Center for Drug Evaluation and Research

APPLICATION NUMBER:
21-369

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICAL REVIEW

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-369
Proprietary Drug Name:	Codeprex (tentative)
Generic Name:	Codeine/Chlorpheniramine polistirex
Indication:	Temporary relief of cough as may occur with the common cold or inhaled irritant and for the temporary relief of symptoms associated with hay fever or other upper respiratory allergies or allergic rhinitis.
Dosage Form:	Extended-Release Suspension
Strength:	40 mg Codeine-8 mg Chlorpheniramine/10 ml
Route of Administration:	Oral
Dosage and administration:	Adults and adolescents, ages ≥12 years: Two teaspoonfuls (10 ml) every 12 hours; do not exceed 4 teaspoonfuls in 24 hrs Children ages 6 to <12: One teaspoonful (5 ml) every 12 hrs; do not exceed two teaspoonfuls in 24 hrs. Not recommended for patients under 6 years of age.
Applicant:	Celltech Pharmaceuticals Inc.
Clinical Division:	DPADP (HFD-570)
Submission Date:	December 22, 2003
Reviewer:	Shinja Kim, Ph.D.
Team Leader:	Emmanuel O. Fadiran, Ph. D.

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1. EXECUTIVE SUMMARY

This is a re-submission of the original NDA in which the sponsor has provided the response to the Approvable (AE) Letter issued on February 13, 2002.

In an effort to address the deficiencies listed in the AE letter, the sponsor modified the original formulation and produced a suspension, Lot CL-02123A (coated codeine polistirex with target polymer coating of [redacted] that showed stable drug release rates over time. Three clinical pharmacology studies were conducted employing lot CL-02123A. The results from these studies are summarized as follows: (1) PK profiles of codeine (COD) and chlorpheniramine (CPM) from Codeprex were similar to the reference Immediate-Release solution following single and multiple doses, (2) food had no effect on bioavailability of COD and CPM.

The sponsor is recommended the dissolution method and the specifications for codeine and CPM as shown in the Comments, below.

Comments: *Reviewer's Note: This comment has been conveyed to the sponsor and they accepted our recommendation.*

- For codeine, the sponsor is recommended to use [redacted] as the dissolution method with the following specifications:

Dissolution Method:	[redacted]
Specifications:	
1 hr	[redacted]
3 hr	[redacted]
6 hr	[redacted]
12 hr	[redacted]

- For chlorpheniramine, the dissolution method is [redacted] as you proposed, however, set the dissolution specifications as follows:

Dissolution Method:	[redacted]
Specifications:	
1 hr	[redacted]
3 hr	[redacted]
6 hr	[redacted]
12 hr	[redacted]

1.1. Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-369. We found this NDA acceptable from a CPB standpoint. The sponsor accepted the Agency's recommendation (*i.e.*, Comments listed above).

Reviewer
Shinja Kim, Ph.D. _____
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Final version signed by Emmanuel Fadiran, Ph.D., Team leader _____

1.2. Summary of clinical Pharmacology and Biopharmaceutics Findings

Celltech Pharmaceuticals re-submitted NDA 21-369 seeking for an approval of an extended release suspension, a new combination drug product of codeine (COD) and chlorpheniramine (CPM). In an effort to address the deficiencies listed in the approvable letter, the sponsor made changes to the original formulation and conducted 3 PK studies with the batch manufactured with the modified manufacturing process. The intention of the PK studies were to determine the *in vivo* BA/BE of Codeprex compared to the reference Immediate-Release (IR) solution, after single and multiple doses (steady state) and to assess the effect of food on the BA of codeine and CPM delivered from the Codeprex ER suspension. Dissolution data was also provided to support the dissolution methods and specifications proposed for this product.

