Study #65 (65 mg codeine, multiple-dose).

A brief summary of the assessment of the above mentioned clinical trials from the Clinical review is extracted and shown below (See Clinical review dated 12/22/08 by Dr. Carolyn Yancey):

“The pain models, patient populations, and study designs across the three major clinical trials include: a randomized, double-blind, placebo-controlled, single-dose trial with 30 mg codeine in patients with episiotomy pain (Study #20); a randomized, double-blind, placebo-controlled, single-dose, 60 mg codeine trial in post oral surgery patients (Study #69); and a randomized, double-blind, placebo-controlled, multiple-dose trial with 60 mg codeine in post oral surgery patients (Study #56). In the supportive clinical trials, the pain models, patient populations, and study designs include: a randomized, double-blind, placebo-controlled, crossover trial with 30 mg codeine (single-dose phase) and 60 mg codeine (multiple-dose phase) in patients with diverse chronic pain conditions (Study #78); a randomized, double-blind, placebo-controlled, multiple-dose trial with 60 mg codeine in patients with episiotomy (Study #24); and a randomized, double-blind, placebo controlled, crossover trial with 65 mg codeine in post orthopedic surgery patients.

The efficacy endpoints included standard measures of patient reported pain assessment including pain intensity (0-100 mm on a visual analogue scale/VAS), pain intensity difference (PID), the largest PID (PEAKPID) score, and the sum of pain intensity (SPID), as well as pain relief, total pain relief (TOPAR), and the largest pain relief (PEAKREL) score, and the time to remedication in the multiple-dose trials. In each of the individual trials reviewed, codeine demonstrated superiority over placebo in relieving mild to moderately severe pain. The well-known placebo effect reported in analgesia clinical trials was also reported in several of these trials, specifically, in the post oral surgery pain populations.”

The following are the brief study designs and summary of the five Clinical Pharmacology and Biopharmaceutics studies conducted by the sponsor:

1.3.1. Study Designs:

Study CODE-T15-30-60-PVFS-1: Dose Proportionality Study

This is a single-dose, 3-period, 3-treatment, 6-sequence, 3-way crossover study of the dose linearity of codeine sulfate tablets under fasting conditions.

Study CODE- T60-PVFS/FD-1: Food Effect Study

This is a single-dose, open-label, randomized, 2-treatment, 2-period, crossover study to evaluate the effect of food on the absorption of codeine from Roxane Laboratories' codeine sulfate 60 mg tablets.

Study CODE-T15-PVFS-1: Steady State Study

This is a steady state, 1-period, 1-treatment study of codeine sulfate 15 mg tablets under steady state conditions to characterize the steady-state pharmacokinetics of codeine and its metabolites morphine, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G) after oral administration of codeine sulfate tablets administered at a dose of 15 mg Q4H x 5 days.

Study CODE-T30-PVFS-1: Comparative Bioavailability Study

This is a single-Dose, 2-period, 2-treatment, 2-way crossover comparative bioavailability study of codeine 30 mg tablets and Tylenol® #3 tablets under fasting conditions.

Study CODE-T60-PLFS-1: Comparative Bioavailability Study of Codeine Sulfate Tablet Formulations Under Fasted Conditions

This is a single dose, 3-period, 3-treatment, 6-sequence crossover pharmacokinetic and comparative bioavailability study of codeine sulfate tablet formulations under fasted conditions.

1.3.2 Summary of Results:

In all these studies the plasma concentrations of the parent drug morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) metabolites were measured.

1.3.2.1 Dose Linearity

Study CODE-T15-30-60-PVFS-1 examined the dose linearity of 15 mg, 30 mg, and 60 mg codeine sulfate tablets under fasted conditions.

Mean plasma concentrations of codeine after administration of codeine as 1 x 15 mg, 1 x 30 mg, and 1 x 60 mg tablets increased in proportion to the increase in dose. Mean values for C_{max}, AUC(0-t) and AUC(inf) also increased in proportion to dose (Table 1.3.2.1.1). The associated 90% confidence intervals for all comparisons among tablet strengths were within the 80% to 125% equivalence window (Table 1.3.2.1.2), demonstrating dose proportionality among the three tablet strengths with respect to codeine. The linearity is further illustrated in Figure 1.3.2.1.3 (log-log plots of the mean C_{max} and AUC(inf) versus dose).

Table 1.3.2.1.1: Summary of pharmacokinetic parameters for codeine after oral administration of 1 x 15 mg, 1 x 30 mg and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fasted conditions.

Parameter ¹	1 x 15 mg	1 x 30 mg	1 x 60 mg
C _{max} (ng/mL)	38.5 ± 14.5 (33)	81.2 ± 27.3 (34)	167 ± 46.9 (34)
T _{max} (h)	1.25 (33) [0.50 - 2.00]	1.01 (34) [0.50 - 2.50]	1.00 (34) [0.50 - 1.50]
AUC(0-t) (h·ng/mL)	149 ± 44.9 (33)	308 ± 93.3 (34)	653 ± 172 (34)
AUC(inf) (h·ng/mL)	154 ± 45.1 (33)	313 ± 95.3 (33)	654 ± 156 (32)
λ _z (h ⁻¹)	0.2761 ± 0.0369 (33)	0.2580 ± 0.0329 (33)	0.2041 ± 0.0634 (32)
t _{1/2} (h)	2.55 ± 0.34 (33)	2.73 ± 0.40 (33)	3.76 ± 1.26 (32)
Ln(C _{max})	3.59 ± 0.34 (33)	4.34 ± 0.34 (34)	5.08 ± 0.29 (34)
Ln[AUC(0-t)]	4.96 ± 0.30 (33)	5.69 ± 0.30 (34)	6.45 ± 0.26 (34)
Ln[AUC(inf)]	5.00 ± 0.29 (33)	5.70 ± 0.30 (33)	6.45 ± 0.24 (32)

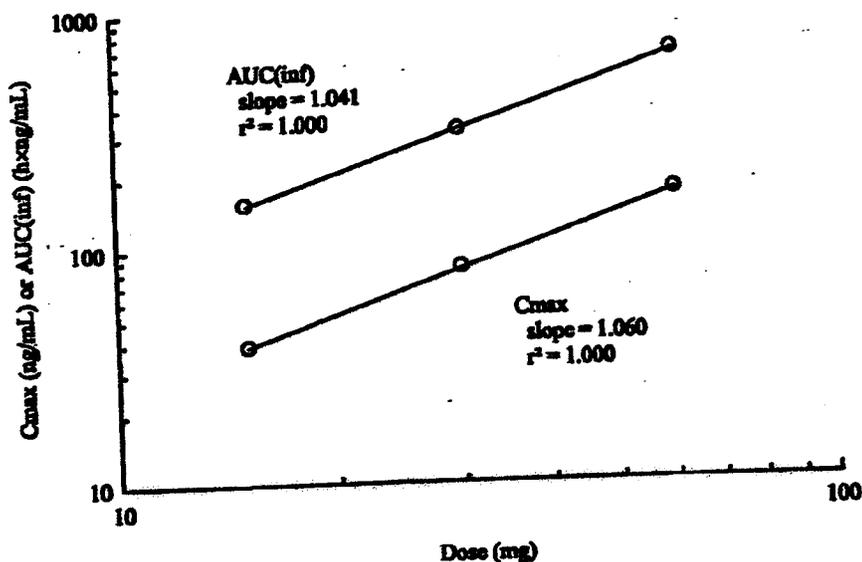
¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Table 1.3.2.1.2: Statistical comparison of pharmacokinetic parameters for codeine after oral administration of 1 x 15 mg, 1 x 30 mg and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fasted conditions.

Parameter	Geometric Mean Ratio (%) ¹			Within Subject CV (%)
	Estimate	90% Confidence Interval		
1 x 15 mg vs. 1 x 30 mg				
C _{max}	95.04	88.28	→ 102.32	18.14
AUC(0-t)	96.51	92.02	→ 101.23	11.66
AUC(inf)	98.38	93.76	→ 103.23	11.62
1 x 15 mg vs. 1 x 60 mg				
C _{max}	90.88	84.42	→ 97.84	18.14
AUC(0-t)	89.93	85.75	→ 94.32	11.66
AUC(inf)	92.58	88.19	→ 97.18	11.62
1 x 30 mg vs. 1 x 60 mg				
C _{max}	95.62	88.90	→ 102.85	18.14
AUC(0-t)	93.18	88.90	→ 97.67	11.66
AUC(inf)	94.10	89.63	→ 98.79	11.62

¹Based on analysis of natural log-transformed data after normalization to the 30 mg dose.

Figure 1.3.2.1.3: Relationships between the mean C_{max} and AUC(inf) of codeine and the dose of codeine after oral administration of 1 x 15 mg, 1 x 30 mg and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fasted conditions.



Further, the increases in C_{max}, AUC(0-t), and AUC(inf) after oral administration of 1 x 15 mg, 1 x 30 mg, and 1 x 60 mg doses of Roxane Laboratories' codeine tablets were dose linear with respect to the other two metabolites measured, morphine and M6G.

1.3.2.2 Food Effect

Study CODE- T60-PVFS/FD-1 assessed the effect of food on the absorption of codeine from a 60 mg codeine sulfate tablet employing the Agency recommended high-fat breakfast.

Mean plasma concentrations of codeine after administration of Roxane Laboratories' Codeine Sulfate 60 mg tablet were comparable after administration under fed and fasted conditions. There was a 50% increase in the median T_{max}, from 1.00 h to 1.54 h (Table 1.3.2.2.1), and an 11% decrease in C_{max}, suggesting a slight decrease in the rate of absorption under fed conditions. However, the 90% confidence intervals for C_{max}, AUC(0-t), and AUC(inf) were within the 80% to 125% equivalence window (Table 1.3.2.2.2), demonstrating no effect of food on the bioavailability with respect to codeine.

Table 1.3.2.2.1.: Summary of pharmacokinetic parameters for codeine after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 60 mg to healthy volunteers under fed and fasted conditions.

Parameter ¹	Fasted	Fed
C _{max} (ng/mL)	167 ± 54.0 (36)	149 ± 49.2 (36)
T _{max} (h)	1.00 (36) [0.50 – 2.50]	1.54 (36) [0.25 – 4.00]
AUC(0-t) (h×ng/mL)	629 ± 175 (36)	711 ± 211 (36)
AUC(inf) (h×ng/mL)	639 ± 175 (36)	720 ± 212 (36)
λ _z (h ⁻¹)	0.2163 ± 0.0490 (36)	0.2174 ± 0.0436 (36)
t _{1/2} (h)	3.41 ± 0.93 (36)	3.33 ± 0.75 (36)
Ln(C _{max})	5.06 ± 0.35 (36)	4.95 ± 0.36 (36)
Ln[AUC(0-t)]	6.41 ± 0.28 (36)	6.52 ± 0.32 (36)
Ln[AUC(inf)]	6.42 ± 0.27 (36)	6.53 ± 0.31 (36)

¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Table 1.3.2.2.2.: Statistical comparison of pharmacokinetic parameters for codeine after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 60 mg to healthy volunteers under fed and fasted conditions.

Parameter	Geometric Mean Ratio (%) ¹		
	Estimate	90% Confidence Interval	
C _{max}	89.34	81.18	→ 98.31
AUC(0-t)	111.98	105.27	→ 119.12
AUC(inf)	111.83	105.20	→ 118.86

¹Based on analysis of natural log-transformed data.

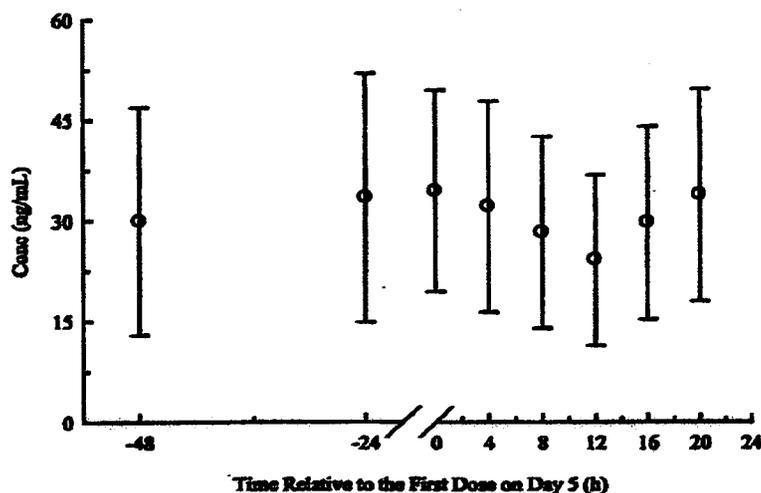
1.3.2.3 Multiple-Dose Pharmacokinetics

Study CODE-T15-PVFS-1 characterized the steady-state pharmacokinetics of codeine and its metabolites morphine, M3G, and M6G after oral administration of Roxane Laboratories' codeine sulfate tablets administered at a dose of 15 mg Q4H x 5 days.

1.3.2.3.1 Attainment of Steady State

The mean pre-dose plasma concentrations for all the four moieties measured were relatively constant from Day 3 - 48 hours after beginning dosing and 48 hours prior to the steady-state day - through the last dose on Day 5 (Figure 1.3.2.3.1.1). This indicates that steady-state had been reached by Day 3.

Figure 1.3.2.3.1.1.: Mean ± standard deviation pre-dose plasma concentrations of codeine during oral administration of Roxane Laboratories' 15 mg codeine sulfate tablets Q4H x 5 days tablets to healthy volunteers.



1.3.2.3.2 Pharmacokinetics at Steady State

The mean plasma concentration-time profiles for all the four moieties measured were relatively consistent across the six doses administered on Day 5 (Table 1.3.2.3.2.1)

Table 1.3.2.3.2.1...: Summary of C_{max}, T_{max}, and AUC (0-4) for codeine, morphine, M3G, and M6G for individual doses on Day 5 during oral administration of Roxane Laboratories' 15 mg codeine sulfate tablets Q4H x 5 days tablets to healthy volunteers.

Parameter ¹	Codeine	Morphine	M3G	M6G
First Dose				
C _{max} (ng/mL)	68.3 ± 27.8 (32)	1.90 ± 1.08 (32)	51.2 ± 25.2 (32)	9.45 ± 4.33 (32)
T _{max} (h) ²	1.5 (32)	1.3 (32)	1.5 (32)	1.5 (32)
AUC (h×ng/mL)	216 ± 88.3 (32)	216.38 ± 3.93 (32)	216 ± 101 (32)	216.4 ± 16.3 (32)
Second Dose				
C _{max} (ng/mL)	70.2 ± 27.7 (32)	2.03 ± 1.33 (32)	50.8 ± 26.1 (32)	9.19 ± 4.43 (32)
T _{max} (h) ²	5.0 (32)	4.5 (32)	5.0 (32)	5.0 (32)
AUC (h×ng/mL)	184 ± 76.2 (32)	4.90 ± 3.16 (32)	165 ± 85.7 (32)	29.9 ± 14.7 (32)
Third Dose				
C _{max} (ng/mL)	55.6 ± 22.9 (32)	1.76 ± 1.01 (32)	53.2 ± 27.2 (32)	10.5 ± 5.27 (32)
T _{max} (h) ²	9.0 (32)	8.5 (32)	9.0 (32)	9.5 (32)
AUC (h×ng/mL)	156 ± 72.7 (32)	5.07 ± 3.27 (32)	171 ± 89.2 (32)	32.3 ± 16.3 (32)
Fourth Dose				
C _{max} (ng/mL)	53.9 ± 24.0 (32)	1.71 ± 1.19 (32)	49.1 ± 25.4 (32)	9.53 ± 4.78 (32)
T _{max} (h) ²	13.5 (32)	13.5 (32)	14.0 (32)	14.0 (32)
AUC (h×ng/mL)	154 ± 70.9 (32)	5.36 ± 3.63 (32)	165 ± 86.6 (32)	31.0 ± 15.6 (32)
Fifth Dose				
C _{max} (ng/mL)	51.2 ± 15.9 (32)	1.86 ± 1.21 (32)	53.0 ± 26.9 (32)	10.2 ± 4.88 (32)
T _{max} (h) ²	17.5 (32)	17.3 (32)	17.5 (32)	17.5 (32)
AUC (h×ng/mL)	164 ± 59.1 (32)	6.10 ± 3.99 (32)	181 ± 95.7 (32)	34.1 ± 17.2 (32)
Sixth Dose				
C _{max} (ng/mL)	62.3 ± 28.0 (32)	2.28 ± 1.44 (32)	57.3 ± 30.3 (32)	10.8 ± 5.39 (32)
T _{max} (h) ²	21.5 (32)	20.5 (32)	21.3 (32)	21.5 (32)
AUC (h×ng/mL)	191 ± 87.1 (32)	6.91 ± 4.36 (32)	192 ± 103 (32)	35.2 ± 17.5 (32)

¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

²T_{max} relative to the first dose on Day 5.

1.3.2.4 Relative Bioavailability

Study CODE-T30-PVFS-1 assessed relative bioavailability of codeine from codeine sulfate 30 mg tablets to reference product Tylenol® #3 (acetaminophen 300 mg with codeine phosphate 30 mg) under fasted conditions.

Difference in Base Content of Codeine:

Roxane Laboratories' Codeine Sulfate 30 mg tablet contains _____ of codeine base b(4)

while Tylenol® #3, with 30 mg of Codeine Phosphate, contains _____, of codeine base. This difference, approximately _____, was not taken into account in the statistical comparisons conducted by the sponsor.

b(4)

Mean plasma concentrations of codeine after administration of Roxane Laboratories' Codeine Sulfate 30 mg tablet and Tylenol® #3 (Codeine Phosphate 30 mg) were essentially super imposable despite the _____ difference in base content. Mean values for all pharmacokinetic parameters were comparable for both formulations with geometric mean ratios for C_{max}, AUC(0-t), and AUC(inf) of approximately 100% (Table 1.3.2.4.2). All of the associated 90% confidence intervals were within the 80% to 125% equivalence window (Table 1.3.2.4.2), demonstrating bioequivalence between products with respect to codeine. After inspection, Division of Scientific Investigations in their final assessment recommended that the study results can be accepted.

b(4)

Table 1.3.2.4.1.: Summary of pharmacokinetic parameters for codeine after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 30 mg and Tylenol® #3 (Codeine Phosphate 30 mg) to healthy volunteers under fasted conditions.

Parameter ¹	Roxane 30 mg	Tylenol #3
C _{max} (ng/mL)	71.2 ± 23.9 (34)	70.1 ± 21.9 (36)
T _{max} (h)	1.25 (34) [0.50 – 2.50]	1.25 (36) [0.50 – 3.00]
AUC(0-t) (h×ng/mL)	282 ± 98.0 (34)	272 ± 84.8 (36)
AUC(inf) (h×ng/mL)	289 ± 98.6 (34)	279 ± 86.3 (36)
λ _z (h ⁻¹)	0.2580 ± 0.0448 (34)	0.2620 ± 0.0419 (36)
t _{1/2} (h)	2.77 ± 0.51 (34)	2.71 ± 0.43 (36)
Ln(C _{max})	4.21 ± 0.34 (34)	4.20 ± 0.31 (36)
Ln[AUC(0-t)]	5.58 ± 0.35 (34)	5.56 ± 0.31 (36)
Ln[AUC(inf)]	5.61 ± 0.34 (34)	5.59 ± 0.30 (36)

¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Table 1.3.2.4.2.: Statistical comparison of pharmacokinetic parameters for codeine after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 30 mg and Tylenol® #3 (Codeine Phosphate 30 mg) to healthy volunteers under fasted conditions.

Parameter	Geometric Mean Ratio (%) ¹	
	Estimate	90% Confidence Interval
C _{max}	100.80	94.06 → 108.02
AUC(0-t)	103.13	98.29 → 108.21
AUC(inf)	102.80	98.11 → 107.72

¹Based on analysis of natural log-transformed data.

1.3.2.5 Dosage Form Bioequivalence

Study CODE-T60-PLFS-1 assessed the comparative bioavailability of Roxane Laboratories' codeine sulfate tablets after oral administration of 60 mg doses as 1 x 60 mg, 2 x 30 mg and 4 x 15 mg under fasted conditions. Study CODE-T60-PLFS-1 is also considered to be developmental because an additional objective of this study was to optimize the study design for a pivotal relative bioavailability study of the relative bioavailability of the three tablet strengths.

Mean plasma concentrations of codeine after administration of 60 mg of codeine as 1 x 60 mg, 2 x 30 mg, and 4 x 15 mg tablets were essentially super imposable. Mean values for all pharmacokinetic parameters were comparable for all three treatments (Table 1.3.2.5.1) with geometric mean ratios for C_{max}, AUC(0-t), and AUC(inf) of approximately 100% for all comparisons (Table 1.3.2.5.2). All of the associated 90% confidence intervals were well within the 80% to 125% equivalence window (Table 1.3.2.5.2), demonstrating bioequivalence among the three tablet strengths with respect to codeine.

Table 1.3.2.5.1.: Summary of pharmacokinetic parameters for codeine after oral administration of 60 mg doses of Roxane Laboratories' codeine tablets as 1 x 60 mg, 2 x 30 mg, and 4 x 15 mg tablets to healthy volunteers under fasted conditions.

Parameter ¹	1 x 60 mg	2 x 30 mg	4 x 15 mg
C _{max} (ng/mL)	169 ± 46.5 (18)	157 ± 37.9 (18)	159 ± 41.5 (18)
T _{max} (h)	1.13 (18) [0.25 – 1.50]	1.00 (18) [0.50 – 2.00]	1.00 (18) [0.50 – 2.00]
AUC(0-t) (h·ng/mL)	614 ± 146 (18)	624 ± 136 (18)	626 ± 140 (18)
AUC(inf) (h·ng/mL)	623 ± 146 (18)	633 ± 136 (18)	634 ± 141 (18)
λ _z (h ⁻¹)	0.2358 ± 0.0376 (18)	0.2287 ± 0.0391 (18)	0.2162 ± 0.0442 (18)
t _{1/2} (h)	3.01 ± 0.49 (18)	3.11 ± 0.52 (18)	3.34 ± 0.71 (18)
Ln(C _{max})	5.09 ± 0.29 (18)	5.03 ± 0.23 (18)	5.03 ± 0.26 (18)
Ln[AUC(0-t)]	6.39 ± 0.26 (18)	6.41 ± 0.21 (18)	6.42 ± 0.23 (18)
Ln[AUC(inf)]	6.41 ± 0.26 (18)	6.43 ± 0.21 (18)	6.43 ± 0.23 (18)

¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Table 1.3.2.5.2: Statistical comparison of pharmacokinetic parameters for codeine after oral administration of 60 mg doses of Roxane Laboratories' codeine tablets as 1 x 60 mg, 2 x 30 mg, and 4 x 15 mg tablets to healthy volunteers under fasted conditions.

Parameter	Geometric Mean Ratio (%) ¹			Within Subject CV (%)
	Estimate	90% Confidence Interval		
2 x 30 mg vs. 1 x 60 mg				
C _{max}	94.06	84.98	→ 104.10	18.11
AUC(0-t)	102.46	94.65	→ 110.90	14.10
AUC(inf)	102.43	94.69	→ 110.80	13.98
4 x 15 mg vs. 1 x 60 mg				
C _{max}	94.12	85.04	→ 104.16	18.11
AUC(0-t)	102.53	94.74	→ 111.01	14.10
AUC(inf)	102.24	94.51	→ 110.59	13.98
4 x 15 mg vs. 2 x 30 mg				
C _{max}	100.06	90.41	→ 110.74	18.11
AUC(0-t)	100.09	92.47	→ 108.35	14.10
AUC(inf)	99.81	92.27	→ 107.97	13.98

¹Based on analysis of natural log-transformed data.

1.4 Special Populations:

No formal studies were conducted in special population in this NDA. However, based on historical data, clinical experience, and the well know metabolic and excretion pathways of codeine and its metabolites, the sponsor included in the draft labeling a language similar to that already in Tylenol® #3 (acetaminophen 300 mg with codeine phosphate 30 mg) approved label to caution the use of codeine morphine in pregnant and nursing women as well as for patients with hepatic or renal insufficiency (see also QBR section).

1.5 Pediatric Indication:

In the pre-IND meeting held on September 12, 2006 (IND # 74,041), the sponsor was advised that the _____

_____ A pediatric plan submitted by the sponsor on January 29, 2009 is summarized as follows:

1. Objective: to evaluate the efficacy, safety, and pharmacokinetics (after single and multiple-doses) of immediate release codeine sulfate in a pediatric population with _____ An age-appropriate formulation will be used for the younger pediatric subjects. b(4)
2. Three (3) studies will be conducted with subjects divided into the following age groups: 1 month – 2 years, 2 years – 12 years and 12 years - _____ b(4)
3. Efficacy studies will be designed as superiority trials.
4. A deferral for the pediatric studies was requested until after approval of codeine for the adult indication.
5. The estimated timeline is as follows:

Study Number	Protocol Submission	Study Initiation	Final Report Submission
Study #1	November 2009	April 2010	October 2011
Study #2	January 2010	June 2010	December 2011
Study #3	May 2010	October 2010	April 2012

The Division presented the agreed upon Pediatric Plan to PeRC on March 11, 2009. Concurrence was obtained from the committee at that time.

1.6 Overall Summary and Conclusions:

The extent and rate of exposure of codeine was dose proportional after oral administration of 1 x 15 mg, 1 x 30 mg, and 1 x 60 mg doses of Codeine Sulfate Tablets.

Oral administration of Codeine Sulfate Tablet 60 mg under fed conditions resulted in no clinically significant change in the rate or extent of absorption of codeine when compared to fasted conditions.

Oral administration of Codeine Sulfate Tablet 15 mg Q4H x 5 days resulted in steady-state plasma concentrations of codeine within 48 hours. Mean plasma concentrations and mean values for C_{max} and AUC(0-4) for codeine were consistent across the six individual doses on Day 5. Codeine comprised the largest portion of circulating material (~55%) followed by M3G (~36%), M6G (~6%), and morphine (~2%) respectively.

Codeine Sulfate Tablet 30 mg was bioequivalent to reference product Tylenol® #3 (Codeine Phosphate 30 mg) with respect to codeine.

After oral administration at a total dose of 60 mg, the 15 mg, 30 mg, and 60 mg codeine sulfate tablets demonstrated formulation bioequivalence with respect to codeine.

Overall, there are no approval related Clinical Pharmacology and Biopharmaceutics issues with 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 Tablets was submitted to the Agency on July 1, 2008.

1980s: Roxane has marketed Codeine Sulfate Tablets, USP, 15 mg, 30 mg, and 60 mg for the relief of mild to moderate severe pain since the early 1980s.

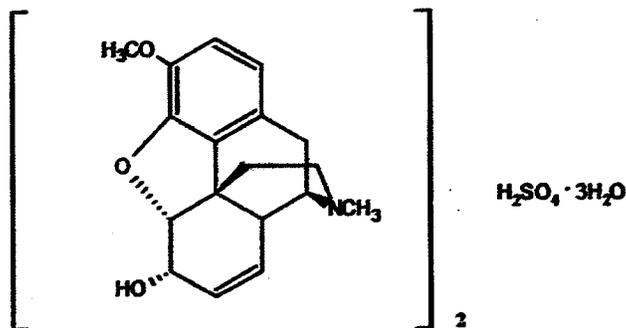
January 24, 2007, Type-B Meeting: The FDA agreed that a 505(b)(2) application could be submitted for Codeine Sulfate Tablets, USP, 15 mg, 30 mg, and 60 mg. For additional details, see the meeting minutes dated February 8, 2007 under IND 75,764. The safety of Roxane's codeine sulfate tablets would be supported by the Agency's previous findings of safety for Orange Book Listed Tylenol® with Codeine # 3 product. Agency agreed that Tylenol® with Codeine # 3 may be an acceptable reference to support the safety as long as 1) the codeine doses used in the combination product are the same or higher doses than used in the proposed doses of the codeine sulfate oral tablets, and 2) as long as the pharmacokinetics of codeine in the reference product are similar to those of Roxane Labs' codeine.

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-, (5 α , 6 α)-, 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 tablets are indicated for the relief of mild to moderately severe pain.

2.1.4 What are the proposed dosage(s) and route(s) of administration?

Codeine Sulfate Tablets: 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.

2.1.5 What is codeine sulfate to-be-marketed formulation?

Codeine Sulfate Tablets, USP, 15 mg, 30 mg and 60 mg will be manufactured and packaged in bottles of 100 tablets (30 mg and 60 mg) and 25 tablets x 4 unit dose blisters (15 mg and 30 mg).

Each 15 mg tablet for oral administration contains: codeine sulfate 15 mg and is a white, biconvex tablet scored on one side with "15" debossed on the scored side and product identification "54 613" debossed on the other side.

Each 30 mg tablet for oral administration contains: codeine sulfate 30 mg and is a white, biconvex tablet scored on one side and product identification "54 783" debossed on the other side.

Each 60 mg tablet for oral administration contains: codeine sulfate 60 mg and is a white, biconvex tablet scored on one side and product identification "54 412" debossed on the other side.

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, five studies conducted by the sponsor were submitted. The pivotal study is the BE study to determine bioavailability of the proposed codeine sulfate tablets to the referenced Tylenol® with Codeine # 3 tablets (Study T30-PVFS-1).

The other four studies include a dose proportionality study, a food effect study, a steady state study and a dosage form equivalence study.

No new clinical studies were conducted by the sponsor in support of this product. The approval of this product relies on the bioavailability comparisons with the approved Tylenol® with Codeine # 3 tablets and historical data summarized from the literature.

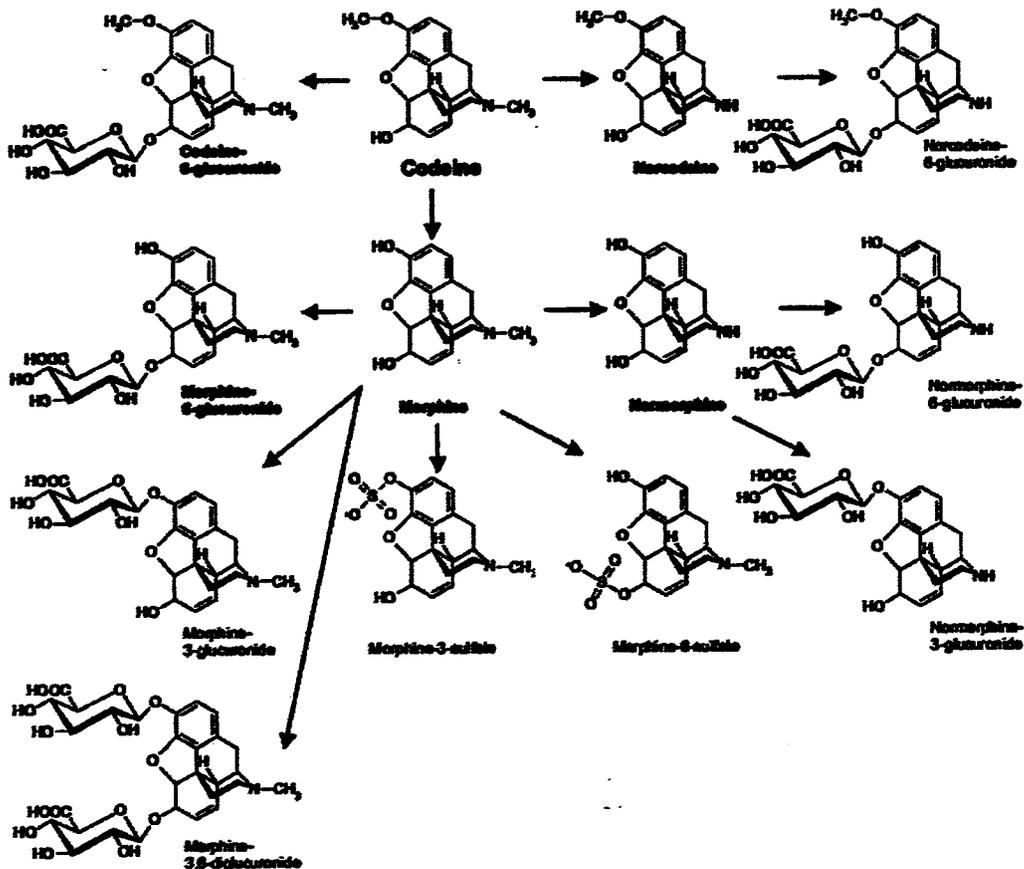
No biological biomarker was used in this NDA. All data in this NDA were presented as comparative PK.

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.

Codeine is metabolized by Phase 1 UGT, CYP2D6 and CYP3A4 enzymes to a variety of metabolites (Shown in Figure 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-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). As agreed in the pre-IND meeting, the sponsor characterized the parent drug codeine, active metabolite morphine and its two metabolites, M3G and M6G in the plasma samples.

From the studies submitted in this NDA, morphine was found to exhibit maximum plasma concentrations within 30-60 min of oral administration and its half life was observed to be 2-3 h.

2.2.3 Exposure Response

2.2.3.1 What are the characteristics of the exposure-response relationships for efficacy?

No formal PK/PD study was conducted in this NDA to establish the relationship between exposure and response/efficacy.

2.2.3.2 What are the characteristics of the exposure-response relationships for safety?

No formal PK/PD study was conducted in this NDA to establish the relationship between exposure and safety.

2.2.3.3 Does this drug prolong the QT or QTc Interval?

No formal QTc study was conducted in this NDA to establish the effect of morphine on QTc.

2.2.4 What are the PK characteristics of the drug?

2.2.4.1 What are the single and multiple dose PK parameters of codeine? How do the PK parameters change with time following chronic dosing?

General PK: Codeine is readily absorbed from the gastrointestinal tract with maximum plasma concentration occurring 60 minutes post administration. At therapeutic doses, the analgesic effect reaches a peak within 2 h and persists between 4 and 6 h.

Single dose PK: Following single oral dose administration of codeine in healthy volunteers, codeine reached maximum plasma concentrations within ~1-2 h. Plasma half life of codeine was found to be 2-4 h in the studies submitted in this NDA.

Multiple dose PK: After a 15 mg Q4H x 5 days administration of codeine sulfate in healthy volunteers (Study CODE-T15-PVFS-1), the exposure levels of codeine after all the six doses administered on the fifth day were comparable indicating no significant changes in PK parameters of codeine after chronic dosing (See individual study reviews).

2.2.4.2 Are the PK of codeine and its metabolites linear and dose-proportional?

In the Study CODE-T15-30-60-PVFS-1 conducted by the sponsor to determine the dose proportionality between 15 mg, 30 mg and 60 mg tablets after a single dose in healthy subjects after fasting conditions, the plasma concentrations of codeine and its metabolites increased in proportion to the increase in dose

Mean plasma concentrations of codeine after administration of codeine as 1 x 15 mg, 1 x

30 mg, and 1 x 60 mg tablets increased in proportion to the increase in dose. Mean values for C_{max}, AUC(0-t) and AUC(inf) also increased in proportion to dose (Table 2.2.4.2.1). The associated 90% confidence intervals for all comparisons among tablet strengths were within the 80% to 125% equivalence window (Table 2.2.4.2.2), demonstrating dose proportionality among the three tablet strengths with respect to codeine. The linearity is further illustrated in Figure 2.2.4.2.3 (log plots of the mean C_{max} and AUC(inf) versus dose were linear with slopes of 1.06 and 1.04, respectively).

Table 2.2.4.2.1. Summary of pharmacokinetic parameters for codeine after oral administration of 1 x 15 mg, 1 x 30 mg and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fasted conditions.

Parameter ¹	1 x 15 mg	1 x 30 mg	1 x 60 mg
C _{max} (ng/mL)	38.5 ± 14.5 (33)	81.2 ± 27.3 (34)	167 ± 46.9 (34)
T _{max} (h)	1.25 (33) [0.50 – 2.00]	1.01 (34) [0.50 – 2.50]	1.00 (34) [0.50 – 1.50]
AUC(0-t) (h×ng/mL)	149 ± 44.9 (33)	308 ± 93.3 (34)	653 ± 172 (34)
AUC(inf) (h×ng/mL)	154 ± 45.1 (33)	313 ± 95.3 (33)	654 ± 156 (32)
λ _z (h ⁻¹)	0.2761 ± 0.0369 (33)	0.2580 ± 0.0329 (33)	0.2041 ± 0.0634 (32)
t _{1/2} (h)	2.55 ± 0.34 (33)	2.73 ± 0.40 (33)	3.76 ± 1.26 (32)
Ln(C _{max})	3.59 ± 0.34 (33)	4.34 ± 0.34 (34)	5.08 ± 0.29 (34)
Ln[AUC(0-t)]	4.96 ± 0.30 (33)	5.69 ± 0.30 (34)	6.45 ± 0.26 (34)
Ln[AUC(inf)]	5.00 ± 0.29 (33)	5.70 ± 0.30 (33)	6.45 ± 0.24 (32)

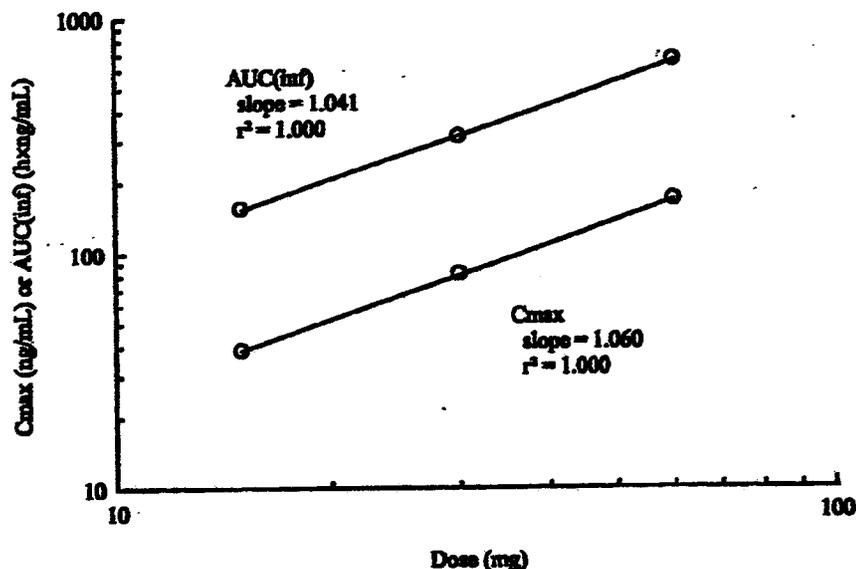
¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Table 2.2.4.2.2. Statistical comparison of pharmacokinetic parameters for codeine after oral administration of 1 x 15 mg, 1 x 30 mg and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fasted conditions.

Parameter	Geometric Mean Ratio (%) ¹		Within Subject CV (%)
	Estimate	90% Confidence Interval	
1 x 15 mg vs. 1 x 30 mg			
C _{max}	95.04	88.28 → 102.32	18.14
AUC(0-t)	96.51	92.02 → 101.23	11.66
AUC(inf)	98.38	93.76 → 103.23	11.62
1 x 15 mg vs. 1 x 60 mg			
C _{max}	90.88	84.42 → 97.84	18.14
AUC(0-t)	89.93	85.75 → 94.32	11.66
AUC(inf)	92.58	88.19 → 97.18	11.62
1 x 30 mg vs. 1 x 60 mg			
C _{max}	95.62	88.90 → 102.85	18.14
AUC(0-t)	93.18	88.90 → 97.67	11.66
AUC(inf)	94.10	89.63 → 98.79	11.62

¹Based on analysis of natural log-transformed data after normalization to the 30 mg dose.

Figure 2.2.4.2.3. Relationships between the mean C_{max} and AUC(inf) of codeine and the dose of codeine after oral administration of 1 x 15 mg, 1 x 30 mg and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fasted conditions.



Further, the increases in C_{max}, AUC(0-t), and AUC(inf) after oral administration of 1 x 15 mg, 1 x 30 mg, and 1 x 60 mg doses of Roxane Laboratories' codeine tablets were dose proportional with respect to M3G and dose linear with respect to the other two metabolites measured, morphine and M6G (See individual study reviews).

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.

Based on historical data, clinical experience, and the well known metabolic and excretion pathways of codeine and its metabolites, the sponsor proposed in the draft labeling that caution should be exercised when administering codeine in patients with hepatic or renal insufficiency. No formal studies have been conducted in patients with hepatic impairment so the pharmacokinetics of codeine sulfate in this patient population are unknown. Based on some literature reports, clearance may be reduced and half-life increased and the metabolites codeine glucuronide, morphine, and morphine glucuronide may accumulate to much higher plasma levels compared to patients with normal renal function after multiple doses of codeine are administered.

Furthermore, based on extensive clinical experience, literature reports and their own experience with Morphine Sulfate Tablets, the sponsor included a language in the proposed label to reflect the following:

- The safety and effectiveness and the pharmacokinetics of Codeine Sulfate Tablets in pediatric patients below the age of 18 have not been established.
- Sedating drugs may cause confusion and over-sedation in the elderly. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
- Codeine is secreted into human milk. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. Caution should be exercised when codeine is administered to a nursing woman

b(4)

The risk of infant exposure to codeine and morphine through breast milk should be weighed against the benefits of breastfeeding for both the mother and the baby.

- As with other opioids, codeine sulfate should be used with caution in elderly or debilitated patients
- Codeine sulfate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- Codeine sulfate is metabolized to pharmacologically active metabolites by the cytochrome P-450 2D6 and 3A4 isoenzymes. The prevalence of the CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups.

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 _____). The sponsor requests deferral of all pediatric ages until after the approval has been granted for oral codeine sulfate tablets (15, 30 and 60 mg), after which, the sponsor proposes to study the pediatric population _____ 17 years of age.

b(4)

b(4)

In the pre-IND meeting held on September 12, 2006 (IND # _____) the sponsor was advised that th_____

b(4)

A revised pediatric plan was submitted to the Division on January 29, 2009 which is summarized as follows:

6. Objective: to evaluate the efficacy, safety, and pharmacokinetics (after single and multiple-doses) of immediate release codeine sulfate in a pediatric population with _____ An age-appropriate formulation will be used for the younger pediatric subjects. b(4)
7. Three (3) studies will be conducted with subjects divided into the following age groups: 1 month – 2 years, 2 years – 12 years and 12 years – _____ b(4)
8. Efficacy studies will be designed as superiority trials.
9. A deferral for the pediatric studies was requested until after approval of codeine for the adult indication.
10. The estimated timeline is as follows:

Study Number	Protocol Submission	Study Initiation	Final Report Submission
Study #1	November 2009	April 2010	October 2011
Study #2	January 2010	June 2010	December 2011
Study #3	May 2010	October 2010	April 2012

The Division presented the agreed upon Pediatric Plan to PeRC on March 11. Concurrence was obtained from the committee at that time.

2.4 Extrinsic factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The effects of herbal products, smoking and alcohol on codeine use were not evaluated. However, based on the clinical experience other CNS depressant drugs such as alcohol, other opioids or illicit drugs may have additive effect on codeine. The sponsor conducted a specific study to investigate the effect of food on the PK of IR tablet. This will be discussed in the next section below.

2.5 General Biopharmaceutics

2.5.1 What is the BCS Class classification for codeine?

This information is not available.

2.5.2 What is the effect of food on the BA of codeine?

In a Study CODE- T60-PVFS/FD-1 conducted by the sponsor to investigate the effect of presence of a high fat (approximately 50% of total caloric content of the meal), high calorie (approximately 1000 calories) meal on the PK of Roxane Laboratories' 60 mg codeine sulfate tablet, presence of food was not found to alter the PK of codeine.

Mean plasma concentrations of codeine after administration of Roxane Laboratories'

Codeine Sulfate 60 mg tablet were comparable after administration under fed and fasted conditions. There was a 50% increase in the median Tmax, from 1.00 h to 1.54 h (Table 2.5.2.1), and an 11% decrease in Cmax, suggesting a slight decrease in the rate of absorption under fed conditions. However, the 90% confidence intervals for Cmax, AUC(0-t), and AUC(inf) were within the 80% to 125% equivalence window (Table 2.5.2.2), demonstrating no effect of food on the bioavailability with respect to codeine.

Table 2.5.2.1.: Summary of pharmacokinetic parameters for codeine after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 60 mg to healthy volunteers under fed and fasted conditions.

Parameter ¹	Fasted	Fed
Cmax (ng/mL)	167 ± 54.0 (36)	149 ± 49.2 (36)
Tmax (h)	1.00 (36) [0.50 – 2.50]	1.54 (36) [0.25 – 4.00]
AUC(0-t) (h×ng/mL)	629 ± 175 (36)	711 ± 211 (36)
AUC(inf) (h×ng/mL)	639 ± 175 (36)	720 ± 212 (36)
λz (h ⁻¹)	0.2163 ± 0.0490 (36)	0.2174 ± 0.0436 (36)
t½ (h)	3.41 ± 0.93 (36)	3.33 ± 0.75 (36)
Ln(Cmax)	5.06 ± 0.35 (36)	4.95 ± 0.36 (36)
Ln[AUC(0-t)]	6.41 ± 0.28 (36)	6.52 ± 0.32 (36)
Ln[AUC(inf)]	6.42 ± 0.27 (36)	6.53 ± 0.31 (36)

¹Arithmetic mean ± standard deviation (N) except for Tmax for which the median (N) [Range] is reported.

Table 2.5.2.2.: Statistical comparison of pharmacokinetic parameters for codeine after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 60 mg to healthy volunteers under fed and fasted conditions.

Parameter	Geometric Mean Ratio (%) ¹		
	Estimate	90% Confidence Interval	
Cmax	89.34	81.18	→ 98.31
AUC(0-t)	111.98	105.27	→ 119.12
AUC(inf)	111.83	105.20	→ 118.86

¹Based on analysis of natural log-transformed data.

The same trend was seen for metabolites morphine, M3G and M6G (See individual study review for details).

2.5.3 Was the to-be-marketed formulation used in the PK/Clinical trials?

For tablets, per the sponsor, all lots were manufactured using the same formula, manufacturing site, equipment and process. There are no differences in the manufacturing process or equipment between the commercial/registration lots used in the biostudies.

2.5.4 What are the biopharmaceutical characteristics of the products?

The formulation compositions for tablets are shown in Table 2.5.4.1.

The 15 mg and 30 mg tablets are not compositionally proportional. Microcrystalline Cellulose, NF was reduced by ~~_____~~ in the 30 mg tablet to keep the tablet weight constant (Table 2.5.4.1). However, the 30 mg and 60 mg tablets are compositionally proportional. There were no differences in the manufacturing process or equipment between the commercial/registration lots used in the biostudies and the historical commercial lots.

b(4)

Table 2.5.4.1. Codeine Formulation Composition For 15 mg, 30 mg and 60 mg Tablets

<u>Ingredients</u>	<u>Purpose</u>	<u>Quality Standard</u>	<u>Amount (mg per tablet)</u>		
			<u>15 mg tablets</u>	<u>30 mg tablets</u>	<u>60 mg tablets</u>
Codeine Sulfate, USP	Active Ingredient	USP; BIRI Spec. No. 6081700R-01-02	15.0 mg	30.0 mg	60.0 mg
Microcrystalline Cellulose, NF _____		NF			
Pregelatinized Starch, NF _____		NF			
Colloidal Silicon Dioxide, NF _____		NF			
Stearic Acid, NF		NF			
Theoretical Tablet Weight		-			

b(4)

2.6 Analytical Section

Plasma concentrations of codeine, morphine, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G) were measured using an LC/MS/MS method validated under various different project codes by —. 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-3 β -glucuronide (M3G) within the nominal range of 2.00 to 200 ng/mL, and morphine- 6 β -glucuronide (M6G) within the nominal range of 0.500 to 50.0 ng/mL from a 250- μ L human plasma aliquot, containing sodium heparin. Overall, the assay validation data are satisfactory.

b(4)

Table 2.6.1 Inter- and Intra- Assay Precision and Accuracy

Analyte	Inter-Assay		Intra-Assay	
	Precision (%)	Accuracy (%)	Precision (%)	Accuracy (%)
Codeine	2.79-7.24	-0.0522-1.21	0.828-12.0	-2.59-3.47
Morphine	3.15-10.5	-3.33-.537	1.18-12.8	-9.23-3.29
Morphine-3-glucuronide	2.61-5.85	-3.56-0.0285	1.40-8.43	-4.01-2.31
Morphine-6-glucuronide	2.65-7.01	0.259-2.64	1.50-10.7	-4.60-5.88

25 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

4.2 Individual Study Reviews:

4.2.1. Study CODE-T15-30-60-PVFS-1: Dose Proportionality Study

Study title	A single-dose, 3-period, 3-treatment, 6-sequence, 3-way crossover study of the dose linearity of Codeine Sulfate Tablets under fasting conditions
Clinical site	Cedra Clinical Research LLC 2455 N.E. Loop 410 Suite 150 San Antonio TX 78217
Principal Investigator	Frederick A. Bieberdorf, M.D., CPI
Dosing dates	Subjects 201 through 232 dosed on March 19, 2008, March 26, 2008, and April 02, 2008. Subjects 233 and 234 dosed on March 26, 2008, April 02, 2008, and April 09, 2008.
Analytical site	
Analytical Director	
Analysis dates	April 18, 2008 – May 30, 2008

b(4)

Objective:

To examine the dose linearity of Roxane Laboratories' 15 mg, 30 mg, and 60 mg codeine sulfate tablets under fasted conditions.