BE/BA Assessment (Study COD03-01): In a single dose, two-way crossover study Codeprex ER suspension was compared to the reference IR solution. The study showed that Codeprex ER suspension was bioequivalent to the reference IR solution based on AUC_{inf} for codeine and CPM as the 90% CI for the ratio of AUC_{inf} were contained within 80% to 125% (Table 1). Based on AUCt, the lower limit of the 90% confidence interval for the LSM ratio was less than 80% for both CPM and codeine. C_{max} was also lower for the test formulation; however, this was expected since Codeprex ER suspension (Trt A) is designed to provide slower drug release.

Table 1. Arithmetic Mean (SD) of COD and CPM PK parameters and statistical analysis following single dose of the treatments

			Codeine			CPM		
Parameter	**TRT**	**N**	**Mean (SD)**	**Ratio A/ B**	**90% CI***	**Mean (SD)†**	**Ratio A/ B**	**90% CI***
C_{max} (ng/mL)	A	20	53.9 (13.4)			7.9 (1.6)		
	B	19	67.3 (13.7)	0.79	73.0-85.5	11.9 (2.1)	0.65	61.9-67.7
AUC_t (ng•hr/mL)	A	20	448.6 (115)			272.3 (80.2)		
	B	19	531.9 (119)	0.83	78.7-86.7	329.8 (86)	0.81	77.6-85.5
AUC_{inf} (ng•hr/mL)	A	20	505.6 (129)			326.7 (126)		
	B	19	550. 3 (121)	0.89	82.5-95	378.9 (142)	0.85	81.0-89.8

A = Codprex ER suspension (codeine 40 mg/CPM 8 mg/10 mL) - test

B = codeine 20 mg/CPM 4 mg/5 mL IR solution q6h for 2 doses – reference (manufactured by Celltech)

*The confidence intervals are obtained from an ANOVA model with treatment, period, sequence as fixed effects and subjects nested within sequence as a random effect in the natural logarithmic transformed parameter.

PK at Steady State (Study CD00900): The multiple twice daily administrations of 10 mL of Codeprex (40 mg codeine/8 mg CPM) ER suspension (Treatment A) and multiple 4 times a day administration of 20 mg codeine/4 mg CPM IR solution (Treatment B) resulted in similar 12-hour extent of exposure to both codeine and CPM as determined during steady-state conditions on Day 7 of repeated dosing. BE was demonstrated for C_{max} and $AUC_{(144-156h)}$ as the 90% CI for treatment comparisons were contained within 80% to 125%. The minimum concentration (C_{min}) for codeine fell slightly outside of the BE range (———), consequently, the fluctuation index, defined as % swing between C_{max} and C_{min}, did decrease substantially for codeine, from 518.8% for the IR formulation to 382.5% for the ER formulation (Table 2).

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Table 2. Arithmetic Mean (SD) of COD and CPM PK parameters and statistical analysis following

multiple dose of the treatments

Parameter	TRT	Codeine			CPM		
		Mean (SD)	Ratio A/ B	90% CI*	Mean (SD)[1]	Ratio A/ B	90% CI*
C_{max} (ng/mL)	A	100.5 (26.8)			35.8 (10.0)		
	B	108.1 (33.8)	0.93	87.7-98.2	42.4 (15.4)	0.90	85.6-93.8
$AUC_{(144-156)}$ (ng•hr/mL)	A	644.4 (182.7)			376.3 (106.2)		
	B	617.4 (195.5)	1.04	99.2-108.9	429 (141.6)	0.92	88.7-95.9
C_{min} (ng/mL)	A	21.4 (6.5)			27.7 (8.6)		
	B	18.8 (8.4)	1.17	105-129.4	30.7 (10.2)	0.95	90.3-99.5
Fluct. Index (%)	A	382.5 (104.6)			31.0 (12.2)		
	B	518.8 (201.3)			38.7 (14.6)		

A = Codprex ER suspension (codeine 40 mg/CPM 8 mg/10 mL) q12 x 13 conseutive doses - test
B = codeine 20 mg/CPM 4 mg/5 mL IR solution q6h x 26 conseutive doses – reference (manufactured by Celltech)
*The confidence intervals are obtained from an ANOVA model with treatment, period, sequence as fixed effects and subjects nested within sequence as a random effect in the natural logarithmic transformed parameter.