Study design:

Thirty-three of 34 study participants were administered a single 15 mg, 30 mg, and 60 mg oral dose of all the following treatments in a randomized, sequenced fashion. Please note that the randomization was changed in a protocol amendment sent to CEDRA by Roxane Labs. dated February 8, 2008.

Treatment A: Codeine Sulfate (1 x 15 mg tablet)
Roxane Laboratories'
Lot # 079089A
Mfg Date: 09/19/2007

Treatment B: Codeine Sulfate (1 x 30 mg tablet)
Roxane Laboratories'
Lot # 757701A
Exp Date: October 2010

Treatment C: Codeine Sulfate (1 x 60 mg tablet)
 Roxane Laboratories'
 Lot # 757627A
 Exp Date: September 2010

Demographic Profile:

		Dose Linearity Study CODE-115316/01/08		
		Treatment Group		
		Treatment A 15mg Tablet N=23	Treatment B 30mg Tablet N=23	Treatment C 60mg Tablet N=23
Age (years)	Mean ± SD	28.4 ± 6.9	28.2 ± 6.8	28.2 ± 6.8
	Range	19.0 - 45.0	19.0 - 45.0	19.0 - 45.0
Age Groups	< 18	0 (0.00%)	0 (0.00%)	0 (0.00%)
	18 - 40	30 (90.91%)	31 (91.18%)	31 (91.18%)
	41 - 64	3 (9.09%)	3 (8.82%)	3 (8.82%)
	65 - 75	0 (0.00%)	0 (0.00%)	0 (0.00%)
	> 75	0 (0.00%)	0 (0.00%)	0 (0.00%)
Sex	Female	10 (30.30%)	10 (29.41%)	10 (29.41%)
	Male	23 (69.70%)	24 (70.59%)	24 (70.59%)
Race	Asian	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Black	12 (36.36%)	12 (35.29%)	12 (35.29%)
	Caucasian	21 (63.64%)	22 (64.71%)	22 (64.71%)
	Hispanic	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Other	0 (0.00%)	0 (0.00%)	0 (0.00%)
BMI (kg/m²)	Mean ± SD	24.3 ± 3.4	24.4 ± 3.3	24.4 ± 3.3
	Range	18.4 - 29.8	18.4 - 29.8	18.4 - 29.8
Height (cm)	Mean ± SD	173.0 ± 10.0	172.8 ± 9.9	172.8 ± 9.9
	Range	153.5 - 192.5	153.5 - 192.5	153.5 - 192.5
Weight (kg)	Mean ± SD	72.7 ± 11.1	72.7 ± 10.9	72.7 ± 10.9
	Range	46.4 - 94.6	46.4 - 94.6	46.4 - 94.6

Blood Samples for PK Analysis:

Blood samples were collected before dose and at 5, 10, 15, 30, 45 minutes, and 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 30, 36, and 48 hours after dosing. Please note that this is the finalized blood sampling schedule included in a protocol amendment sent to CEDRA by Roxane Labs. dated February 8, 2008.

Bioanalytical Analysis:

Plasma concentrations of codeine, morphine, morphine-3-glucuronide (M3G), and

morphine-6-glucuronide (M6G) were measured using an LC/MS/MS method validated under the project code "EKR2" by _____. The method is applicable to the quantitation of codeine within a nominal range of 1.00 to 100 ng/mL, morphine within a nominal range of 0.200 to 20.0 ng/mL, morphine-3 β -glucuronide within a nominal range of 2.00 to 200 ng/mL, and morphine-6 β -glucuronide within a nominal range of 0.500 to 50.0 ng/mL and requires a 250- μ L human plasma aliquot containing sodium heparin. The lower limit of quantitation was the lowest non-zero concentration level that was quantified with acceptable accuracy and precision. For this validation, the lower limit of quantitation was nominally 1.00 ng/mL for codeine, 0.200 ng/mL for morphine, 2.00 ng/mL for morphine-3 β -glucuronide and 0.500 ng/mL for morphine-6 β -glucuronide.

b(4)

PK and Statistical Analyses:

The pharmacokinetic and statistical analyses were done by _____

All PK

b(4)

parameters were calculated using non-compartmental analysis. Only those plasma concentrations equal to or greater than the LOQs (codeine - 1 ng/mL; morphine - 0.20 ng/mL; M3G - 2.0 ng/mL; M6G - 0.5 ng/mL) were used in the analysis. Actual sampling times were used in all pharmacokinetic analyses.

Population for PK Analysis:

Thirty-four (34) subjects were enrolled into the study. Subject #214 did not return for Period 3 (1 x 15 mg) but was included in the analyses of the other two treatments. The analysis population was therefore comprised of 34 subjects - 33 subjects completed all three treatments and one (1) subject completed two of three treatments. For Subject #205, all plasma morphine concentrations for all treatments and all plasma M3G and M6G concentrations for the 15 mg and 30 mg treatments were lesser than LOQ. No pharmacokinetic analyses were done for that subject for those analytes for those treatments.

a. Codeine

Mean plasma concentrations of codeine after administration of codeine as 1 x 15 mg, 1 x 30 mg, and 1 x 60 mg tablets increased in proportion to the increase in dose (Figure 4.2.1.1). Mean values for C_{max}, AUC(0-t) and AUC(inf) also increased in proportion to dose (Table 4.2.1.2). The associated 90% confidence intervals for all comparisons among tablet strengths were within the 80% to 125% equivalence window (Table 4.2.1.3), demonstrating dose proportionality among the three tablet strengths with respect to codeine. The linearity is further illustrated in Figure 4.2.1.4 (log plots of the mean C_{max} and AUC(inf) versus dose were linear with slopes of 1.06 and 1.04, respectively).

Figure 4.2.1.1: Mean plasma concentrations of codeine after oral administration of 1 x 15 mg, 1 x 30 mg, and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fasted conditions - linear axes.

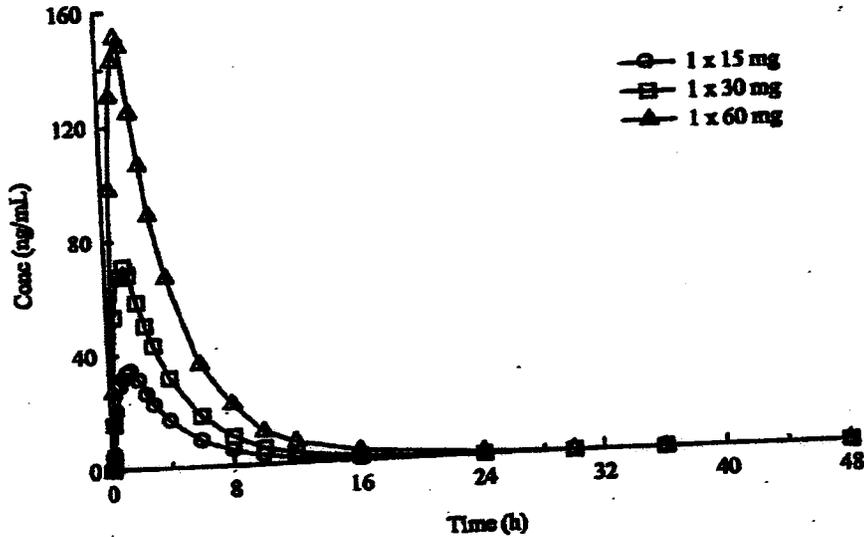


Table 4.2.1.2: Summary of pharmacokinetic parameters for codeine after oral administration of 1 x 15 mg, 1 x 30 mg and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fasted conditions.

Parameter ¹	1 x 15 mg	1 x 30 mg	1 x 60 mg
C _{max} (ng/mL)	38.5 ± 14.5 (33)	81.2 ± 27.3 (34)	167 ± 46.9 (34)
T _{max} (h)	1.25 (33) [0.50 - 2.00]	1.01 (34) [0.50 - 2.50]	1.00 (34) [0.50 - 1.50]
AUC(0-t) (h·ng/mL)	149 ± 44.9 (33)	308 ± 93.3 (34)	653 ± 172 (34)
AUC(∞) (h·ng/mL)	154 ± 45.1 (33)	313 ± 95.3 (33)	654 ± 156 (32)
λ _z (h ⁻¹)	0.2761 ± 0.0369 (33)	0.2580 ± 0.0329 (33)	0.2041 ± 0.0634 (32)
t _{1/2} (h)	2.55 ± 0.34 (33)	2.73 ± 0.40 (33)	3.76 ± 1.26 (32)
Ln(C _{max})	3.59 ± 0.34 (33)	4.34 ± 0.34 (34)	5.08 ± 0.29 (34)
Ln[AUC(0-t)]	4.96 ± 0.30 (33)	5.69 ± 0.30 (34)	6.45 ± 0.26 (34)
Ln[AUC(∞)]	5.00 ± 0.29 (33)	5.70 ± 0.30 (33)	6.45 ± 0.24 (32)

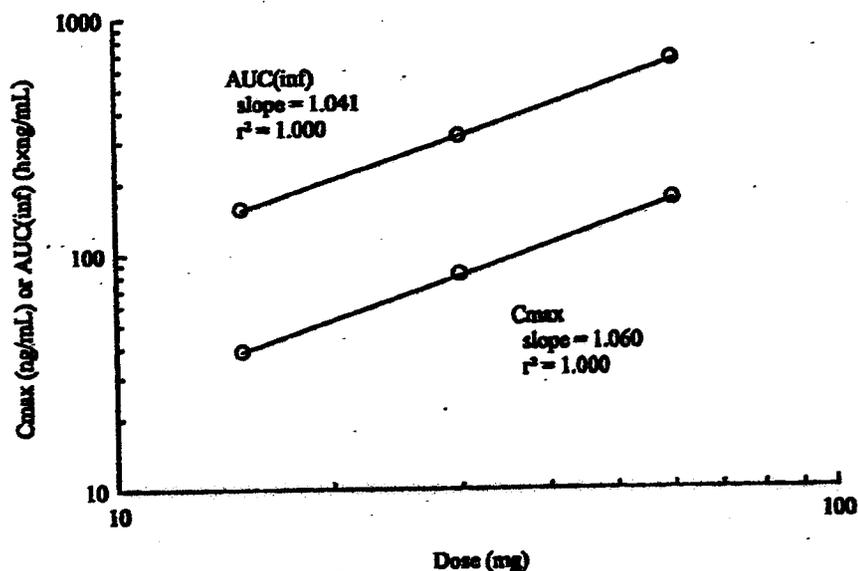
¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Table 4.2.1.3: Statistical comparison of pharmacokinetic parameters for codeine after oral administration of 1 x 15 mg, 1 x 30 mg and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fasted conditions.

Parameter	Geometric Mean Ratio (%) ¹		Within Subject CV (%)
	Estimate	90% Confidence Interval	
1 x 15 mg vs. 1 x 30 mg			
C _{max}	95.04	88.28 → 102.32	18.14
AUC(0-t)	96.51	92.02 → 101.23	11.66
AUC(inf)	98.38	93.76 → 103.23	11.62
1 x 15 mg vs. 1 x 60 mg			
C _{max}	90.88	84.42 → 97.84	18.14
AUC(0-t)	89.93	85.75 → 94.32	11.66
AUC(inf)	92.58	88.19 → 97.18	11.62
1 x 30 mg vs. 1 x 60 mg			
C _{max}	95.62	88.90 → 102.85	18.14
AUC(0-t)	93.18	88.90 → 97.67	11.66
AUC(inf)	94.10	89.63 → 98.79	11.62

¹Based on analysis of natural log-transformed data after normalization to the 30 mg dose.

Figure 4.2.1.4: Relationships between the mean C_{max} and AUC(inf) of codeine and the dose of codeine after oral administration of 1 x 15 mg, 1 x 30 mg and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fasted conditions.



b. Morphine

Mean plasma concentrations of morphine after administration of codeine as 1 x 15 mg, 1 x 30 mg, and 1 x 60 mg tablets increased in proportion to the increase in dose (Figure 4.2.1.5 - linear axes). Mean values for C_{max} increased in proportion to dose (Table 4.2.1.6) and the associated 90% confidence intervals for all comparisons among tablet strengths were within the 80% to 125% equivalence window (Table 4.2.1.7, demonstrating dose proportionality among the three tablet strengths with respect to morphine. The linearity is further illustrated in Figure 4.2.1.8 (a log plot of the mean C_{max} versus dose was linear with a slope of 1.06). There were dose-related but somewhat more than dose-proportional increases in $AUC(0-t)$ and $AUC(inf)$ (Table 4.2.1.7), with least squares geometric mean ratios for the comparisons of the lower to the higher doses ranging from 47% to 86% and associated 90% confidence intervals below the 80% to 125% equivalence window (Table 4.2.1.7). This is also shown in Figure 4.2.1.8 in which the mean $AUC(inf)$ versus dose was linear but with a slope of 1.26, suggesting a greater than dose-proportional increase. The sponsor reasons that the more than dose proportional increases in morphine concentrations observed with the different dose strengths was most likely an artifact of the inability to follow morphine concentrations for the same period of time at the 15 mg dose compared to the 30 mg and 60 mg doses rather than to a true non-linearity in the pharmacokinetics. This explanation seems reasonable.

Figure 4.2.1.5: Mean plasma concentrations of morphine after oral administration of 1 x 15 mg, 1 x 30 mg, and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fasted conditions - linear axes.

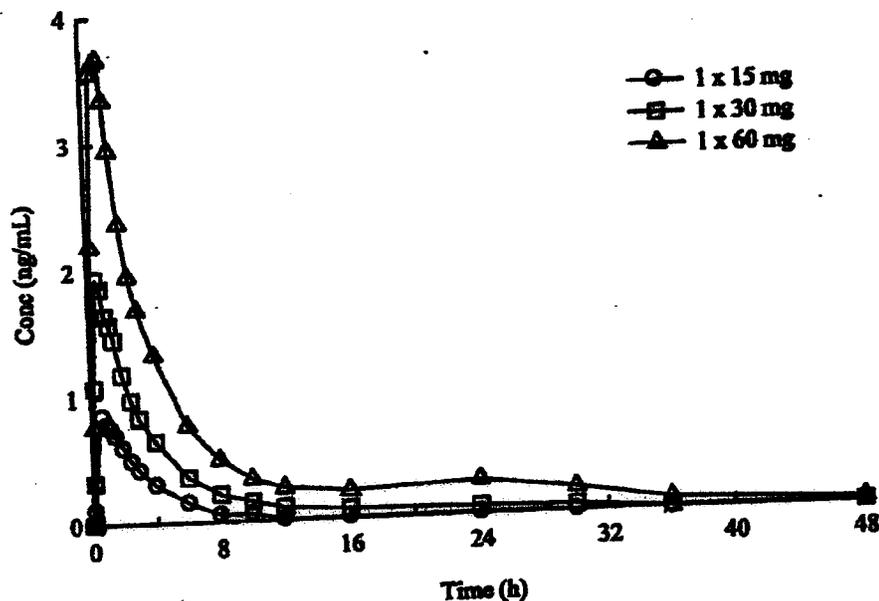


Table 4.2.1.6: Summary of pharmacokinetic parameters for morphine after oral administration of 1 x 15 mg, 1 x 30 mg, and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fed and fasted conditions.

Parameter ¹	1 x 15 mg	1 x 30 mg	1 x 60 mg
C _{max} (ng/mL)	1.08 ± 0.70 (32)	2.40 ± 1.42 (33)	4.68 ± 2.89 (33)
T _{max} (h)	0.66 (32) [0.25 – 2.00]	0.50 (33) [0.25 – 2.50]	0.75 (33) [0.25 – 1.25]
AUC(0-t) (h·ng/mL)	2.89 ± 2.51 (32)	8.25 ± 6.41 (33)	19.9 ± 12.3 (33)
AUC(inf) (h·ng/mL)	4.22 ± 2.36 (19)	7.36 ± 5.33 (18)	24.2 ± 20.3 (10)
λ _z (h ⁻¹)	0.2830 ± 0.0872 (19)	0.2213 ± 0.0840 (18)	0.1837 ± 0.1478 (10)
t _{1/2} (h)	2.65 ± 0.81 (19)	3.71 ± 1.76 (18)	8.25 ± 7.28 (10)
Ln(C _{max})	-0.10 ± 0.62 (32)	0.66 ± 0.73 (33)	1.34 ± 0.68 (33)
Ln[AUC(0-t)]	0.65 ± 1.09 (32)	1.69 ± 1.06 (33)	2.73 ± 0.84 (33)
Ln[AUC(inf)]	1.32 ± 0.48 (19)	1.78 ± 0.68 (18)	2.67 ± 1.20 (10)

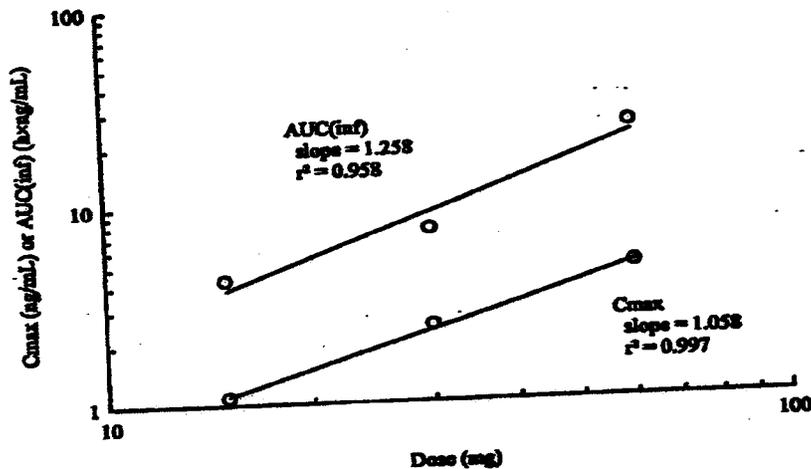
¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Table 4.2.1.7: Statistical comparison of pharmacokinetic parameters for morphine after oral administration of 1 x 15 mg, 1 x 30 mg and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fed and fasted conditions.

Parameter	Geometric Mean Ratio (%) ¹		Within Subject CV (%)
	Estimate	90% Confidence Interval	
1 x 15 mg vs. 1 x 30 mg			
C _{max}	90.42	80.88 → 101.08	27.18
AUC(0-t)	66.99	57.25 → 78.40	39.05
AUC(inf)	86.47	69.90 → 106.96	27.72
1 x 15 mg vs. 1 x 60 mg			
C _{max}	90.95	81.37 → 101.66	27.18
AUC(0-t)	47.32	40.44 → 55.37	39.05
AUC(inf)	67.96	50.54 → 91.40	27.72
1 x 30 mg vs. 1 x 60 mg			
C _{max}	100.59	90.12 → 112.28	27.18
AUC(0-t)	70.63	60.48 → 82.48	39.05
AUC(inf)	78.60	58.03 → 106.46	27.72

¹Based on analysis of natural log-transformed data after normalization to the 30 mg dose.

Figure 4.2.1.8: Relationships between the mean C_{max} and AUC(inf) of morphine and the dose of codeine after oral administration of 1 x 15 mg, 1 x 30 mg and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fasted conditions.



c. Morphine-3-glucuronide

Mean plasma concentrations of morphine-3-glucuronide after administration of codeine as 1 x 15 mg, 1 x 30 mg and 1 x 60 mg tablets increased in proportion to the increase in dose (Figure 4.2.1.9 - linear axes). Mean values for C_{max}, AUC(0-t), and AUC(inf) increased in reasonable proportion to dose (Table 4.2.1.10). The associated 90% confidence intervals for all comparisons among tablet strengths for C_{max} were within the 80% to 125% equivalence window (Table 4.2.1.11) and the slope of a log-log plot of the mean C_{max} versus dose was linear with a slope of 0.963 (Figure 4.2.1.12) demonstrating dose linearity among the three tablet strengths with respect to M3G. Although the lower limits of some of the 90% confidence intervals for AUC(0-t) and/or AUC(inf) were less than 80.00%, a log-log plot of the mean AUC(inf) versus dose was linear with a slope of 1.113 (Figure 4.2.1.12), suggesting a linear increase in exposure with the dose of codeine.

Figure 4.2.1.9: Mean plasma concentrations of M3G after oral administration of 1 x 15 mg, 1 x 30 mg and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fasted conditions - linear axes.

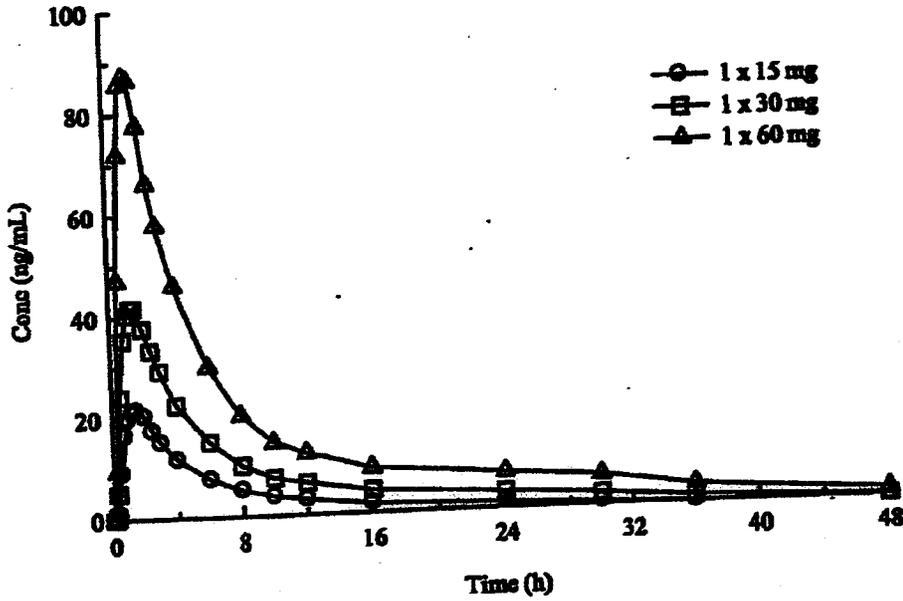


Table 4.2.1.10: Summary of pharmacokinetic parameters for M3G after oral administration of 1 x 15 mg, 1 x 30 mg and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fasted conditions.

Parameter ¹	1 x 15 mg	1 x 30 mg	1 x 60 mg
C _{max} (ng/mL)	24.6 ± 15.5 (32)	46.9 ± 27.7 (33)	93.5 ± 68.3 (34)
T _{max} (h)	1.25 (32)	1.25 (33)	1.25 (34)
	[0.75 - 2.50]	[0.75 - 2.50]	[0.75 - 2.50]
AUC(0-t) (h×ng/mL)	135 ± 81.8 (32)	300 ± 177 (33)	625 ± 386 (34)
AUC(inf) (h×ng/mL)	152 ± 101 (23)	354 ± 193 (23)	710 ± 421 (28)
λ _z (h ⁻¹)	0.1535 ± 0.0797 (23)	0.0784 ± 0.0455 (23)	0.0624 ± 0.0431 (28)
t _{1/2} (h)	6.33 ± 4.53 (23)	11.1 ± 4.72 (23)	13.1 ± 3.85 (28)
Ln(C _{max})	3.03 ± 0.61 (32)	3.67 ± 0.64 (33)	4.26 ± 0.86 (34)
Ln[AUC(0-t)]	4.67 ± 0.79 (32)	5.48 ± 0.76 (33)	6.14 ± 1.03 (34)
Ln[AUC(inf)]	4.77 ± 0.79 (23)	5.65 ± 0.76 (23)	6.28 ± 0.98 (28)

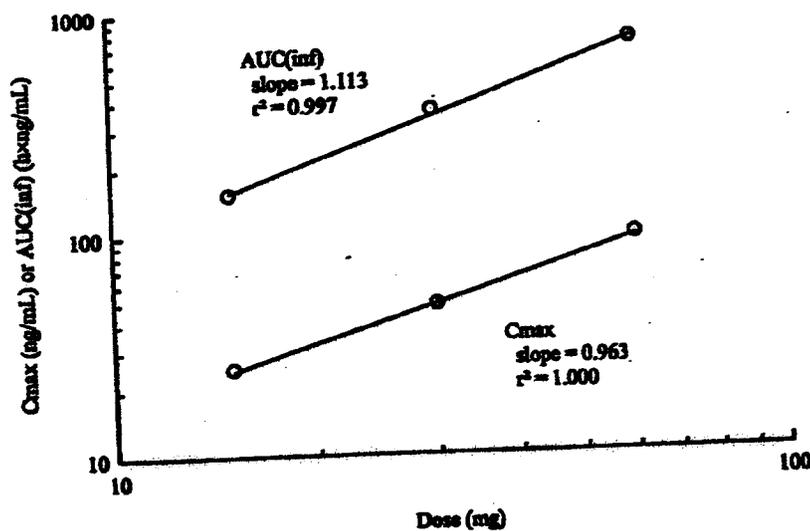
¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Table 4.2.1.11: Statistical comparison of pharmacokinetic parameters for M3G after oral administration of 1 x 15 mg, 1 x 30 mg and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fasted conditions.

Parameter	Geometric Mean Ratio (%) ¹		Within Subject CV (%)
	Estimate	90% Confidence Interval	
1 x 15 mg vs. 1 x 30 mg			
C _{max}	101.60	95.56 → 108.02	14.77
AUC(0-t)	85.00	78.82 → 91.66	18.23
AUC(inf)	83.82	75.78 → 92.70	18.59
1 x 15 mg vs. 1 x 60 mg			
C _{max}	101.92	95.86 → 108.36	14.77
AUC(0-t)	76.65	71.09 → 82.66	18.23
AUC(inf)	80.46	72.91 → 88.78	18.59
1 x 30 mg vs. 1 x 60 mg			
C _{max}	100.31	94.43 → 106.57	14.77
AUC(0-t)	90.18	83.71 → 97.15	18.23
AUC(inf)	95.99	87.34 → 105.50	18.59

¹Based on analysis of natural log-transformed data after normalization to the 30 mg dose.

Figure 4.2.1.12: Relationships between the mean C_{max} and AUC(inf) of morphine-3-glucuronide and the dose of codeine after oral administration of 1 x 15 mg, 1 x 30 mg, and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fasted conditions.



d. Morphine-6-glucuronide

Mean plasma concentrations of morphine-6-glucuronide after administration of codeine as 1 x 15 mg, 1 x 30 mg, and 1 x 60 mg tablets increased in proportion to the increase in dose (Figure 4.2.1.13 - linear axes). Mean values for C_{max} , $AUC(0-t)$, and $AUC(\infty)$ increased in reasonable proportion to dose (Table 4.2.1.14). The associated 90% confidence intervals for all comparisons among tablet strengths for C_{max} were within the 80% to 125% equivalence window (Table 4.2.1.15) and the slope of a log plot of the mean C_{max} versus dose was linear with a slope of 0.961 (Figure 4.2.1.16) demonstrating dose linearity among the three tablet strengths with respect to M6G. Although the lower limits of some of the 90% confidence intervals for $AUC(0-t)$ and/or $AUC(\infty)$ were less than 80.00, a log plot of the mean $AUC(\infty)$ versus dose was linear with a slope of 1.144 (Figure 4.2.1.16), suggesting a linear increase in exposure with the dose of codeine.

Figure 4.2.1.13: Mean plasma concentrations of M6G after oral administration of 1 x 15 mg, 1 x 30 mg, and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fasted conditions - linear axes.

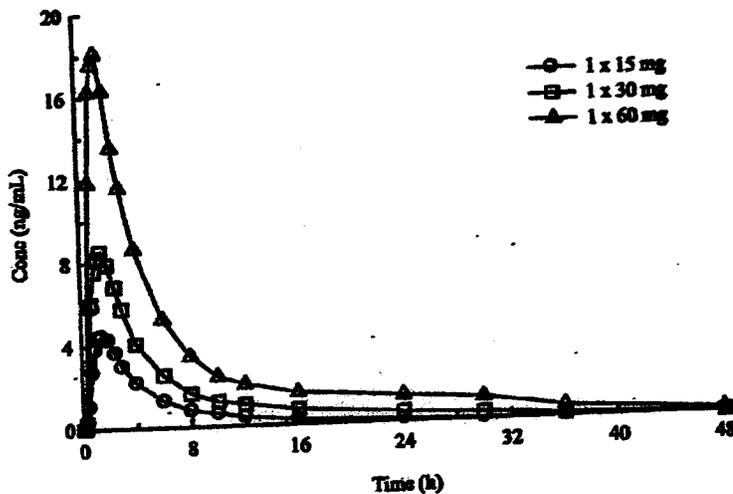


Table 4.2.1.14: Summary of pharmacokinetic parameters for M6G after oral administration of 1 x 15 mg, 1 x 30 mg and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fasted conditions.

Parameter ¹	1 x 15 mg	1 x 30 mg	1 x 60 mg
C _{max} (ng/mL)	5.16 ± 3.21 (32)	9.55 ± 4.87 (33)	19.5 ± 12.9 (34)
T _{max} (h)	1.50 (32) [1.00 – 2.50]	1.50 (33) [0.75 – 3.00]	1.50 (34) [1.00 – 2.00]
AUC(0-t) (h·ng/mL)	22.4 ± 14.8 (32)	51.3 ± 31.2 (33)	112 ± 68.8 (34)
AUC(inf) (h·ng/mL)	25.7 ± 17.3 (27)	59.6 ± 35.6 (20)	125 ± 75.1 (21)
λ _z (h ⁻¹)	0.1974 ± 0.1129 (27)	0.1242 ± 0.0918 (20)	0.0916 ± 0.0899 (21)
t _{1/2} (h)	5.40 ± 4.11 (27)	8.96 ± 6.10 (20)	10.8 ± 4.76 (21)
Ln(C _{max})	1.48 ± 0.57 (32)	2.12 ± 0.57 (33)	2.75 ± 0.73 (34)
Ln[AUC(0-t)]	2.86 ± 0.79 (32)	3.70 ± 0.77 (33)	4.45 ± 0.90 (34)
Ln[AUC(inf)]	3.00 ± 0.74 (27)	3.85 ± 0.78 (20)	4.53 ± 0.99 (21)

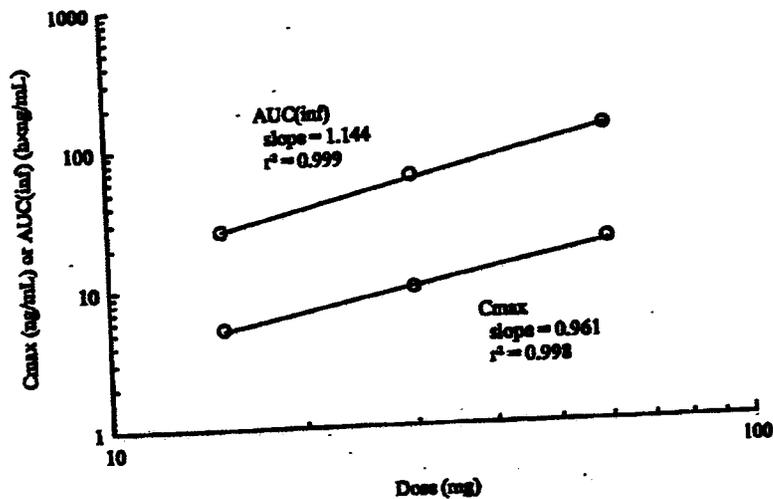
¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Table 4.2.1.15: Statistical comparison of pharmacokinetic parameters for M6G after oral administration of 1 x 15 mg, 1 x 30 mg and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fasted conditions.

Parameter	Geometric Mean Ratio (%) ¹		Within Subject CV (%)
	Estimate	90% Confidence Interval	
1 x 15 mg vs. 1 x 30 mg			
C _{max}	102.23	96.66 → 108.12	13.48
AUC(0-t)	82.18	76.46 → 88.33	17.43
AUC(inf)	90.88	82.20 → 100.48	18.03
1 x 15 mg vs. 1 x 60 mg			
C _{max}	100.64	95.16 → 106.43	13.48
AUC(0-t)	70.46	65.55 → 75.73	17.43
AUC(inf)	83.20	74.85 → 92.48	18.03
1 x 30 mg vs. 1 x 60 mg			
C _{max}	98.45	93.16 → 104.04	13.48
AUC(0-t)	85.74	79.84 → 92.07	17.43
AUC(inf)	91.55	82.22 → 101.93	18.03

¹Based on analysis of natural log-transformed data after normalization to the 30 mg dose.

Figure 4.2.1.16: Relationships between the mean C_{max} and AUC(inf) of morphine-6-glucuronide and the dose of codeine after oral administration of 1 x 15 mg, 1 x 30 mg, and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fasted conditions.



AUC Ratios:

The differences in the AUC(0-t) ratios for morphine-to-codeine (Figure 4.2.1.17), M3G-to-morphine (Figure 4.2.1.18), and M6G-to-morphine (Figure 4.2.1.19) after oral administration of 1 x 15 mg, 1 x 30 mg, and 1 x 60 mg doses of Roxane Laboratories' codeine tablets were not statistically different. This indicates that the extent of metabolism of codeine to morphine and then morphine to the two glucuronides was not affected by the dose.

Figure 4.2.1.17: Individual subject AUC(inf) ratios, of morphine-to-codeine, after oral administration of 1 x 15 mg, 1 x 30 mg, and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fasted conditions.

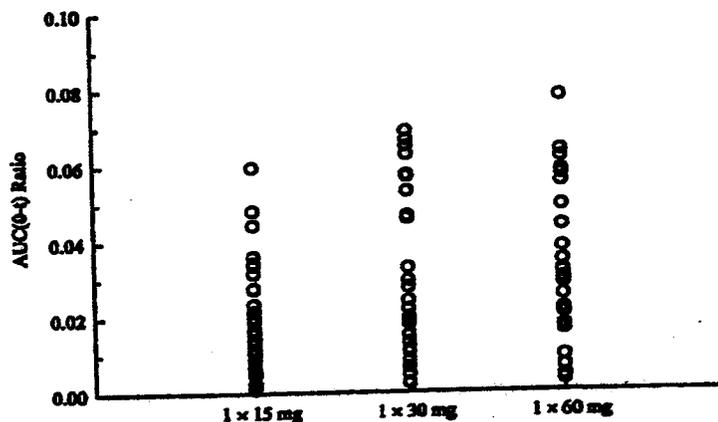


Figure 4.2.1.18: Individual subject AUC(inf) ratios, of M3G to-morphine, after oral administration of 1 x 15 mg, 1 x 30 mg, and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fasted conditions.

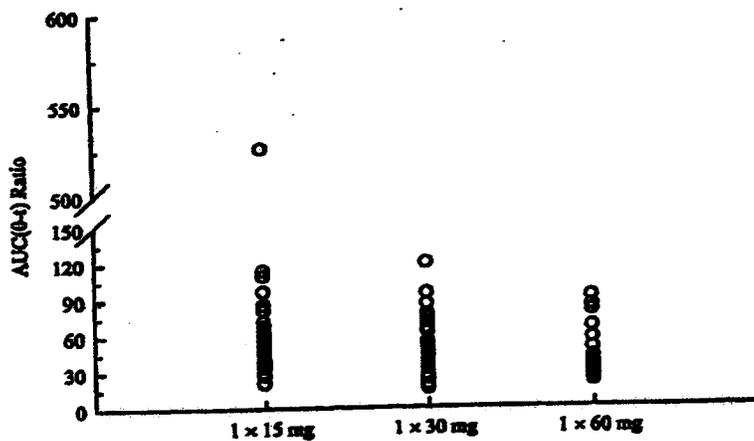
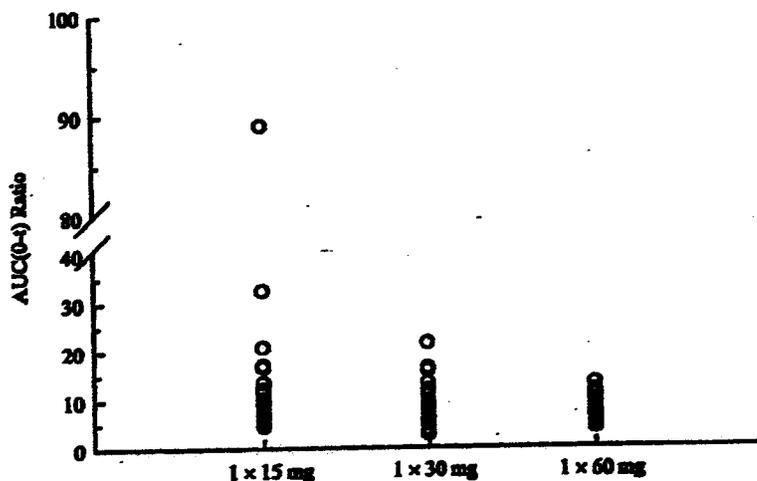


Figure 4.2.1.19: Individual subject AUC(0-t) ratios, of M6G to-morphine, after oral administration of 1 x 15 mg, 1 x 30 mg, and 1 x 60 mg doses of Roxane Laboratories' codeine tablets to healthy volunteers under fasted conditions.



Reviewer's comments:

1. The increases in C_{max} , $AUC(0-t)$, and $AUC(inf)$ after oral administration of 1 x 15 mg, 1 x 30 mg, and 1 x 60 mg doses of Roxane Laboratories' codeine tablets were dose proportional with respect to the parent, codeine and major metabolite measured, M3G.
2. The increases in C_{max} , $AUC(0-t)$, and $AUC(inf)$ after oral administration of 1 x 15 mg, 1 x 30 mg, and 1 x 60 mg doses of Roxane Laboratories' codeine tablets were dose linear with respect to the other two metabolites measured, morphine and M6G.
3. 15 mg, 1 x 30 mg, and 1 x 60 mg doses of Roxane Laboratories' codeine tablets can be considered dose proportional with respect to codeine or dose linear with respect to all the four moieties measured.

4.2.2. Study CODE- T60-PVFS/FD-1: Food Effect Study

Study title	A single-dose, open-label, randomized, 2-treatment, 2-period, crossover study to evaluate the effect of food on the absorption of codeine from Roxane Laboratories' Codeine Sulfate 60 mg tablets
Clinical site	Cedra Clinical Research LLC 2455 N.E. Loop 410 Suite 150 San Antonio TX 78217
Principal Investigator	Jolene K. Berg, M.D.
Dosing dates	Period I: Jan 12 2008 Period 2: Jan 19 2008
Analytical site	
Analytical Director	
Analysis dates	February 27, 2008 – March 26, 2008

b(4)

Objective:

To assess the effect of food on the absorption of codeine from Roxane Laboratories' 60 mg Codeine Sulfate tablet.

Study design:

Thirty-six of 36 study participants were administered a single 60 mg oral dose of both the following treatments in a randomized, sequenced fashion on January 12, 2008 and January 19, 2008.

Test Product: Treatment A

Fasting conditions
Codeine Sulfate (1 x 60 mg tablet)
Roxane Laboratories, Inc.
Lot #757627A
Mfg Date 9/24/2007

Reference Product: Treatment B

Fed conditions
Codeine Sulfate (1 x 60 mg tablet)
Roxane Laboratories, Inc.
Lot # 757627A
Mfg Date 9/24/2007

Demographic Profile:

22 females; 14 males
31 caucasian; 2 black; 1 asian; 2 others
Mean age = 29 ± 7 years
Mean BMI = 24.6 ± 3 kg/m²
Mean weight = 67.6 ± 10 kg

Fasting/meals

Fasting arm: Fast overnight for at least 10 hours prior to dosing.
Fed arm: After the overnight fast, the following high fat (approximately 50% of total caloric content of the meal), high calorie (approximately 1000 calories) breakfast was served starting approximately 30 minutes prior to dosing.

2 eggs fried in butter
2 strips of bacon
2 slice of toast with butter
4 ounces of hash brown potatoes
8 ounces of whole milk

This meal contains approximately 150 protein calories, 250 carbohydrate calories, and 500-600 fat calories.

Blood Samples for PK Analysis:

Blood samples were collected before dose and at 5, 10, 15, 30, 45 minutes and 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours after dosing.

Bioanalytical Analysis:

Plasma concentrations of codeine, morphine, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G) were measured using an LC/MS/MS method validated under the project code "JHS" by _____

b(4)

PK and Statistical Analyses:

The pharmacokinetic and statistical analyses were done by _____

b(4)

_____ All PK parameters were calculated using non-compartmental analysis. Only those plasma concentrations equal to or greater than the LOQs (codeine - 1 ng/mL; morphine - 0.20 ng/mL; M3G - 2.0 ng/mL; M6G - 0.5 ng/mL) were used in the analysis. Actual sampling times were used in all pharmacokinetic analyses.

Population for PK Analysis:

Thirty-six subjects were enrolled into and all subjects completed both periods of the study and comprise the analysis population.

a. Codeine

Mean plasma concentrations of codeine after administration of Roxane Laboratories' Codeine Sulfate 60 mg tablet were comparable after administration under fed and fasted conditions (Figure 4.2.2.1 - linear axes). There was a 50% increase in the median T_{max} , from 1.00 h to 1.54 h (Table 4.2.2.2), and an 11% decrease in C_{max} , suggesting a slight decrease in the rate of absorption under fed conditions. However, the 90% confidence intervals for C_{max} , $AUC(0-t)$, and $AUC(\infty)$ were within the 80% to 125% equivalence window (Table 4.2.2.3), demonstrating no effect of food on the bioavailability with respect to codeine.

Figure 4.2.2.1: Mean plasma concentrations of codeine after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 60 mg to healthy volunteers under fed and fasted conditions - linear axes.

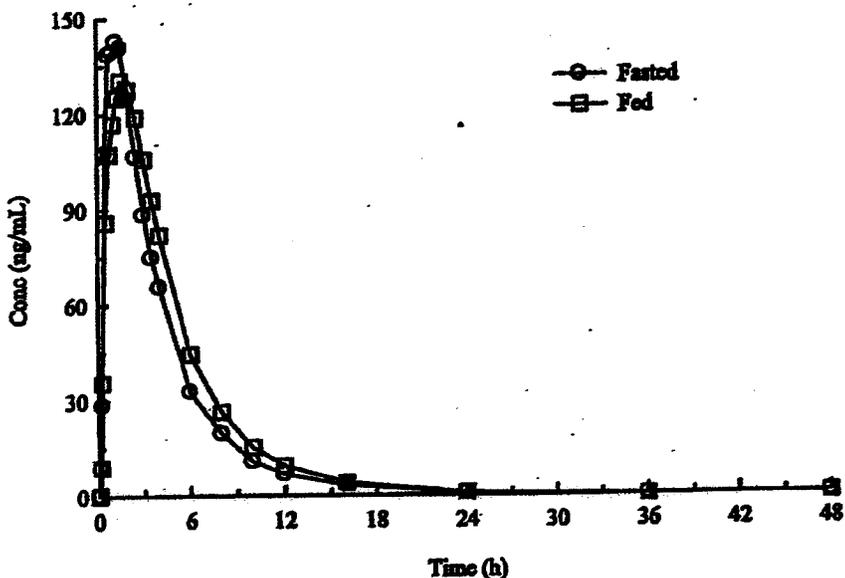


Table 4.2.2.2: Summary of pharmacokinetic parameters for codeine after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 60 mg to healthy volunteers under fed and fasted conditions.

Parameter ¹	Fasted	Fed
C _{max} (ng/mL)	167 ± 54.0 (36)	149 ± 49.2 (36)
T _{max} (h)	1.00 (36) [0.50 – 2.50]	1.54 (36) [0.25 – 4.00]
AUC(0-t) (h×ng/mL)	629 ± 175 (36)	711 ± 211 (36)
AUC(inf) (h×ng/mL)	639 ± 175 (36)	720 ± 212 (36)
λ _z (h ⁻¹)	0.2163 ± 0.0490 (36)	0.2174 ± 0.0436 (36)
t _{1/2} (h)	3.41 ± 0.93 (36)	3.33 ± 0.75 (36)
Ln(C _{max})	5.06 ± 0.35 (36)	4.95 ± 0.36 (36)
Ln[AUC(0-t)]	6.41 ± 0.28 (36)	6.52 ± 0.32 (36)
Ln[AUC(inf)]	6.42 ± 0.27 (36)	6.53 ± 0.31 (36)

¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Table 4.2.2.3: Statistical comparison of pharmacokinetic parameters for codeine after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 60 mg to healthy volunteers under fed and fasted conditions.

Parameter	Geometric Mean Ratio (%) ¹		
	Estimate	90% Confidence Interval	
C _{max}	89.34	81.18	→ 98.31
AUC(0-t)	111.98	105.27	→ 119.12
AUC(inf)	111.83	105.20	→ 118.86

¹Based on analysis of natural log-transformed data.

b. Morphine

Mean plasma concentrations of morphine over the initial two to three hours after administration of 60 mg of codeine sulfate under fed conditions were substantially reduced compared to administration under fasted conditions (Figure 4.2.2.4 - linear axes). There was a 30% reduction in C_{max} under fed conditions, consistent with the 7-fold increase in T_{max} (Table 4.2.2.5), with a 90% confidence interval for the geometric mean ratio for C_{max} below the 80% to 125% equivalence window (Table 4.2.2.5) demonstrating significant effect of food on the bioavailability with respect to morphine. However, the geometric mean ratio for AUC(0-t) was essentially 100% with a confidence interval of 84.94% to 119.80%, indicating no effect of food possibly on the

extent of conversion of codeine to morphine. Taking into account that AUC(inf) parameter could only be calculated for both treatments for a limited number of subjects, the results were consistent with those observed for AUC(0-t) (Table 4.2.2.6). Overall, the data indicate a decrease in the rate of formation of morphine from codeine, consistent with the slightly decreased absorption rate observed with codeine (as seen with codeine in Part a) but no change in the extent of conversion of codeine to morphine when codeine was administered under fed conditions.

Figure 4.2.2.4: Mean plasma concentrations of morphine after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 60 mg to healthy volunteers under fed and fasted conditions - linear axes.

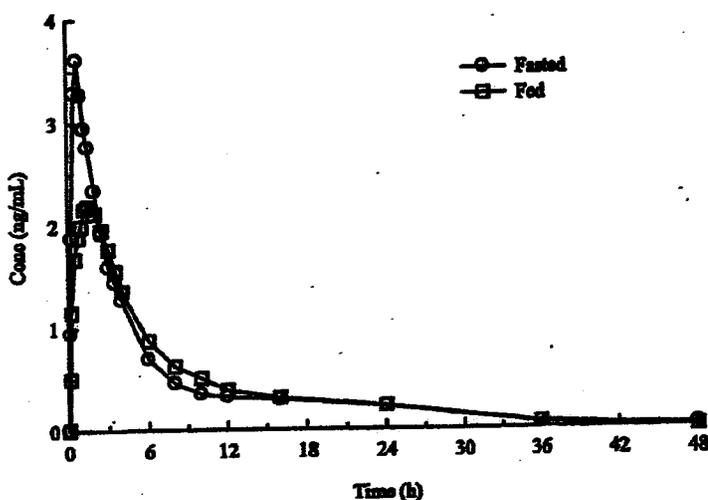


Table 4.2.2.5: Summary of pharmacokinetic parameters for morphine after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 60 mg to healthy volunteers under fed and fasted conditions.