Effect of Food (Study CD00800): The effect of food on the bioavailability of codeine and CPM from the Codeprex ER suspension was assessed in a 2-way crossover design. The study showed that a high-fat meal had no effect on the bioavailability of codeine and CPM from the Codeprex ER suspension, however, T_{max} of CPM was delayed by approximately 2.5 hours (Table 3). This reviewer is of the opinion that the delay on T_{max} of CPM may not be clinically relevant.

Table 3. Arithmetic Mean (SD) of COD and CPM PK parameters and statistical analysis following single dose of the treatments

Parameter	TRT	N	Codeine			CPM		
			Mean (SD)	Ratio A/ B	90% CI*	Mean (SD)[1]	Ratio A/ B	90% CI*
C_{max} (ng/mL)	A	36	71 (19.1)			7.5 (1.8)		
	B	35	61.7 (18.5)	1.16	108.4-124.2	7.4 (1.6)	1.0	95.4-104.0
AUC_t (ng•hr/mL)	A	36	533.1 (160)			271.2 (103.7)		
	B	35	457.7 (116.4)	1.16	111-121.8	250.1 (75.8)	1.03	98.1-107.4
AUC_{inf} (ng•hr/mL)	A	36	561.8 (166.2)			323.8 (172.3)		
	B	35	500.2 (128.3)	1.12	107.4-117.4	293.7 (112.1)	1.01	95.8-105.8
T_{max} (hr)	A	36	2.42 (0.65)			9.06 (6.0)		
	B	35	2.56 (0.91)			6.8 (3.21)	*P*=0.004*	

A = Extended release suspension (fed)
B = Extended release suspension (fasted)
*Non parametric analysis

Dissolution: Change in manufacturing process for Codeprex ER suspension resulted in different *in-vitro* release profiles for both codeine and CPM compared to those obtained from Codeprex ER suspension manufactured using the original process.

Codeine: The sponsor developed a new method ———) for codeine due to the change in manufacturing process, coupled with meeting the criteria of *in-vitro* release rate of —— at 1 hour and —— , at 12 hours. However, this new method is considered inadequate because the method requires the replacement of the ——————— at each sampling times, *i.e.*, the method is designed to deliberately ——————————————————————————— Therefore, the sponsor is recommended to use the method ——— for codeine as the dissolution method with specifications as shown in Table 4.

Table 4. Recommended method ——— and specifications for Codeine

Ingredients	mg/10 ml
Dye, D&C Red #33 Certified	
Microcrystalline cellulose and carboxyethylcellulose sodium, NF	
Sucrose, NF	
Glycerin, USP	
Propylen glycol, USP	
Methyparaben, NF	
Propylparaben, NF	
Xanthan Gum, NF	
Citric acid (anhydrous), USP	
Edetate Disodium, USP	
Flavor, Artificial Cherry Cream	
Polysorbate 80, NF	
Coated codeine polistirex	
Chlorpheniramine maleate, USP	
Water, Purified, USP QS	

*Based on theoretical assay of for coated codeine polistirex. Input quantities vary slightly based on assay resin bound codeine. The total amount of coated codeine polistirex is equivalent to 40 mg of codeine base. The calculation is based on the following equation: Coated codeine polistirex = (40 mg) x (100) / (% assay)

2.1.2. What are the mechanism of action, proposed therapeutic indications and dosage recommendations for Codeprex ER suspension?

Mechanism of Action: The precise mechanism of action of codeine is not known but it is believed to act in the medulla with depression of the cough center and to a lesser degree the respiratory center. CPM is an antihistamine (H_1-receptor antagonist) and also possesses anticholinergic and sedative activity.

Proposed Indication: Temporary relief of cough as may occur with the common cold or inhaled irritant and for the temporary relief of symptoms associated with hay fever or other upper respiratory allergies or allergic rhinitis.