Parameter ¹	Fasted	Fed
C _{max} (ng/mL)	4.07 ± 3.20 (36)	2.83 ± 2.01 (36)
T _{max} (h)	0.75 (36) [0.17 - 2.00]	1.28 (36) [0.25 - 8.00]
AUC(0-t) (h×ng/mL)	17.4 ± 13.9 (36)	17.3 ± 13.1 (36)
AUC(inf) (h×ng/mL)	21.0 ± 15.1 (14)	24.4 ± 14.9 (17)
λ _z (h ⁻¹)	0.1506 ± 0.1244 (14)	0.1012 ± 0.0781 (17)
t _{1/2} (h)	9.53 ± 7.20 (14)	11.5 ± 7.76 (17)
Ln(C _{max})	1.10 ± 0.88 (36)	0.74 ± 0.87 (36)
Ln[AUC(0-t)]	2.39 ± 1.30 (36)	2.40 ± 1.17 (36)
Ln[AUC(inf)]	2.69 ± 0.98 (14)	2.95 ± 0.81 (17)

¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Table 4.2.2.6: Statistical comparison of pharmacokinetic parameters for morphine after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 60 mg to healthy volunteers under fed and fasted conditions.

Parameter	Geometric Mean Ratio (%) ¹		
	Estimate	90% Confidence Interval	
C _{max}	69.69	60.43 →	80.36
AUC(0-t)	100.88	84.94 →	119.80
AUC(inf)	116.98	91.18 →	150.06

¹Based on analysis of natural log-transformed data.

c. Morphine-3-glucuronide

The mean plasma concentrations of the major metabolite measured, M3G were lower after administration of Roxane Laboratories' Codeine Sulfate 60 mg tablet under fed conditions than under fasted conditions (Figure 4.2.2.7 - linear axes). The lower limit of the 90% confidence interval for C_{max} was below 80% (Table 6) and T_{max} increased 1.7-fold (Table 4.2.2.8), indicating a slight decrease in the rate of formation of the metabolite. The geometric mean ratios for AUC(0-t) and AUC(inf) were essentially 100% and the associated 90% confidence intervals were within the 80% to 125% equivalence window (Table 4.2.2.9), demonstrating no change in the extent of formation of M3G in the presence of food. The data indicate a slight decrease in the rate but no change in the extent of formation of M3G from morphine when codeine was administered under fed conditions.

Figure 4.2.2.7: Mean plasma concentrations of M3G after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 60 mg to healthy volunteers under fed and fasted conditions - linear axes.

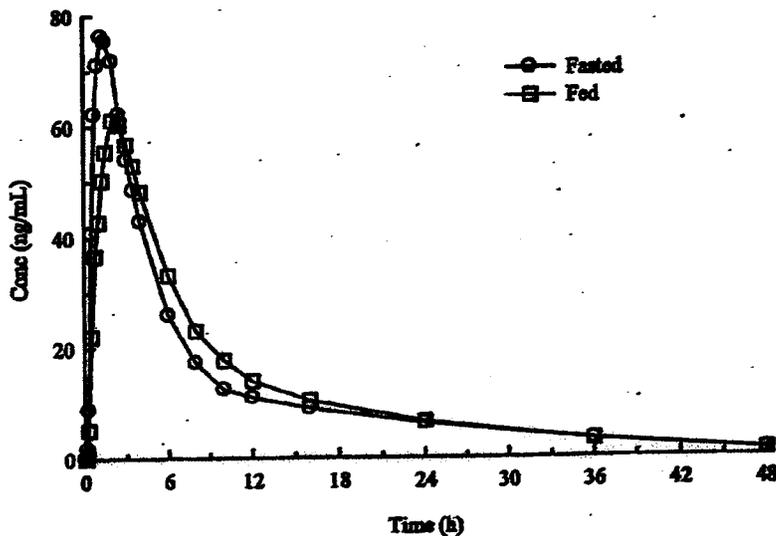


Table 4.2.2.8: Summary of pharmacokinetic parameters for M3G after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 60 mg to healthy volunteers under fed and fasted conditions.

Parameter ¹	Fasted	Fed
C _{max} (ng/mL)	82.0 ± 50.1 (36)	68.3 ± 47.2 (36)
T _{max} (h)	1.32 (36) [1.00 – 2.50]	2.25 (36) [1.00 – 8.00]
AUC(0-t) (h×ng/mL)	553 ± 320 (36)	585 ± 381 (36)
AUC(inf) (h×ng/mL)	621 ± 261 (25)	632 ± 407 (29)
λ _z (h ⁻¹)	0.0667 ± 0.0265 (25)	0.0764 ± 0.0460 (29)
t _{1/2} (h)	11.6 ± 3.59 (25)	10.9 ± 3.90 (29)
Ln(C _{max})	4.14 ± 0.87 (36)	3.94 ± 0.86 (36)
Ln[AUC(0-t)]	5.99 ± 1.07 (36)	6.04 ± 1.01 (36)
Ln[AUC(inf)]	6.31 ± 0.58 (25)	6.14 ± 0.96 (29)

¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Table 4.2.2.9: Statistical comparison of pharmacokinetic parameters for M3G after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 60 mg to healthy volunteers under fed and fasted conditions.

Parameter	Geometric Mean Ratio (%) ¹		
	Estimate	90% Confidence Interval	
C _{max}	81.77	76.18	→ 87.78
AUC(0-t)	104.28	95.01	→ 114.45
AUC(inf)	101.13	92.52	→ 110.54

¹Based on analysis of natural log-transformed data.

d. Morphine-6-glucuronide

The mean plasma concentrations of M6G were lower after administration of Roxane Laboratories' Codeine Sulfate 60 mg tablet under fed conditions than under fasted conditions (Figure 4.2.2.10 - linear axes). The lower limit of the 90% confidence interval for C_{max} was below 80% (Table 4.2.2.11) and T_{max} increased 1.7- fold (Table 4.2.2.11), indicating a slight decrease in the rate of formation of the metabolite. The 90% confidence intervals for the geometric mean ratios for AUC(0-t) and AUC(inf) were within the 80% to 125% equivalence window (Table 4.2.2.12), demonstrating no change in the extent of formation of M6G in the presence of food. The data indicate a slight decrease in the rate but no change in the extent of formation of M6G from morphine when codeine was administered under fed conditions.

Figure 4.2.2.10: Mean plasma concentrations of M6G after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 60 mg to healthy volunteers under fed and fasted conditions - linear axes.

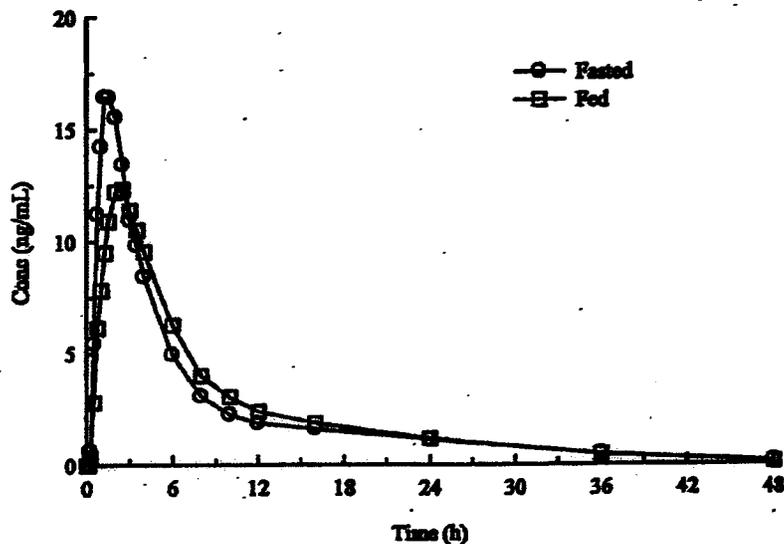


Table 4.2.2.11: Summary of pharmacokinetic parameters for M6G after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 60 mg to healthy volunteers under fed and fasted conditions.

Parameter ¹	Fasted	Fed
C_{max} (ng/mL)	18.2 ± 10.1 (36)	14.2 ± 9.57 (36)
T_{max} (h)	1.50 (36) [1.00 – 2.50]	2.50 (36) [1.25 – 8.00]
AUC(0-t) (h×ng/mL)	103 ± 57.4 (36)	104 ± 65.2 (36)
AUC(inf) (h×ng/mL)	122 ± 71.1 (20)	129 ± 70.5 (25)
λ_z (h⁻¹)	0.0988 ± 0.0878 (20)	0.0786 ± 0.0519 (25)
t_{1/2} (h)	11.0 ± 5.61 (20)	11.0 ± 4.12 (25)
Ln(C_{max})	2.70 ± 0.71 (36)	2.41 ± 0.77 (36)
Ln[AUC(0-t)]	4.39 ± 0.87 (36)	4.36 ± 0.91 (36)
Ln[AUC(inf)]	4.49 ± 1.02 (20)	4.66 ± 0.75 (25)

¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Table 4.2.2.12: Statistical comparison of pharmacokinetic parameters for M6G after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 60 mg to healthy volunteers under fed and fasted conditions.

Parameter	Geometric Mean Ratio (%) ¹		
	Estimate	90% Confidence Interval	
C _{max}	74.48	69.38	→ 79.96
AUC(0-t)	97.69	90.66	→ 105.26
AUC(inf)	111.19	102.90	→ 120.15

¹Based on analysis of natural log-transformed data.

AUC Ratios:

There were essentially no differences in the AUC(inf) ratios for morphine-to-codeine (Figure 4.2.2.13), M3G-to-morphine (Figure 4.2.2.14), and M6G-to-morphine (Figure 4.2.2.15) after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 60 mg under fed and fasted conditions. This indicates that the extent of metabolism of codeine to morphine and then morphine to the two glucuronides was not affected by administration under fed conditions.

Figure 4.2.2.13: Individual subject AUC(inf) ratios, of morphine-to-codeine, after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 60 mg to healthy volunteers under fed and fasted conditions.

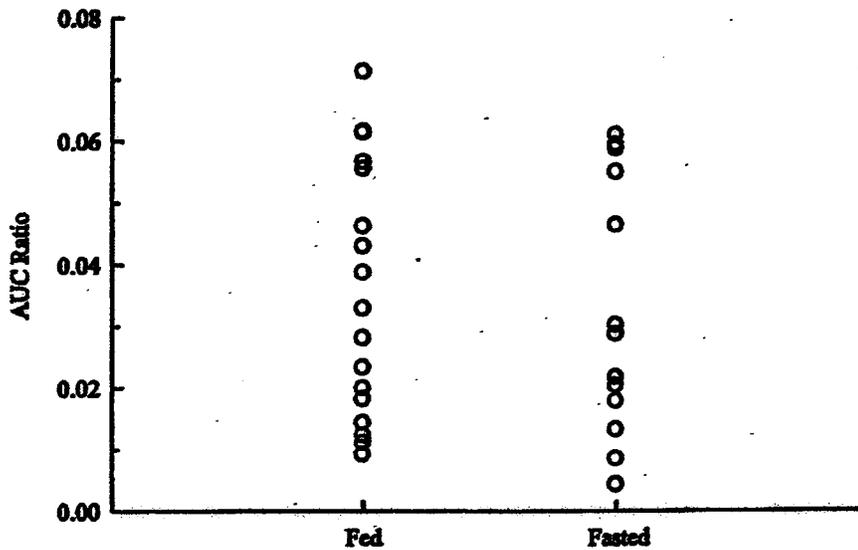


Figure 4.2.2.14: Individual subject AUC(inf) ratios, of M3G to-morphine, after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 60 mg to healthy volunteers under fed and fasted conditions.

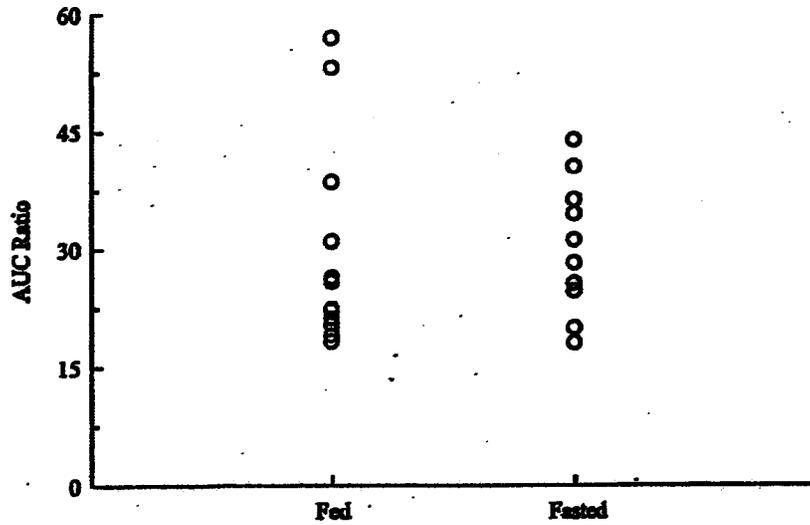
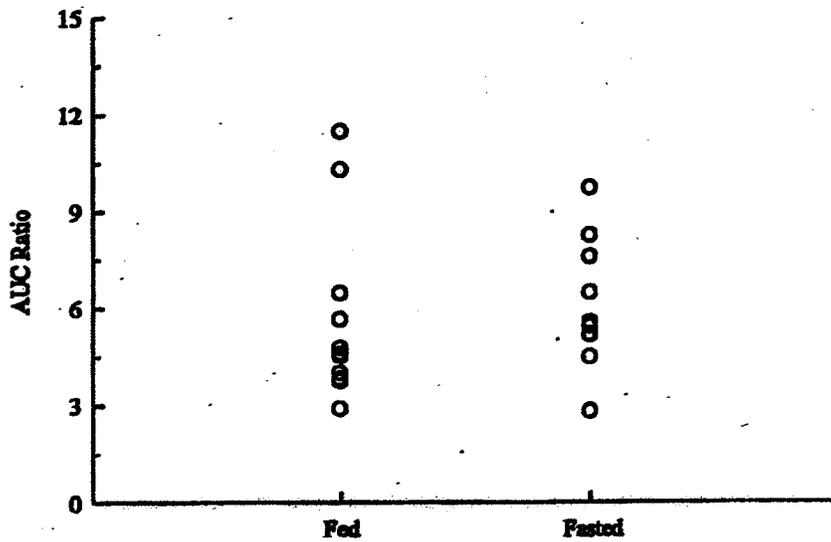


Figure 4.2.2.15: Individual subject AUC(inf) ratios, of M6G to-morphine, after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 60 mg to healthy volunteers under fed and fasted conditions.



Reviewer's comments:

1. Administration of Roxane Laboratories' Codeine Sulfate Tablet 60 mg under fed conditions resulted in no change in the rate or extent of absorption of parent, codeine.
2. The rates of formation of morphine from codeine and M3G and M6G from morphine under fed conditions were lower as compared with the rates of formation under fasted conditions. However, there were no differences in the AUC(inf) ratios for morphine-to-codeine, M3G-to morphine, and M6G-to-morphine after oral administration under fed and fasted conditions, indicating that the extent of metabolism of codeine to morphine and then morphine to the two glucuronides may not be affected by food.

Overall, it can be reasonably assumed that food will not have a clinically significant effect on the oral absorption of parent codeine, when Roxane Laboratories' Codeine Sulfate Tablets are administered.

4.2.3. Study CODE-T15-PVFS-1: Steady State Study

Study title	A steady state, 1-period, 1-treatment study of Codeine Sulfate 15 mg tablets under steady state conditions
Clinical site	Cedra Clinical Research LLC 2455 N.E. Loop 410 Suite 150 San Antonio TX 78217
Principal Investigator	Frederick A. Bieberdorf, M.D., CPI
Dosing dates	January 04, 2008 – January 09, 2008
Analytical site	_____ 3
Analytical Director	_____
Analysis dates	January 31, 2008 – March 07, 2008

b(4)

Objective:

To characterize the steady-state pharmacokinetics of codeine and its metabolites morphine, M3G, and M6G after oral administration of Roxane Laboratories' codeine sulfate tablets administered at a dose of 15 mg Q4H x 5 days.

Study design:

This was an open-label study of the pharmacokinetics of codeine after 15 mg oral doses of codeine sulfate tablets every 4 hours (Q4H) for 5 days performed at one study site in normal healthy volunteers. Thirty-six (36) subjects were enrolled and 32 subjects completed the study. Due to the nature of the study (1-period, 1-treatment), no randomization was required.

Demographic Profile:

13 females; 19 males
22 caucasian; 9 black; 1 asian
Mean age = 30 ± 9 years
Mean weight = 79 ± 21 kg
Mean BMI = 25.4 ± 2.6 kg/m²

Blood Samples for PK Analysis:

Doses were administered 4 hour intervals at approximately the following times: 0800, 1200, 1600, 2000, 2400, and 0400. Blood samples were collected prior to the first dose on Day 1, prior to the 0800 dose on Days 2, 3, and 4, and at the following times on Day 5 relative to the 0800 dose: before, 0.5, 0.75, 1, 1.25, 1.5, 2, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 8.5, 9, 9.5, 10, 10.5, 11, 12, 12.5, 13, 13.5, 14, 14.5, 15.5, 15, 16, 16.5, 17, 17.5, 18, 18.5, 19, 20, 20.5, 21, 21.5, 22, 22.5, 23, and 24 hours.

Bioanalytical Analysis:

Plasma concentrations of codeine, morphine, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G) were measured using an LC/MS/MS method validated under the project code "KHS" by _____

b(4)

PK and Statistical Analyses:

The pharmacokinetic and statistical analyses were done by _____

All PK

b(4)

parameters were calculated using non-compartmental analysis. Only those plasma concentrations equal to or greater than the LOQs (codeine - 1 ng/mL; morphine - 0.20 ng/mL; M3G - 2.0 ng/mL; M6G - 0.5 ng/mL) were used in the analysis. Actual sampling times were used in all pharmacokinetic analyses.

The areas under the curve over each 4 hour dosing interval at steady-state (Day 5) [AUC(0-4)] and for the 24-hour period [AUC(0-24)] were calculated using the linear trapezoidal method. The degree of fluctuation (DFL) was calculated using $DFL = 100\% \times C_{max} - C_{min} / AUC(0-24) / 24$

Population for PK Analysis:

Thirty-six (36) subjects were enrolled into the study. Three (3) subjects, #513, #514, and #526 did not complete the study and no samples were analyzed. Subject #520 withdrew after the blood sample at 0.75 h on Day 5; samples collected through that time were analyzed. Thirty-two (32) subjects therefore comprise the analysis population.

a. Attainment of Steady State

The mean pre-dose plasma concentrations for all the four moieties measured were relatively constant from Day 3 - 48 hours after beginning dosing and 48 hours prior to the steady-state day - through the last dose on Day 5. This indicates that steady-state had been reached by Day 3.

Figure 4.2.3.1: Mean \pm standard deviation pre-dose plasma concentrations of codeine during oral administration of Roxane Laboratories' 15 mg codeine sulfate tablets Q4H x 5 days tablets to healthy volunteers.

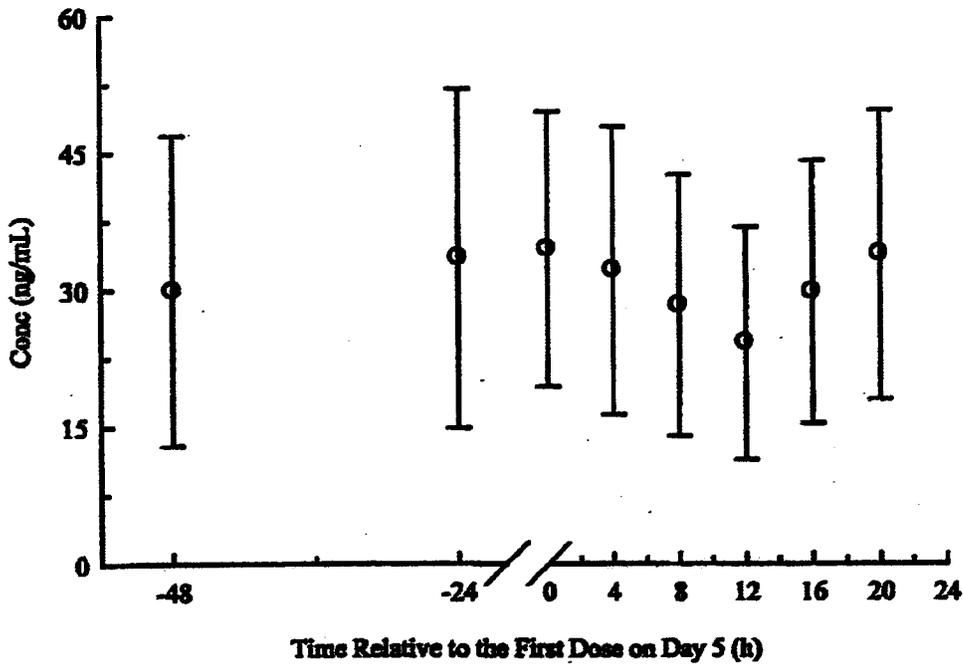


Figure 4.2.3.2: Mean \pm standard deviation pre-dose plasma concentrations of morphine during oral administration of Roxane Laboratories' 15 mg codeine sulfate tablets Q4H x 5 days tablets to healthy volunteers.

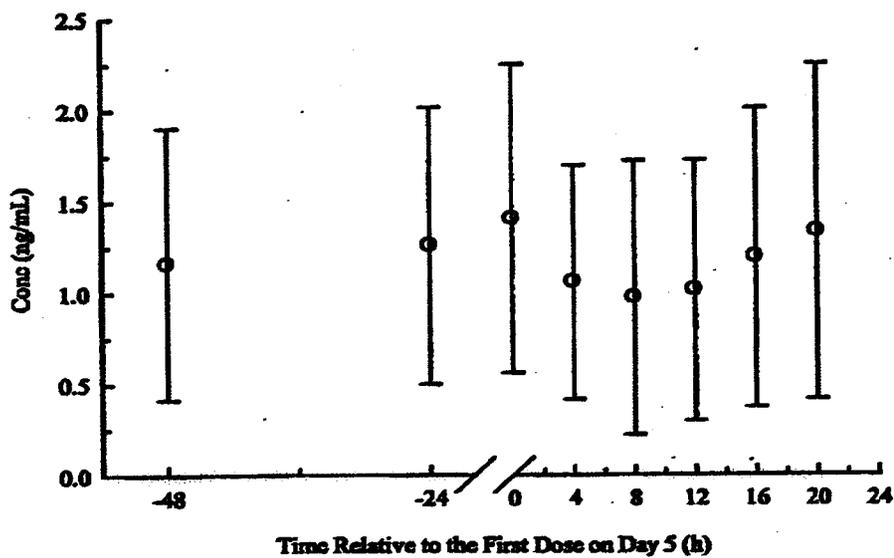


Figure 4.2.3.3: Mean \pm standard deviation pre-dose plasma concentrations of M3G during oral administration of Roxane Laboratories' 15 mg codeine sulfate tablets Q4H x 5 days tablets to healthy volunteers.

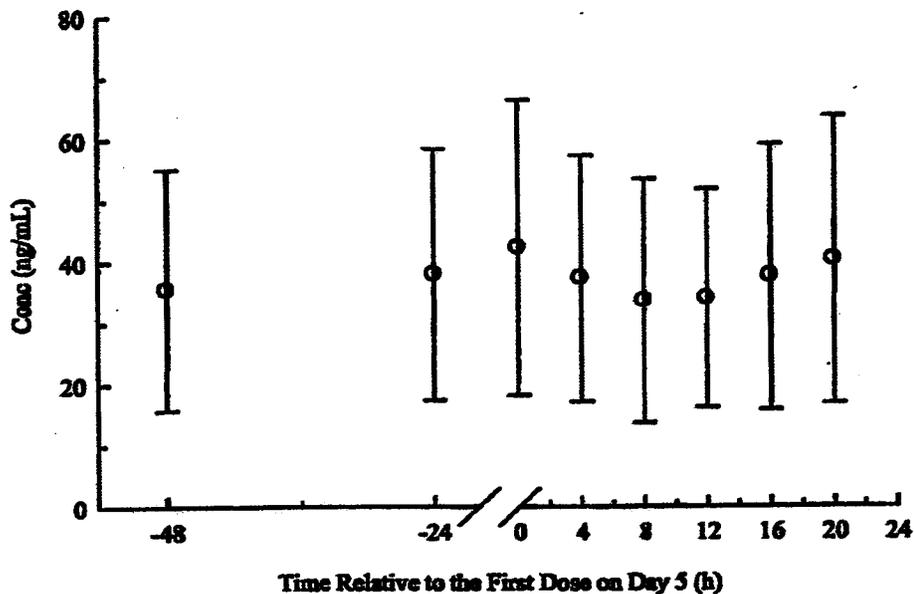
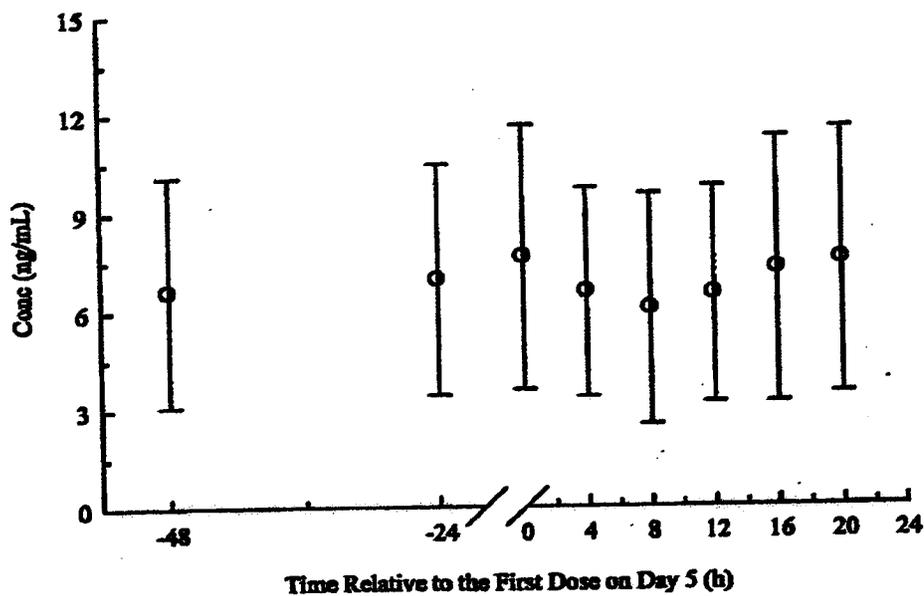


Figure 4.2.3.4: Mean \pm standard deviation pre-dose plasma concentrations of M6G during oral administration of Roxane Laboratories' 15 mg codeine sulfate tablets Q4H x 5 days tablets to healthy volunteers.



b. Pharmacokinetics at Steady State

The mean plasma concentration-time profiles for all the four moieties measured were relatively consistent across the six doses administered on Day 5 (Table 4.2.3.5, Figures 4.2.3.7-10).

Codeine and M3G, the major metabolite, comprised the greatest percentages, 55% and 36%, respectively of total circulating material (Table 4.2.3.6). Morphine comprised approximately 2%, reflecting its rapid conversion to the glucuronides conjugates. The remaining 6.6% of circulating material was M6G, the other metabolite measured.

Table 4.2.3.5: Summary of C_{max}, T_{max}, and AUC(0-4) for codeine, morphine, M3G, and M6G for individual doses on Day 5 during oral administration of Roxane Laboratories' 15 mg codeine sulfate tablets Q4H x 5 days tablets to healthy volunteers.

Parameter ¹	Codeine	Morphine	M3G	M6G
First Dose				
C _{max} (ng/mL)	68.3 ± 27.8 (32)	1.90 ± 1.08 (32)	51.2 ± 25.2 (32)	9.45 ± 4.33 (32)
T _{max} (h) ²	1.5 (32)	1.3 (32)	1.5 (32)	1.5 (32)
AUC (h·ng/mL)	216 ± 88.3 (32)	216.38 ± 3.93 (32)	216 ± 101 (32)	216.4 ± 16.3 (32)
Second Dose				
C _{max} (ng/mL)	70.2 ± 27.7 (32)	2.03 ± 1.33 (32)	50.8 ± 26.1 (32)	9.19 ± 4.43 (32)
T _{max} (h) ²	5.0 (32)	4.5 (32)	5.0 (32)	5.0 (32)
AUC (h·ng/mL)	184 ± 76.2 (32)	4.90 ± 3.16 (32)	165 ± 85.7 (32)	29.9 ± 14.7 (32)
Third Dose				
C _{max} (ng/mL)	55.6 ± 22.9 (32)	1.76 ± 1.01 (32)	53.2 ± 27.2 (32)	10.5 ± 5.27 (32)
T _{max} (h) ²	9.0 (32)	8.5 (32)	9.0 (32)	9.5 (32)
AUC (h·ng/mL)	156 ± 72.7 (32)	5.07 ± 3.27 (32)	171 ± 89.2 (32)	32.3 ± 16.3 (32)
Fourth Dose				
C _{max} (ng/mL)	53.9 ± 24.0 (32)	1.71 ± 1.19 (32)	49.1 ± 25.4 (32)	9.53 ± 4.78 (32)
T _{max} (h) ²	13.5 (32)	13.5 (32)	14.0 (32)	14.0 (32)
AUC (h·ng/mL)	154 ± 70.9 (32)	5.36 ± 3.63 (32)	165 ± 86.6 (32)	31.0 ± 15.6 (32)
Fifth Dose				
C _{max} (ng/mL)	51.2 ± 15.9 (32)	1.86 ± 1.21 (32)	53.0 ± 26.9 (32)	10.2 ± 4.88 (32)
T _{max} (h) ²	17.5 (32)	17.3 (32)	17.5 (32)	17.5 (32)
AUC (h·ng/mL)	164 ± 59.1 (32)	6.10 ± 3.99 (32)	181 ± 95.7 (32)	34.1 ± 17.2 (32)
Sixth Dose				
C _{max} (ng/mL)	62.3 ± 28.0 (32)	2.28 ± 1.44 (32)	57.3 ± 30.3 (32)	10.8 ± 5.39 (32)
T _{max} (h) ²	21.5 (32)	20.5 (32)	21.3 (32)	21.5 (32)
AUC (h·ng/mL)	191 ± 87.1 (32)	6.91 ± 4.36 (32)	192 ± 103 (32)	35.2 ± 17.5 (32)

¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

²T_{max} relative to the first dose on Day 5.

Table 4.2.3.6: Relative exposure to codeine, morphine, M3G, and M6G on Day 5 during oral administration of Roxane Laboratories' 15 mg codeine sulfate tablets Q4H x 5 days tablets to healthy volunteers.

Analyte	Molecular Weight	Mean AUC(0-24)		Percent of Total ¹
		(h·ng/mL)	(h·nmol/mL)	
Codeine	299.36	1,048.19	3.50	55.37
Morphine	285.33	34.61	0.12	1.92
M3G	461.46	1,052.60	2.28	36.07
M6G	461.46	193.75	0.42	6.64

¹Percent of total AUC(0-24).

Figure 4.2.3.7: Mean plasma concentrations of codeine on Day 5 during oral administration of Roxane Laboratories' 15 mg codeine sulfate tablets Q4H x 5 days tablets to healthy volunteers.

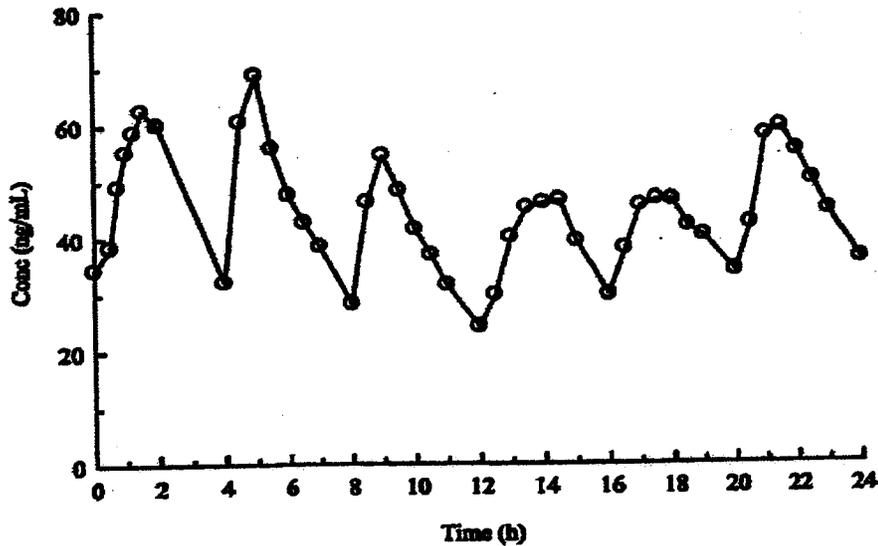


Figure 4.2.3.8: Mean plasma concentrations of morphine on Day 5 during oral administration of Roxane Laboratories' 15 mg codeine sulfate tablets Q4H x 5 days tablets to healthy volunteers.

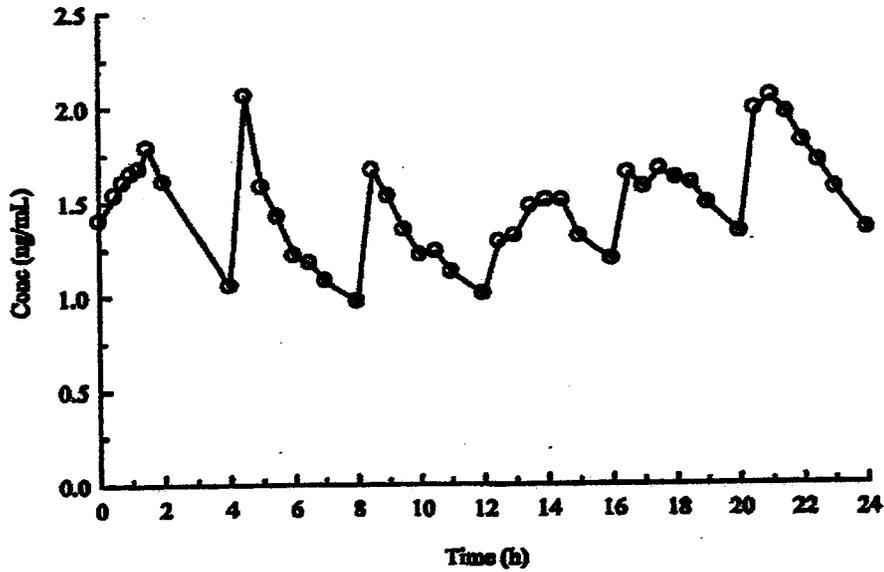


Figure 4.2.3.9: Mean plasma concentrations of M3G on Day 5 during oral administration of Roxane Laboratories' 15 mg codeine sulfate tablets Q4H x 5 days tablets to healthy volunteers.

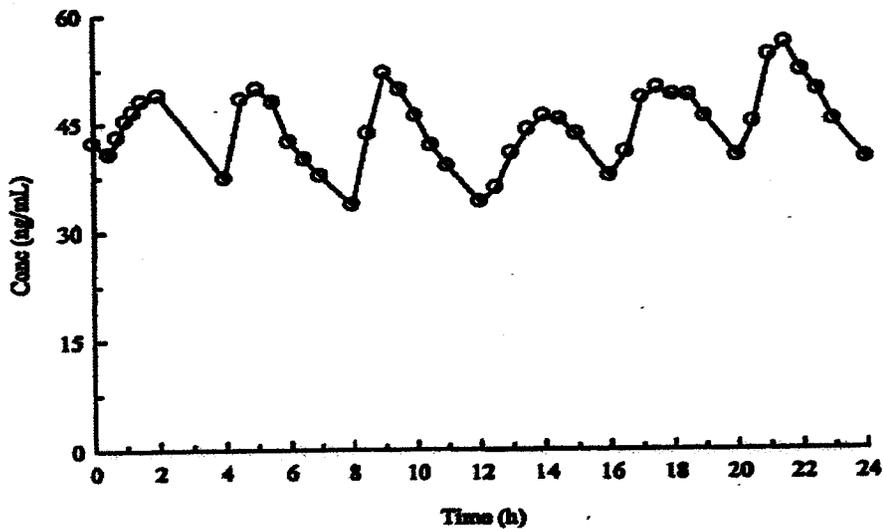
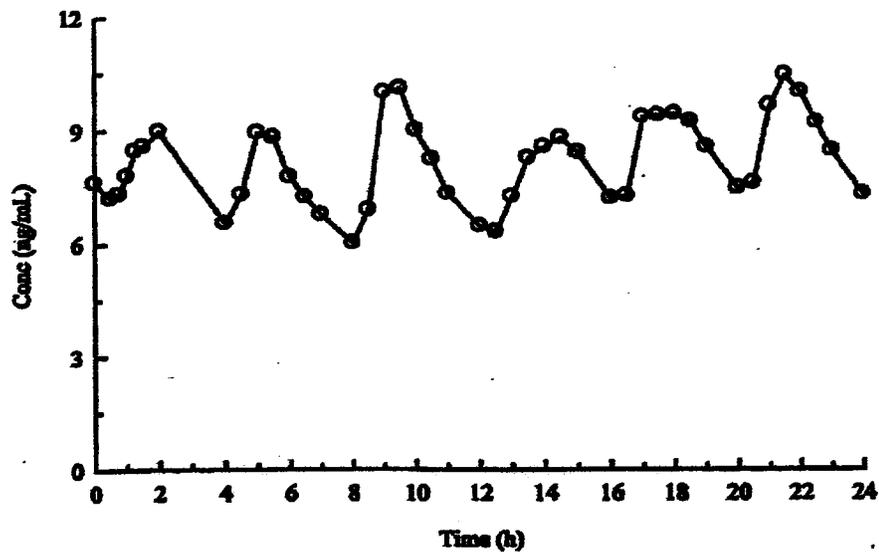


Figure 4.2.3.10: Mean plasma concentrations of M6G on Day 5 during oral administration of Roxane Laboratories' 15 mg codeine sulfate tablets Q4H x 5 days tablets to healthy volunteers.



Reviewer's comments:

1. Oral administration of Roxane Laboratories' codeine sulfate tablet 15 mg Q4H x 5 days resulted in steady-state plasma concentrations of codeine, morphine, M3G, and M6G within 48 hours. Mean plasma concentrations and mean values for C_{max} and AUC(0-4) were consistent across the six individual doses on Day 5.
2. Mean plasma concentrations and mean values for C_{max} and AUC(0-4) were consistent across the six individual doses on Day 5. Codeine comprised the largest portion of circulating material followed by M3G, M6G, and morphine.

4.2.4 Study CODE-T30-PVFS-1: Comparative Bioavailability Study

Study title	A Single-Dose, 2-Period, 2-Treatment, 2-Way Crossover Comparative Bioavailability Study of Codeine 30 mg Tablets and Tylenol® #3 Tablets Under Fasting Conditions
Clinical site	Cedra Clinical Research LLC 2455 N.E. Loop 410 Suite 150 San Antonio TX 78217
Principal Investigator	Jolene K. Berg, M.D.
Dosing dates	Period 1: January 9, 2008 Period 2: January 16, 2008
Analytical site	[REDACTED]
Analytical Director	[REDACTED]
Analysis dates	February 18, 2008 – March 4, 2008

b(4)

Objective:

To assess the comparative bioavailability of codeine from Roxane Laboratories' Codeine Sulfate 30 mg tablets to Tylenol® #3 (acetaminophen 300 mg with codeine phosphate 30 mg) under fasted conditions.

Study design:

This was an open label, single dose, two-treatment, two-period, two-sequence study. Thirty six (36) male and female subjects were enrolled to receive a single dose of each of two treatments in two assigned dosing periods following a minimum of 10-hour overnight fasting. Each dose administration was separated by a seven day washout period. Thirty four of 36 study participants were administered a single oral tablet dose of both the following treatments in a randomized, sequenced fashion.

Test Product: Treatment A
Codeine Sulfate (1 x 30 mg tablet)
Roxane Laboratories Inc.
Lot # 757701A
Mfg Date 10/03/2007

Reference Product: Treatment B
Tylenol® #3 (1 x acetaminophen 300 mg with codeine phosphate 30 mg tablet)
Ortho-McNeil Pharmaceutical, Inc.
Lot # 7EG005
Expiration Date 04/2010

Difference in Base Content of Codeine:

Roxane Laboratories' Codeine Sulfate 30 mg tablet contains _____ of codeine base while Tylenol® #3, with 30 mg of Codeine Phosphate, contains _____ of codeine base. This difference, approximately 8%, was not taken into account in the statistical comparisons conducted by the sponsor. b(4)

Demographic Profile:

12 females; 22 males
30 caucasian; 3 black; 1 other
Mean age = 28 ± 7 years
Mean weight = 73 ± 12 kg
Mean BMI = 24.5 ± 3 kg/m²

Blood Samples for PK Analysis:

Blood samples were drawn prior to each dose administration and at 5, 10, 15, 30, 45 minutes and 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 30, 36 and 48 hours after dosing.

Bioanalytical Analysis:

Plasma concentrations of codeine, morphine, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G) were measured using an LC/MS/MS method validated under the project code "ZGS" by _____. b(4)

PK and Statistical Analyses:

The pharmacokinetic and statistical analyses were done by _____ All PK parameters were calculated using non-compartmental analysis. Only those plasma concentrations equal to or greater than the LOQs (codeine - 1 ng/mL; morphine - 0.20 ng/mL; M3G - 2.0 ng/mL; M6G - 0.5 ng/mL) were used in the analysis. Actual sampling times were used in all pharmacokinetic analyses. b(4)

Population for PK analysis:

Thirty four subjects completed both periods of the study and comprised the evaluable population for pharmacokinetics.

a. Codeine

Mean plasma concentrations of codeine after administration of Roxane Laboratories' Codeine Sulfate 30 mg tablet and Tylenol® #3 (Codeine Phosphate 30 mg) were essentially super imposable despite the -8% difference in base content (Figure 4.2.4.1 – linear axes; Figure 4.2.4.2 - semi-logarithmic axes). Mean values for all pharmacokinetic parameters were comparable for both formulations (Table 4.2.4.3) with geometric mean ratios for C_{max}, AUC(0-t), and AUC(in of approximately 100% (Table 4.2.4.4). All of the associated 90% confidence intervals were within the 80% to 125% equivalence window (Table 4.2.4.4), demonstrating bioequivalence between products with respect to codeine.

Figure 4.2.4.1.: Mean plasma concentrations of codeine after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 30 mg and Tylenol® #3 (Codeine Phosphate 30 mg) to healthy volunteers under fasted conditions - linear axes.

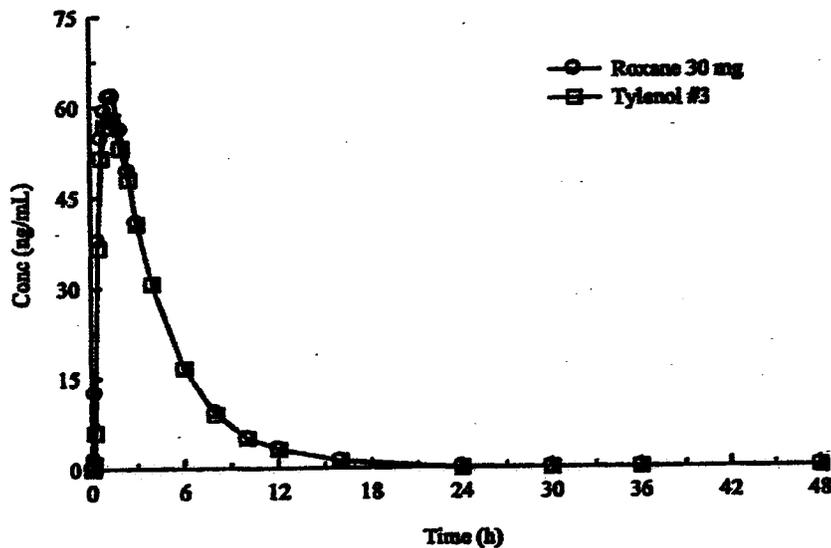


Figure 4.2.4.2: Mean plasma concentrations of codeine after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 30 mg and Tylenol® #3 (Codeine Phosphate 30 mg) to healthy volunteers under fasted conditions – semi logarithmic axes.

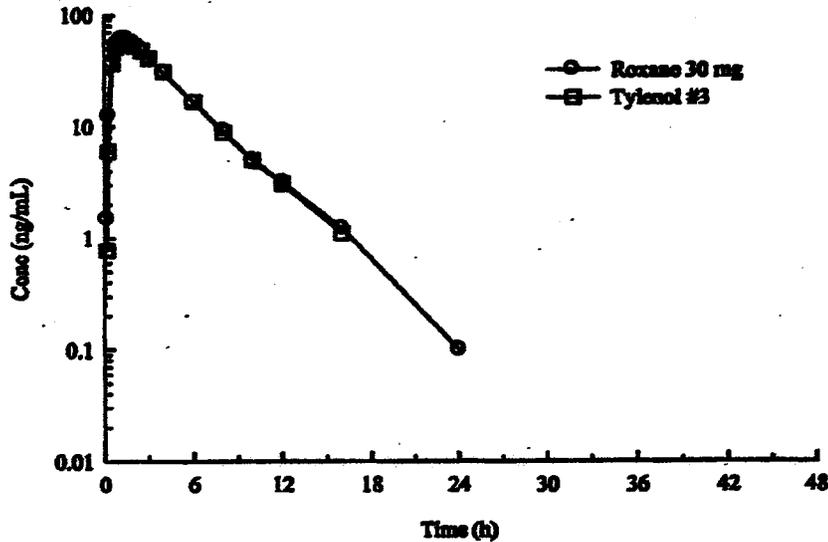


Table 4.2.4.3: Summary of pharmacokinetic parameters for codeine after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 30 mg and Tylenol® #3 (Codeine Phosphate 30 mg) to healthy volunteers under fasted conditions.

Parameter ¹	Roxane 30 mg	Tylenol #3
C _{max} (ng/mL)	71.2 ± 23.9 (34)	70.1 ± 21.9 (36)
T _{max} (h)	1.25 (34) [0.50 – 2.50]	1.25 (36) [0.50 – 3.00]
AUC(0-t) (h·ng/mL)	282 ± 98.0 (34)	272 ± 84.8 (36)
AUC(inf) (h·ng/mL)	289 ± 98.6 (34)	279 ± 86.3 (36)
λ _z (h ⁻¹)	0.2580 ± 0.0448 (34)	0.2620 ± 0.0419 (36)
t _{1/2} (h)	2.77 ± 0.51 (34)	2.71 ± 0.43 (36)
Ln(C _{max})	4.21 ± 0.34 (34)	4.20 ± 0.31 (36)
Ln[AUC(0-t)]	5.58 ± 0.35 (34)	5.56 ± 0.31 (36)
Ln[AUC(inf)]	5.61 ± 0.34 (34)	5.59 ± 0.30 (36)

¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Table 4.2.4.4: Statistical comparison of pharmacokinetic parameters for codeine after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 30 mg and Tylenol® #3 (Codeine Phosphate 30 mg) to healthy volunteers under fasted conditions.

Parameter	Geometric Mean Ratio (%) ¹	
	Estimate	90% Confidence Interval
C _{max}	100.80	94.06 → 108.02
AUC(0-t)	103.13	98.29 → 108.21
AUC(inf)	102.80	98.11 → 107.72

¹Based on analysis of natural log-transformed data.

b. Morphine

Mean plasma concentrations of morphine after administration of 30 mg of codeine phosphate as Tylenol® #3 were higher than after administration of 30 mg of codeine sulfate (Figure 4.2.4.5 - linear axes; Figure 4.2.4.6- semi-logarithmic axes) as were the mean values for C_{max}, AUC(0-t), and AUC(inf) (Table 4.2.4.7). The geometric mean ratios for C_{max} and the AUCs ranged from 108% to 124% (Table 4.2.4.8) and the upper limits of the associated 90% confidence intervals were above 125% (Table 4.2.4.8), indicating a lack of bioequivalence with respect to morphine.