Dosage:

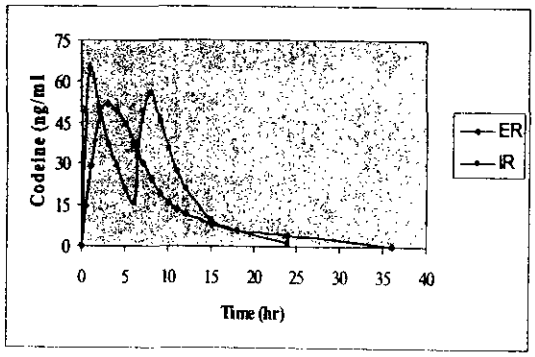
- ≥12 years of age: 2 teaspoonfuls (10 mL) every 12 hours; do not exceed 4 teaspoonfuls in 24 hrs
- Children ages 6 - <12: 1 teaspoonfuls (5 mL) every 12 hours; do not exceed 2 teaspoonfuls in 24 hrs.
- Not recommended for patients under 6 years of age.

2.2. General Clinical Pharmacology

2.2.1. Is the systemic exposure after single administration of the ER formulation comparable to that after the administration of the reference IR formulation?

Study COD03-01 was an open-label, single dose, randomized, 2-way crossover study. Objective of the study was to compare the oral bioavailability of a single dose of 10 mL ER suspension of codeine 40 mg and CPM 8 mg (Trt A) relative to 5 mL IR solution of codeine 20 mg and CPM 4 mg administered every 6 hours for 2 consecutive doses (Trt B) under fasting conditions. A total of 20 subjects were enrolled in the study, and 19 subjects completed both treatments. Mean codeine and CPM plasma concentration-time profiles are shown in Figure 1. Mean and statistical analysis of the PK parameters for codeine and CPM are shown in Table 7.

Figure 1. Mean codeine (left) and CPM (right) plasma concentration-time course following single dose of 10 mL ER suspension and 5 mL IR solution administered q6h x 2 doses



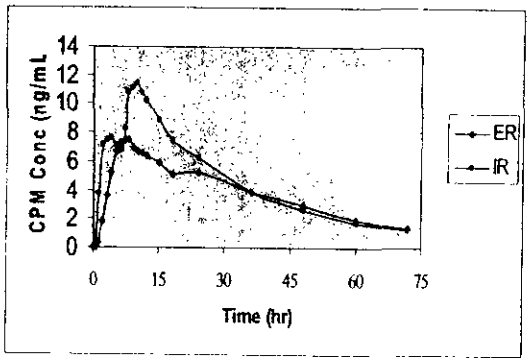


Table 7. Arithmetic Mean (SD) of codeine and CPM PK parameters and statistical analysis following single dose of the treatments

Parameter	TRT	N	Mean (SD)	Ratio ER/ IR	90% CI*	Mean (SD)[1]	Ratio ER/ IR	90% CI*
			Codeine			CPM		
C_{max} (ng/mL)	ER	20	53.9 (13.4)			7.9 (1.6)		
	IR	19	67.3 (13.7)	0.79	73.0-85.5	11.9 (2.1)	0.65	61.9-67.7
AUC_t (ng•hr/mL)	ER	20	448.6 (115.4)			272.3 (80.2)		
	IR	19	531.9 (119)	0.83	78.7-86.7	329.8 (86)	0.81	77.6-85.5
AUC_{inf} (ng•hr/mL)	ER	20	505.6 (129.4)			326.7 (126.2)		
	IR	19	550.3 (120.6)	0.89	82.5-95	378.9 (141.5)	0.85	81.0-89.8
T_{max} (hr)	ER	20	3.05 (0.94)			7.13 (1.4)		
	IR	19	2.66 (2.9)			9.11 (0.9)		
$T_{1/2}$ (hr)	ER	20	6.97 (2.5)			22.51 (8.6)		
	IR	19	3.46 (0.9)			21.58 (8.1)		

ER = Extended release suspension

IR = Immediate release solution

* The confidence intervals are obtained from an ANOVA model with treatment, period, sequence as fixed effects and subjects nested within sequence as a random effect in the natural logarithmic transformed parameter.