Figure 4.2.4.5: Mean plasma concentrations of morphine after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 30 mg and Tylenol® #3 (Codeine Phosphate 30 mg) to healthy volunteers under fasted conditions - linear axes.

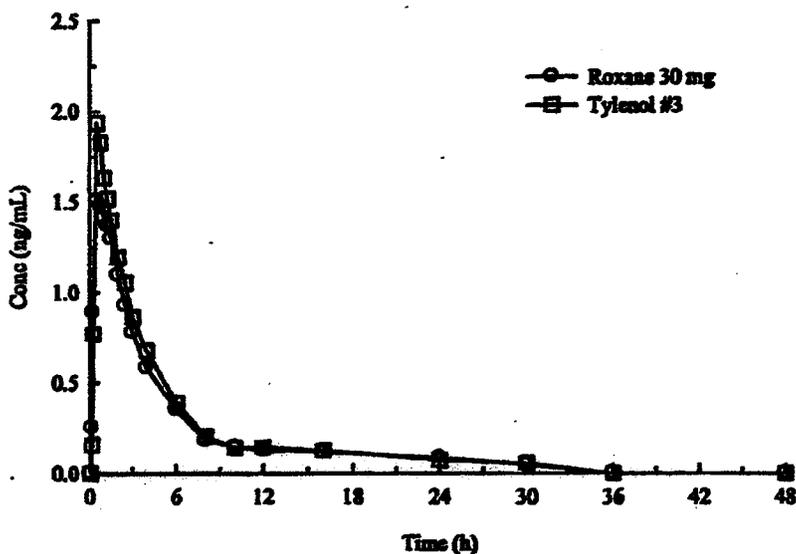


Figure 4.2.4.6: Mean plasma concentrations of morphine after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 30 mg and Tylenol® #3 (Codeine Phosphate 30 mg) to healthy volunteers under fasted conditions – semi logarithmic axes.

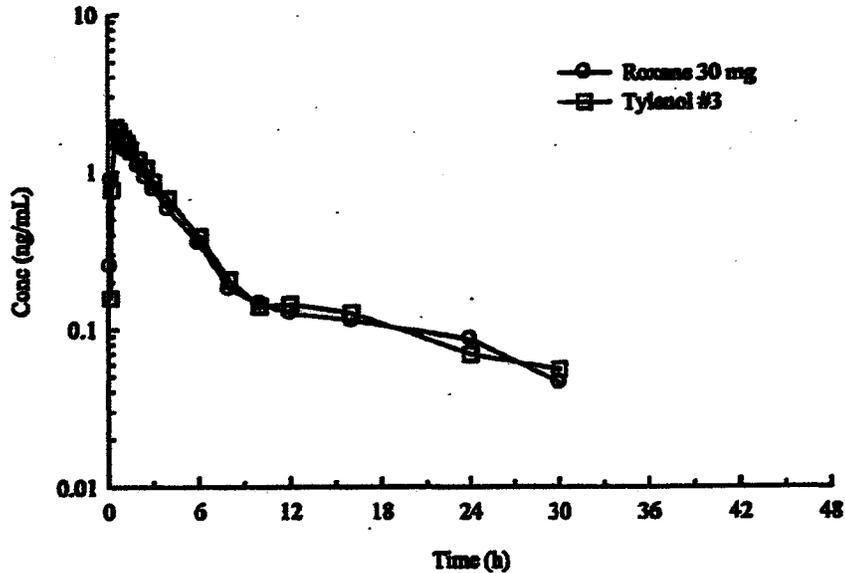


Table 4.2.4.7: Summary of pharmacokinetic parameters for morphine after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 30 mg and Tylenol® #3 (Codeine Phosphate 30 mg) to healthy volunteers under fasted conditions.

Parameter ¹	Roxane 30 mg	Tylenol #3
C _{max} (ng/mL)	1.94 ± 1.20 (33)	2.42 ± 1.47 (35)
T _{max} (h)	0.75 (33) [0.25 – 2.50]	0.75 (35) [0.25 – 2.50]
AUC(0-4) (h×ng/mL)	7.68 ± 5.80 (33)	8.61 ± 6.34 (35)
AUC(∞) (h×ng/mL)	5.14 ± 4.11 (15)	5.80 ± 3.50 (12)
λ _z (h ⁻¹)	0.2704 ± 0.0935 (15)	0.2660 ± 0.0816 (12)
t _{1/2} (h)	2.95 ± 1.42 (15)	2.88 ± 1.03 (12)
Ln(C _{max})	0.48 ± 0.64 (33)	0.70 ± 0.65 (35)
Ln[AUC(0-t)]	1.74 ± 0.81 (33)	1.86 ± 0.83 (35)
Ln[AUC(∞)]	1.44 ± 0.60 (15)	1.62 ± 0.52 (12)

¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Table 4.2.4.8: Statistical comparison of pharmacokinetic parameters for morphine after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 30 mg and Tylenol® #3 (Codeine Phosphate 30 mg) to healthy volunteers under fasted conditions.

Parameter	Geometric Mean Ratio (%) ¹		
	Estimate	90% Confidence Interval	
C _{max}	81.27	71.40	→ 92.50
AUC(0-t)	92.20	79.61	→ 106.79
AUC(∞)	80.44	61.37	→ 105.43

¹Based on analysis of natural log-transformed data.

c. Morphine-3-glucuronide (M3G)

Mean plasma concentrations of M3G after administration of after Roxane Laboratories' Codeine Sulfate 30 mg tablet and Tylenol® #3 (Codeine Phosphate 30 mg) were essentially super imposable (Figure 4.2.4.9 -linear axes; Figure 4.2.4.10 - semi-logarithmic axes) and the mean values for all pharmacokinetic parameters were comparable (Table 4.2.4.11). The geometric mean ratios for C_{max}, AUC (0-t), and AUC (in ranged from 95.9% to 99.4% and the associated 90% confidence intervals were well with the 80% to 125% equivalence window (Table 4.2.4.12) indicating bioequivalence with respect to M3G.

Figure 4.2.4.9: Mean plasma concentrations of M3G after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 30 mg and Tylenol® #3 (Codeine Phosphate 30 mg) to healthy volunteers under fasted conditions - linear axes.

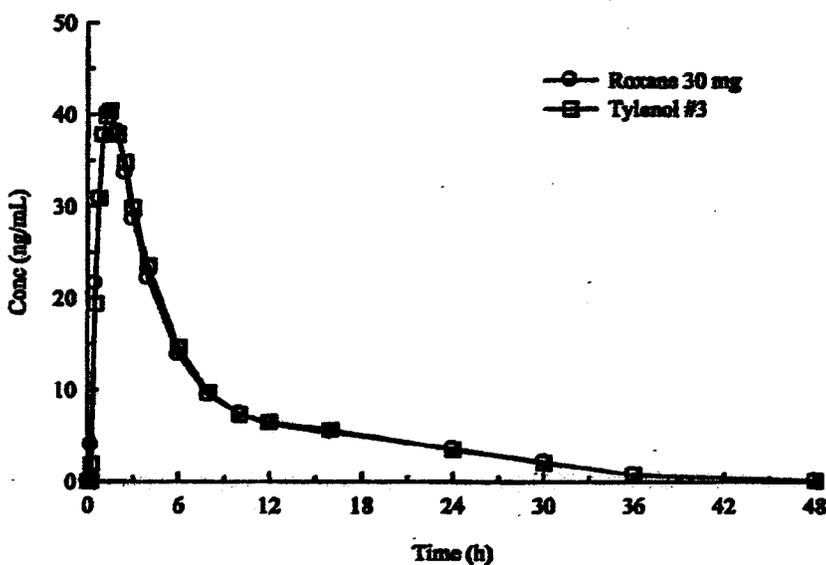


Figure 4.2.4.10: Mean plasma concentrations of M3G after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 30 mg and Tylenol® #3 (Codeine Phosphate 30 mg) to healthy volunteers under fasted conditions – semi-logarithmic axes.

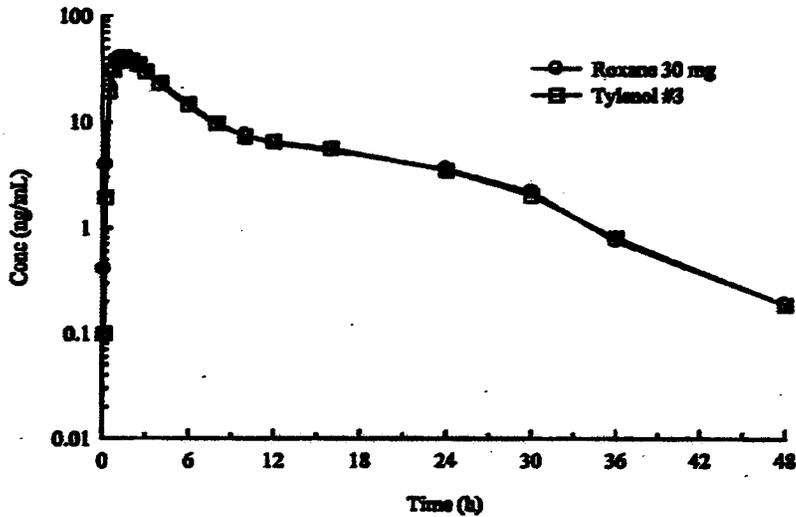


Table 4.2.4.11.: Summary of pharmacokinetic parameters for M3G after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 30 mg and Tylenol® #3 (Codeine Phosphate 30 mg) to healthy volunteers under fasted conditions.

Parameter ¹	Roxane 30 mg	Tylenol #3
C _{max} (ng/mL)	43.8 ± 19.6 (33)	44.5 ± 19.2 (35)
T _{max} (h)	1.27 (33) [1.00 – 2.00]	1.25 (35) [0.75 – 3.00]
AUC(0-t) (h×ng/mL)	288 ± 142 (33)	299 ± 137 (35)
AUC(inf) (h×ng/mL)	362 ± 155 (24)	354 ± 139 (22)
λ _z (h ⁻¹)	0.0739 ± 0.0346 (24)	0.0717 ± 0.0313 (22)
t _{1/2} (h)	11.2 ± 4.66 (24)	11.6 ± 5.84 (22)
Ln(C _{max})	3.67 ± 0.49 (33)	3.69 ± 0.49 (35)
Ln[AUC(0-t)]	5.53 ± 0.54 (33)	5.58 ± 0.52 (35)
Ln[AUC(inf)]	5.79 ± 0.50 (24)	5.78 ± 0.49 (22)

¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Table 4.2.4.12.: Statistical comparison of pharmacokinetic parameters for M3G after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 30 mg and Tylenol® #3 (Codeine Phosphate 30 mg) to healthy volunteers under fasted conditions.

Parameter	Geometric Mean Ratio (%) ¹		
	Estimate	90% Confidence Interval	
C _{max}	99.41	93.56	→ 105.62
AUC(0-t)	96.66	90.22	→ 103.55
AUC(inf)	95.93	85.42	→ 107.74

¹Based on analysis of natural log-transformed data.

d. Morphine-6-glucuronide (M6G)

Mean plasma concentrations of M6G after administration of after Roxane Laboratories' Codeine Sulfate 30 mg tablet and Tylenol® #3 (Codeine Phosphate 30 mg) were essentially super imposable (Figure 4.2.4.13 -linear axes; Figure 4.2.4.14 - semi-logarithmic axes) and the mean values for all pharmacokinetic parameters were comparable (Table 4.2.4.15). The geometric mean ratios for C_{max}, AUC(0-t), and AUC(inf) ranged from 104% to 112% (Table 4.2.4.16). The associated 90% confidence intervals for C_{max} and AUC (0-t) were well within the 80% to 125% equivalence window while the upper limit for AUC(inf), which could not be estimated for all subjects, was slightly above 125.00% (Table 4.2.4.16) narrowly missing the bioequivalence criteria.

Figure 4.2.4.13: Mean plasma concentrations of M6G after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 30 mg and Tylenol® #3 (Codeine Phosphate 30 mg) to healthy volunteers under fasted conditions - linear axes.

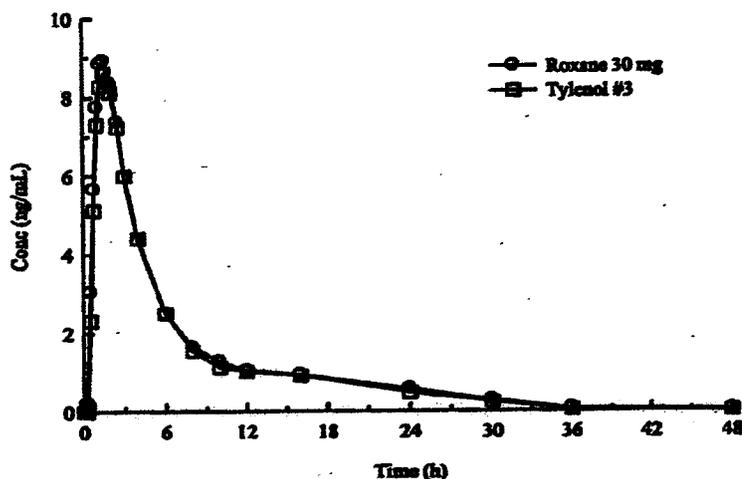


Figure 4.2.4.14: Mean plasma concentrations of M6G after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 30 mg and Tylenol® #3 (Codeine Phosphate 30 mg) to healthy volunteers under fasted conditions – semi-logarithmic axes.

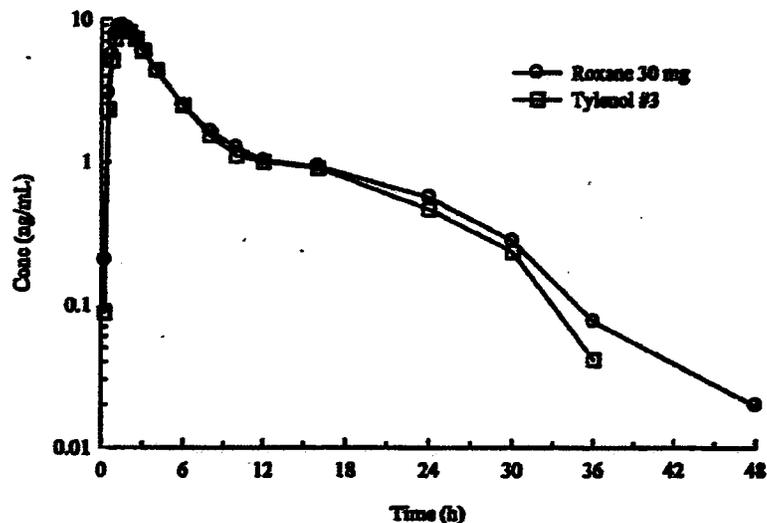


Table 4.2.4.15: Summary of pharmacokinetic parameters for M6G after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 30 mg and Tylenol® #3 (Codeine Phosphate 30 mg) to healthy volunteers under fasted conditions.

Parameter ¹	Roxane 30 mg	Tylenol #3
C _{max} (ng/mL)	9.77 ± 4.36 (33)	9.48 ± 3.94 (35)
T _{max} (h)	1.27 (33) [1.00 – 2.50]	1.50 (35) [1.00 – 3.00]
AUC(0-t) (h×ng/mL)	52.6 ± 26.0 (33)	50.7 ± 22.6 (35)
AUC(inf) (h×ng/mL)	65.6 ± 26.4 (21)	58.0 ± 29.7 (15)
λ _z (h ⁻¹)	0.0777 ± 0.0479 (21)	0.1060 ± 0.0748 (15)
t _{1/2} (h)	11.1 ± 3.99 (21)	9.45 ± 5.26 (15)
Ln(C _{max})	2.18 ± 0.47 (33)	2.15 ± 0.48 (35)
Ln[AUC(0-t)]	3.82 ± 0.56 (33)	3.81 ± 0.52 (35)
Ln[AUC(inf)]	4.08 ± 0.49 (21)	3.90 ± 0.64 (15)

¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Table 4.2.4.16: Statistical comparison of pharmacokinetic parameters for M6G after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 30 mg and Tylenol® #3 (Codeine Phosphate 30 mg) to healthy volunteers under fasted conditions.

Parameter	Geometric Mean Ratio (%) ¹	
	Estimate	90% Confidence Interval
C _{max}	104.19	97.48 → 111.36
AUC(0-∞)	103.59	95.61 → 112.23
AUC(inf)	111.56	99.40 → 125.21

¹Based on analysis of natural log-transformed data.

AUC Ratios:

There were essentially no differences in the AUC(inf) ratios for morphine-to-codeine (Figure 4.2.4.17) and the major metabolite M3G-to-morphine (Figure 4.2.4.18) between Roxane Laboratories' Codeine Sulfate 30 mg and Tylenol® #3 (Codeine Phosphate 30 mg). This indicates that the extent of metabolism of codeine to morphine and then M3G was not affected by either the formulation or the salt form. The AUC(inf) ratios for morphine-to-M6G (Figure 4.2.4.19) were somewhat different which can be attributed to the scarce number of data points available for M6G concentrations as mentioned before.

Figure 4.2.4.17: Individual subject AUC(inf) ratios, of morphine-to-codeine, after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 30 mg and Tylenol® #3 (Codeine Phosphate 30 mg) to healthy volunteers under fasted conditions.

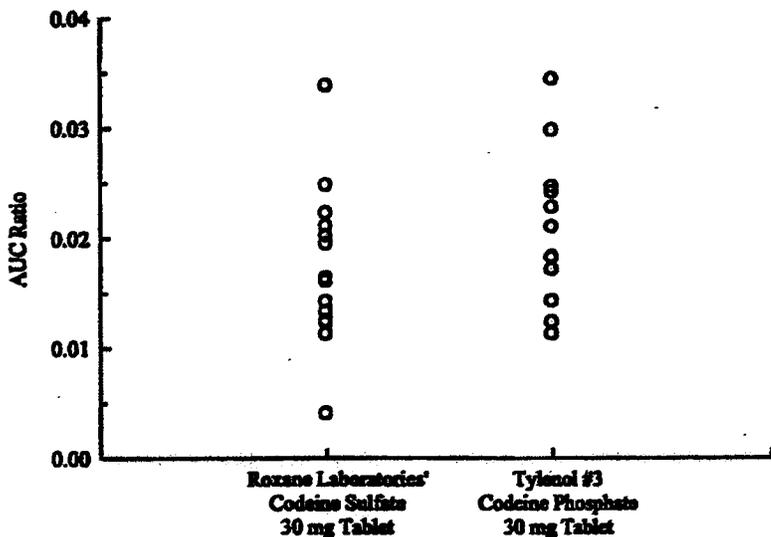


Figure 4.2.4.18: Individual subject AUC(inf) ratios, of M3G to-morphine, after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 30 mg and Tylenol® #3 (Codeine Phosphate 30 mg) to healthy volunteers under fasted conditions.

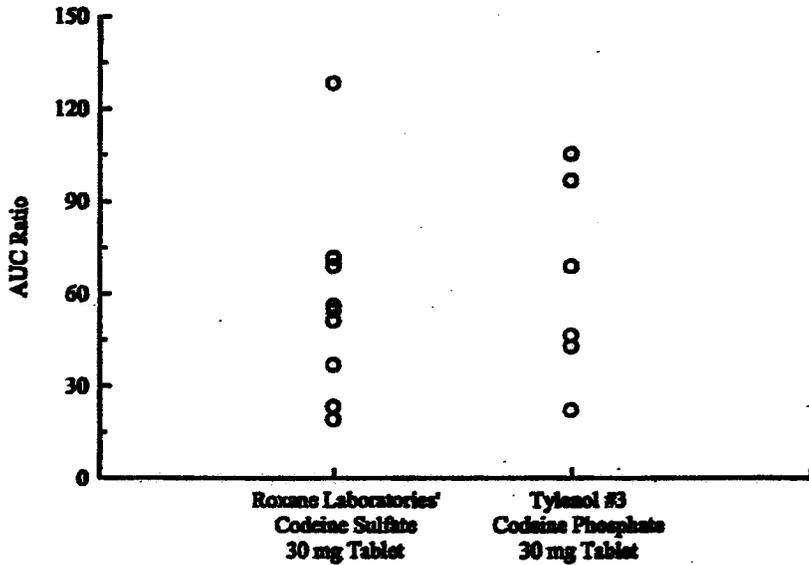
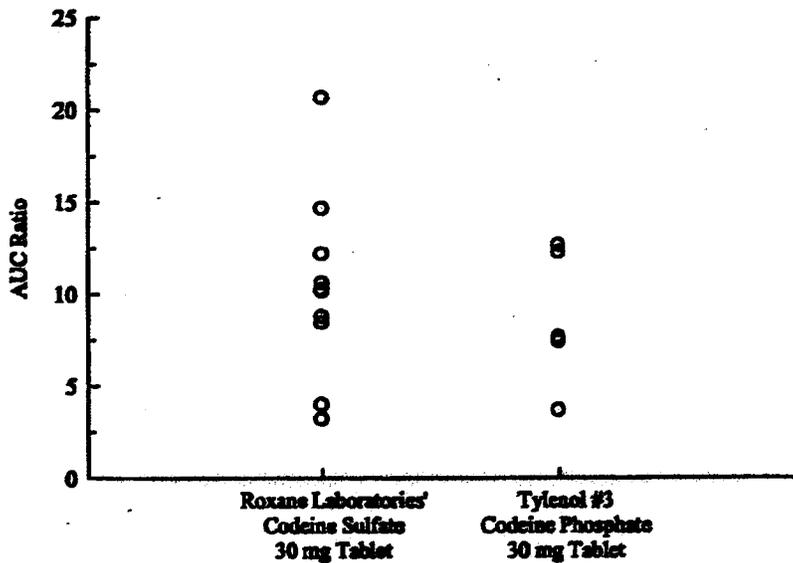


Figure 4.2.4.19: Individual subject AUC(inf) ratios, of M6G to-morphine, after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 30 mg and Tylenol® #3 (Codeine Phosphate 30 mg) to healthy volunteers under fasted conditions.



Reviewer's comments:

1. Roxane Laboratories' Codeine Sulfate Tablet 30 mg was bioequivalent to Tylenol® #3 (Codeine Phosphate 30 mg) with respect to the parent, codeine and M3G, the second highest metabolite seen in plasma. In addition, there were essentially no differences in the AUC(inf) ratios for morphine-to-codeine and M3G-to-morphine after oral administration of Roxane Laboratories' Codeine Sulfate Tablet 30 mg and Tylenol® #3 (Codeine Phosphate 30 mg), indicating that the extent of metabolism of codeine to morphine and then to M3G, was not affected by either the formulation or the salt form.
2. Roxane Laboratories' Codeine Sulfate Tablet 30 mg was not bioequivalent to Tylenol® #3 (Codeine Phosphate 30 mg) with respect to morphine and M6G, the other metabolite measured. However, since morphine and M6G represent only 2 and 6% of the total plasma concentrations observed with codeine at steady state, and we already know that the two products are bioequivalent with respect to the major moieties observed in plasma i.e., codeine and M3G, this finding is not of much clinical significance.

Demographic Profile:

		Treatment Groups		
		Treatment A (5mg Tablet) N=31	Treatment B (30mg Tablet) N=31	Treatment C (60mg Tablet) N=31
Age (years)	Mean ± SD	28.4 ± 6.9	28.2 ± 6.8	28.2 ± 6.8
	Range	19.0 - 45.0	19.0 - 45.0	19.0 - 45.0
Age Groups	< 18	0 (0.00%)	0 (0.00%)	0 (0.00%)
	18 - 40	30 (90.91%)	31 (91.18%)	31 (91.18%)
	41 - 64	3 (9.09%)	3 (8.82%)	3 (8.82%)
	65 - 75	0 (0.00%)	0 (0.00%)	0 (0.00%)
	> 75	0 (0.00%)	0 (0.00%)	0 (0.00%)
Sex	Female	10 (30.30%)	10 (29.41%)	10 (29.41%)
	Male	23 (69.70%)	24 (70.59%)	24 (70.59%)
Race	Asian	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Black	12 (36.36%)	12 (35.29%)	12 (35.29%)
	Caucasian	21 (63.64%)	22 (64.71%)	22 (64.71%)
	Hispanic	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Other	0 (0.00%)	0 (0.00%)	0 (0.00%)
BMI (kg/m²)	Mean ± SD	24.3 ± 3.4	24.4 ± 3.3	24.4 ± 3.3
	Range	18.4 - 29.8	18.4 - 29.8	18.4 - 29.8
Height (cm)	Mean ± SD	173.0 ± 10.0	172.8 ± 9.9	172.8 ± 9.9
	Range	153.5 - 192.5	153.5 - 192.5	153.5 - 192.5
Weight (kg)	Mean ± SD	72.7 ± 11.1	72.7 ± 10.9	72.7 ± 10.9
	Range	46.4 - 94.6	46.4 - 94.6	46.4 - 94.6

Blood Samples for PK Analysis:

Blood samples were collected before and 5, 10, 15, 30, 45 minutes and 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours after dosing.

Bioanalytical Analysis:

Plasma concentrations of codeine, morphine, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G) were measured using an LC/MS/MS method validated under the project code "VTQ" by _____

b(4)

PK and Statistical Analyses:

The pharmacokinetic and statistical analyses were done by _____

b(4)

All PK

b(4)

parameters were calculated using non-compartmental analysis. Only those plasma concentrations equal to or greater than the LOQs (codeine - 1 ng/mL; morphine - 0.20 ng/mL; M3G - 2.0 ng/mL; M6G - 0.5 ng/mL) were used in the analysis. Actual sampling times were used in all pharmacokinetic analyses.

Population for PK Analysis:

Eighteen (18) subjects were enrolled into, completed all three (3) periods of the study, and comprise the analysis population.

a. Codeine

Mean plasma concentrations of codeine after administration of 60 mg of codeine as 1 x 60 mg, 2 x 30 mg, and 4 x 15 mg tablets were essentially superimposable. Mean values for all pharmacokinetic parameters were comparable for all three treatments (Table 4.2.5.1) with geometric mean ratios for C_{max}, AUC(0-t), and AUC(inf) of approximately 100% for all comparisons (Table 4.2.5.2). All of the associated 90% confidence intervals were well within the 80% to 125% equivalence window (Table 2), demonstrating bioequivalence among the three tablet strengths with respect to codeine.

Table 4.2.5.1: Summary of pharmacokinetic parameters for codeine after oral administration of 60 mg doses of Roxane Laboratories' codeine tablets as 1 x 60 mg, 2 x 30 mg, and 4 x 15 mg tablets to healthy volunteers under fasted conditions.

Parameter ¹	1 x 60 mg	2 x 30 mg	4 x 15 mg
C _{max} (ng/mL)	169 ± 46.5 (18)	157 ± 37.9 (18)	159 ± 41.5 (18)
T _{max} (h)	1.13 (18) [0.25 - 1.50]	1.00 (18) [0.50 - 2.00]	1.00 (18) [0.50 - 2.00]
AUC(0-t) (h·ng/mL)	614 ± 146 (18)	624 ± 136 (18)	626 ± 140 (18)
AUC(inf) (h·ng/mL)	623 ± 146 (18)	633 ± 136 (18)	634 ± 141 (18)
λ _z (h ⁻¹)	0.2358 ± 0.0376 (18)	0.2287 ± 0.0391 (18)	0.2162 ± 0.0442 (18)
t _{1/2} (h)	3.01 ± 0.49 (18)	3.11 ± 0.52 (18)	3.34 ± 0.71 (18)
Ln(C _{max})	5.09 ± 0.29 (18)	5.03 ± 0.23 (18)	5.03 ± 0.26 (18)
Ln[AUC(0-t)]	6.39 ± 0.26 (18)	6.41 ± 0.21 (18)	6.42 ± 0.23 (18)
Ln[AUC(inf)]	6.41 ± 0.26 (18)	6.43 ± 0.21 (18)	6.43 ± 0.23 (18)

¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Table 4.2.5.2: Statistical comparison of pharmacokinetic parameters for codeine after oral administration of 60 mg doses of Roxane Laboratories' codeine tablets as 1 x 60 mg, 2 x 30 mg, and 4 x 15 mg tablets to healthy volunteers under fasted conditions.

Parameter	Geometric Mean Ratio (%) ¹		Within Subject CV (%)
	Estimate	90% Confidence Interval	
2 x 30 mg vs. 1 x 60 mg			
C _{max}	94.06	84.98 → 104.10	18.11
AUC(0-t)	102.46	94.65 → 110.90	14.10
AUC(inf)	102.43	94.69 → 110.80	13.98
4 x 15 mg vs. 1 x 60 mg			
C _{max}	94.12	85.04 → 104.16	18.11
AUC(0-t)	102.55	94.74 → 111.01	14.10
AUC(inf)	102.24	94.51 → 110.59	13.98
4 x 15 mg vs. 2 x 30 mg			
C _{max}	100.06	90.41 → 110.74	18.11
AUC(0-t)	100.09	92.47 → 108.35	14.10
AUC(inf)	99.81	92.27 → 107.97	13.98

¹Based on analysis of natural log-transformed data.

b. Morphine

Mean plasma concentrations of morphine after administration of 60 mg of codeine as 1 x 60 mg, 2 x 30 mg, and 4 x 15 mg tablets were mostly comparable. The geometric mean ratios for C_{max} and AUC(0-t) ranged from 87% to 103% (Table 4.2.5.3); however, the lower limits of some of the associated 90% confidence intervals were below within 80% (Table 4.2.5.4) demonstrating a lack of bioequivalence among the three tablet strengths with respect to morphine. Per the sponsor, there were too few subjects for whom AUC(inf) could be calculated for two treatments to allow for a reasonable statistical assessment.

Table 4.2.5.3: Summary of pharmacokinetic parameters for morphine after oral administration of 60 mg doses of Roxane Laboratories' codeine tablets as 1 x 60 mg, 2 x 30 mg, and 4 x 15 mg tablets to healthy volunteers under fasted conditions.

Parameter ¹	1 x 60 mg	2 x 30 mg	4 x 15 mg
C _{max} (ng/mL)	5.32 ± 3.06 (18)	4.49 ± 2.58 (18)	4.45 ± 2.11 (18)
T _{max} (h)	0.50 (18) [0.17 - 1.25]	0.75 (18) [0.25 - 1.25]	0.50 (18) [0.25 - 1.25]
AUC(0-t) (h×ng/mL)	19.8 ± 12.8 (17)	18.4 ± 11.2 (17)	17.2 ± 8.20 (17)
AUC(inf) (h×ng/mL)	47.0 ± 8.95 (2)	22.9 ± 17.5 (9)	17.2 ± 11.6 (7)
λ _z (h ⁻¹)	0.0420 ± 0.0144 (2)	0.1336 ± 0.1185 (9)	0.1595 ± 0.1189 (7)
t _{1/2} (h)	17.5 ± 5.99 (2)	12.8 ± 10.1 (9)	7.41 ± 5.58 (7)
Ln(C _{max})	1.41 ± 0.88 (18)	1.27 ± 0.81 (18)	1.30 ± 0.77 (18)
Ln[AUC(0-t)]	2.75 ± 0.77 (17)	2.67 ± 0.79 (17)	2.67 ± 0.69 (17)
Ln[AUC(inf)]	3.84 ± 0.19 (2)	2.74 ± 1.03 (9)	2.56 ± 0.90 (7)

¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Table 4.2.5.4: Statistical comparison of pharmacokinetic parameters for morphine after oral administration of 60 mg doses of Roxane Laboratories' codeine tablets as 1 x 60 mg, 2 x 30 mg, and 4 x 15 mg tablets to healthy volunteers under fasted conditions.

Parameter	Geometric Mean Ratio (%) ¹			Within Subject CV (%)
	Estimate	90% Confidence Interval		
2 x 30 mg vs. 1 x 60 mg				
C _{max}	86.73	74.32 →	101.20	27.85
AUC(0-t)	93.44	78.38 →	111.38	30.82
AUC(inf)	75.05	46.87 →	120.18	16.81
4 x 15 mg vs. 1 x 60 mg				
C _{max}	89.57	76.76 →	104.52	27.85
AUC(0-t)	93.13	78.12 →	111.01	30.82
AUC(inf)	69.74	44.31 →	109.78	16.81
4 x 15 mg vs. 2 x 30 mg				
C _{max}	103.28	88.51 →	120.51	27.85
AUC(0-t)	99.67	83.61 →	118.81	30.82
AUC(inf)	92.92	74.73 →	115.55	16.81

¹Based on analysis of natural log-transformed data.

c. Morphine-3-glucuronide

Mean plasma concentrations of morphine-3-glucuronide after administration of 60 mg of codeine as 1 x 60 mg, 2 x 30 mg, and 4 x 15 mg tablets were essentially superimposable. Mean values for all pharmacokinetic parameters were comparable for all three treatments (Table 4.2.5.5) with geometric mean ratios for C_{max}, AUC(0-t), and AUC(inf) ranging from 93% to 104% for all comparisons (Table 4.2.5.6). All of the associated 90% confidence intervals were well within the 80% to 125% equivalence window (Table 4.2.5.6) demonstrating bioequivalence among the three tablet strengths with respect to M3G.

Table 4.2.5.5: Summary of pharmacokinetic parameters for morphine-3-glucuronide after oral administration of 60 mg doses of Roxane Laboratories' codeine tablets as 1 x 60 mg, 2 x 30 mg, and 4 x 15 mg tablets to healthy volunteers under fasted conditions.

Parameter ¹	1 x 60 mg	2 x 30 mg	4 x 15 mg
C _{max} (ng/mL)	117 ± 68.4 (18)	111 ± 70.2 (18)	111 ± 61.8 (18)
T _{max} (h)	1.25 (18) [0.75 – 2.00]	1.25 (18) [0.75 – 2.00]	1.25 (18) [0.75 – 2.00]
AUC(0-t) (h·ng/mL)	807 ± 429 (17)	799 ± 442 (17)	773 ± 368 (17)
AUC(inf) (h·ng/mL)	1,050 ± 416 (12)	909 ± 460 (12)	932 ± 325 (14)
λ _z (h ⁻¹)	0.0658 ± 0.0179 (12)	0.0623 ± 0.0151 (12)	0.0666 ± 0.0263 (14)
t _{1/2} (h)	11.5 ± 4.18 (12)	11.6 ± 2.42 (12)	11.9 ± 4.90 (14)
Ln(C _{max})	4.48 ± 1.00 (18)	4.41 ± 1.02 (18)	4.46 ± 0.93 (18)
Ln[AUC(0-t)]	6.52 ± 0.64 (17)	6.51 ± 0.65 (17)	6.53 ± 0.53 (17)
Ln[AUC(inf)]	6.85 ± 0.54 (12)	6.68 ± 0.57 (12)	6.78 ± 0.34 (14)

¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Table 4.2.5.6: Statistical comparison of pharmacokinetic parameters for morphine-3-glucuronide after oral administration of 60 mg doses of Roxane Laboratories' codeine tablets as 1 x 60 mg, 2 x 30 mg, and 4 x 15 mg tablets to healthy volunteers under fasted conditions.

Parameter	Geometric Mean Ratio (%) ¹		Within Subject CV (%)
	Estimate	90% Confidence Interval	
2 x 30 mg vs. 1 x 60 mg			
C _{max}	93.72	84.02 → 104.54	19.53
AUC(0-t)	98.43	87.31 → 110.97	20.78
AUC(inf)	92.67	81.50 → 105.36	15.75
4 x 15 mg vs. 1 x 60 mg			
C _{max}	97.74	87.62 → 109.02	19.53
AUC(0-t)	100.42	89.07 → 113.21	20.78
AUC(inf)	92.29	82.29 → 103.51	15.75
4 x 15 mg vs. 2 x 30 mg			
C _{max}	104.28	93.49 → 116.32	19.53
AUC(0-t)	102.02	90.49 → 115.02	20.78
AUC(inf)	99.60	88.95 → 111.52	15.75

¹Based on analysis of natural log-transformed data.

d. Morphine-6-glucuronide

Mean plasma concentrations of morphine-6-glucuronide after administration of 60 mg of codeine as 1 x 60 mg, 2 x 30 mg, and 4 x 15 mg tablets were comparable. Mean values for C_{max} and AUC(0-t) were comparable for all three treatments (Table 4.2.5.7) with geometric mean ratios ranging from 93% to 103% for all comparisons (Table 6). All of the associated 90% confidence intervals were well within the 80% to 125% equivalence window (Table 4.2.5.8) demonstrating bioequivalence among the three tablet strengths with respect to M6G.

Table 4.2.5.7: Summary of pharmacokinetic parameters for morphine-6-glucuronide after oral administration of 60 mg doses of Roxane Laboratories' codeine tablets as 1 x 60 mg, 2 x 30 mg, and 4 x 15 mg tablets to healthy volunteers under fasted conditions.

Parameter ¹	1 x 60 mg	2 x 30 mg	4 x 15 mg
C _{max} (ng/mL)	18.5 ± 9.16 (18)	17.3 ± 9.20 (18)	17.2 ± 7.50 (18)
T _{max} (h)	1.38 (18) [1.00 – 1.50]	1.50 (18) [0.75 – 2.00]	1.50 (18) [1.00 – 3.00]
AUC(0-t) (h×ng/mL)	102 ± 49.1 (17)	107 ± 57.2 (17)	101 ± 45.3 (17)
AUC(inf) (h×ng/mL)	109 ± 67.6 (6)	131 ± 52.3 (13)	132 ± 29.5 (7)
λ _z (h ⁻¹)	0.1052 ± 0.0729 (6)	0.0779 ± 0.0636 (13)	0.0688 ± 0.0137 (7)
t _{1/2} (h)	10.7 ± 8.76 (6)	11.3 ± 3.69 (13)	10.4 ± 1.99 (7)
Ln(C _{max})	2.70 ± 0.87 (18)	2.63 ± 0.84 (18)	2.66 ± 0.80 (18)
Ln[AUC(0-t)]	4.48 ± 0.59 (17)	4.50 ± 0.65 (17)	4.51 ± 0.48 (17)
Ln[AUC(inf)]	4.47 ± 0.80 (6)	4.78 ± 0.47 (13)	4.86 ± 0.23 (7)

¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Table 4.2.5.8: Statistical comparison of pharmacokinetic parameters for morphine-6-glucuronide after oral administration of 60 mg doses of Roxane Laboratories' codeine tablets as 1 x 60 mg, 2 x 30 mg, and 4 x 15 mg tablets to healthy volunteers under fasted conditions.

Parameter	Geometric Mean Ratio (%) ¹		Within Subject CV (%)
	Estimate	90% Confidence Interval	
2 x 30 mg vs. 1 x 60 mg			
C _{max}	93.46	85.29 → 102.41	16.31
AUC(0-t)	102.13	88.96 → 117.26	24.02
AUC(inf)	115.86	99.70 → 134.64	14.50
4 x 15 mg vs. 1 x 60 mg			
C _{max}	96.27	87.85 → 105.49	16.31
AUC(0-t)	103.46	90.11 → 118.78	24.02
AUC(inf)	98.63	82.91 → 117.34	14.50
4 x 15 mg vs. 2 x 30 mg			
C _{max}	103.01	94.00 → 112.88	16.31
AUC(0-t)	101.29	88.23 → 116.30	24.02
AUC(inf)	85.13	73.76 → 98.25	14.50

¹Based on analysis of natural log-transformed data.

Reviewer's Comments:

- After oral administration at a dose of 60 mg to fasted subjects, Roxane Laboratories' 15 mg, 30 mg, and 60 mg codeine sulfate tablets were bioequivalent with respect to the parent compound, codeine and the glucuronide metabolites M3G and M6G.

2. **Roxane Laboratories' 15 mg, 30 mg, and 60 mg codeine sulfate tablets were not bioequivalent with respect to the metabolite, morphine. However, morphine is a minor metabolite and this finding is not clinically significant.**

4.2.6 Across Studies Analysis:

Single dose administration:

The bioavailability and pharmacokinetics of codeine and the metabolites morphine, M3G, and M6G from the 15 mg, 30 mg, and 60 mg codeine sulfate tablets have been examined in four studies, CODE-T60-PLFS-1, CODE-T30-PVFS-1, CODE-T60-PVFS/FD-1, and CODE-T15/30/60-PVFS-1. As demonstrated in the comparative bioavailability study in which all treatment arms were administered as a 60 mg dose of codeine (15 mg tablet x 4, 30 mg tablet x 2, or 60 mg tablet x 1) (CODE-T60-PLFS-1), mean values of the geometric mean ratios for C_{max}, AUC(0-t), and AUC(inf) for the parent compound codeine and metabolites morphine, M3G, and M6G were comparable for all three treatment arms. Bioequivalence was established among the three tablet strengths with respect to codeine (See Food effects). When the 60 mg tablet was administered to a different cohort of subjects (CODE-T15/30/60-PVFS-1), mean plasma concentrations for codeine were comparable, as were the mean values for C_{max} and AUC(inf) (see Individual study reviews). In addition, dose linearity between the three formulations was established (CODE-T15/30/60-PVFS-1) with respect to codeine, and was supported by the metabolites morphine, M3G, and M6G. Comparisons of the mean C_{max} and AUC (in among the three tablet strengths and between the studies for codeine (Figure 4.2.6.1 and Figure 4.2.6.2), morphine, M3G and M6G demonstrates consistency in the performance of the different tablet strengths and dose proportionality.

Figure 4.2.6.1.: Comparison of mean \pm standard deviation C_{max} for codeine after oral administration of 15 mg, 30 mg, and 60 mg codeine sulfate tablets under fasted conditions.

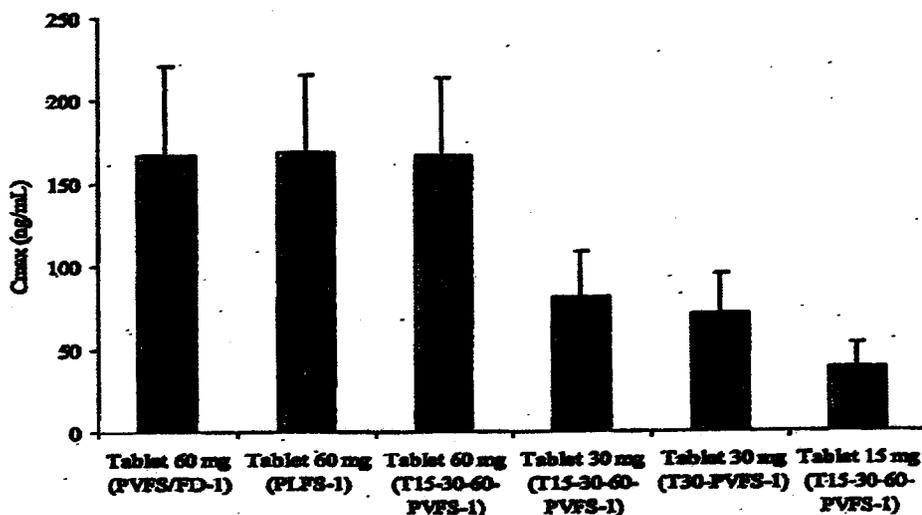
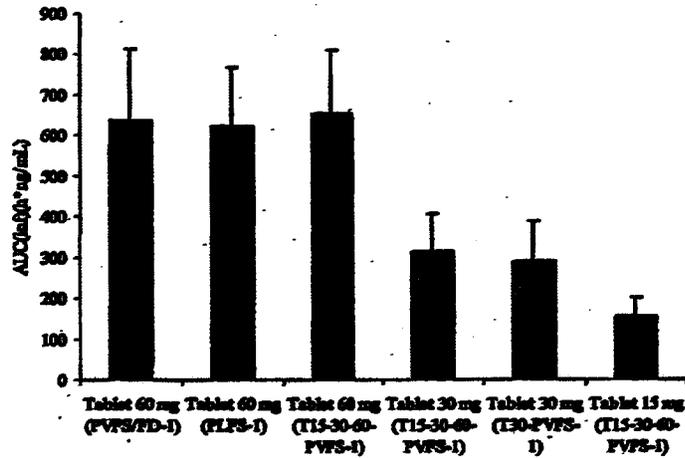
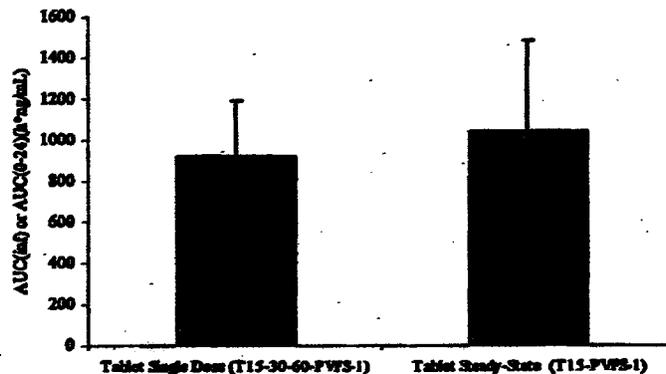


Figure 4.6.2.2.: Comparison of mean \pm standard deviation AUC (inf) for codeine after oral administration of 15 mg, 30 mg, and 60 mg codeine sulfate tablets under fasted conditions.



Multiple dose administration: There was concordance between the single-dose AUC(inf) (Code T15-30-60-PVFS-I) and the 24-hour AUC at steady-state (AUC(0-24)) (Code T15-PVFS-I) of codeine for the 15 mg tablet, demonstrating linear pharmacokinetics (Figure 4.2.6.3).

Figure 4.2.6.3.: Comparison of mean \pm standard deviation codeine AUC(inf) after a single dose of the 15 mg tablet and AUC(0-24) at steady-state after oral administration of the 15 mg tablet Q4H for five days.



Overall Conclusion:

The exposure characteristics observed for the parent codeine and the three metabolites, morphine, M3G and M6G are comparable across studies.

4.3. Filing checklist

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
General Information About the Submission				
	Information		Information	
NDA/BLA Number	22402	Brand Name	Codeine Sulfate Tablets, USP	
OCP Division (I, II, III, IV, V)	2	Generic Name	Codeine Sulfate Tablets	
Medical Division	DAARP	Drug Class	Opioid analgesic	
OCP Reviewer	Sheetal Agarwal	Indication(s)	Relief of mild to moderately severe pain in adults	
OCP Team Leader	Suresh Doddapaneni	Dosage Form	Immediate-release oral tablets, 15 mg, 30 mg and 60 mg	
Pharmacometrics Reviewer	-	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.	
Date of Submission	07/02/2008	Route of Administration	Oral	
Estimated Due Date of OCP Review	03/02/2009	Sponsor	Roxane Labs	
Medical Division Due Date	03/02/2009	Priority Classification	S	
PDUFA Due Date	05/02/2009			
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:				
Isocyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			
multiple dose:	X			
Patients-				
single dose:				
multiple dose:				

Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	15, 30 and 60 mg tablets are dose proportional w.r.t codeine
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:	X (1 literature reference submitted)	1	1	Guay DR, Awani WM, Findlay JWA, et al. Pharmacokinetics and pharmacodynamics of codeine in end-stage renal disease. <i>Clin Pharmacol Ther.</i> 1988 Jan; 43: 63-71.
hepatic impairment:				
PD -				
Phase 2:				
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:	X	1	1	Codeine Sulfate 30 mg v/s Tylenol with codeine # 3 (containing codeine phosphate 30 mg)
Alternate ROUTE as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	2	2	Dosage form bioequivalence Steady state (multiple dose)
replicate design; single / multi dose:				
Food-drug interaction studies	X	1	1	
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	X	1	1	
Literature References	X			
Total Number of Studies		8	8	

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	Paper submission
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	Required data sets in EDR
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
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?				The clinical and the Clin Pharm review teams will work on the proposed pediatric plan
16	Did the applicant submit all the pediatric exclusivity		X		The clinical and the Clin

	data, as described in the WR?				Pharm review teams will work on the proposed pediatric plan
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.

 Reviewing Clinical Pharmacologist

 Date

 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/

Sheetal Agarwal
4/3/2009 06:35:29 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
4/3/2009 08:24:52 PM
BIOPHARMACEUTICS