From this study the following conclusions were reached:

- The test ER suspension met the criteria for comparable bioavailability to the reference IR treatment based on $AUC_{0\text{-}inf}$ for both codeine and CPM by falling within the 80% to 125% BE range.
- For AUC_t, the lower limit of the 90% confidence interval for the LSM ratio was less than 80% for both CPM and codeine. C_{max} was also lower for the test formulation; however, this was expected since Codeprex ER suspension is designed to provide slower drug release.
- The measured terminal codeine half-lives were 7 and 3.5 hours following ER suspension and IR solution respective, indicating a flip-flop model for the terminal phase of the ER suspension.

2.2.2. Is the systemic exposure after multiple administrations (steady-state) of the ER formulation comparable to that after the administration of the reference IR product?

Study CD00900 was an open-label, multiple dose, randomized, 2-way crossover study to assess the steady-state BA of Codeprex ER suspension and IR solution. The subjects (n = 24) were randomized and placed into one of two treatment groups as follows:

- **TRT A:** 10 mL Codeprex ER suspension (codeine 40 mg and CPM 8 mg) q12 hrs for 13 consecutive doses.
- **TRT B:** 5 mL IR solution (codeine 20 mg and CPM 4 mg) every 6 hrs for 26 consecutive doses.

The PK of both analytes were assessed at hours 144 through 156 from the first dose of each study period, which corresponded to the 13th dose (hour 144) of the ER formulation and the 25th (hour 144) and 26th (hour 150) doses of the IR formulation. The 90% CI for the ratios of PK parameters the test and reference means were calculated for these log transformed PK parameters and for un-transformed C(144) and C(156). The summary of the PK parameters and statistical results are presented in Table 8. The mean concentration-time plots for codeine and CPM following each treatment at steady-state and a graphical representation of the individual C_{min} of codeine is presented in Figure 2 and 3, respectively.

Table 8. Arithmetic Mean (SD) of codeine and CPM PK parameters and statistical analysis following multiple dose of the treatments

		Codeine			CPM		
Parameter	**TRT**	**Mean (SD)**	**Ratio ER/IR**	**90% CI***	**Mean (SD)[1]**	**Ratio ER/IR**	**90% CI***
C_{max} (ng/mL)	ER	100.5 (26.8)			35.8 (10.0)		
	IR	108.1 (33.8)	0.93	87.7-98.2	42.4 (15.4)	0.90	85.6-93.8
$AUC_{(144-156)}$ (ng•hr/mL)	ER	644.4 (182.7)			376.3 (106.2)		
	IR	617.4 (195.5)	1.04	99.2-108.9	429 (141.6)	0.92	88.7-95.9
C_{min} (ng/mL)	ER	21.4 (6.5)			27.7 (8.6)		
	IR	18.8 (8.4)	1.17	105-129.4	30.7 (10.2)	0.95	90.3-99.5
C (144)** (ng/mL)	ER	26 (8.4)			30.3 (9.6)		
	IR	26.1 (9.5)	0.99	89.8-107.9	34.7 (13.4)	0.94	88.8-99.2
C (156)** (ng/mL)	ER	21.8 (6.4)			28.1 (8.5)		
	IR	24.7 (9.4)	0.88	79.1-96.5	31.4 (10.7)	0.94	89.4-98.8
C_{avg} (ng/mL)	ER	53.7 (15.2)			31.3 (8.9)		
	IR	51.5 (16.3)			35.8 (11.8)		
T_{max} (hr)	ER	2.04 (0.2)			3.22 (0.9)		
	IR	1.1 (1.25)			3 (2.3)		
Fluct. Index (%)	ER	382.5 (104.6)			31.0 (12.2)		
	IR	518.8 (201.3)			38.7 (14.6)		
Degree of Fluctuation.	ER	1.48 (0.17)			0.27 (0.09)		
	IR	1.74 (0.33)			0.32 (0.11)		

ER = Extended release suspension
IR = Immediate release solution
* The confidence intervals are obtained from an ANOVA model with treatment, period, sequence as fixed effects and subjects nested within sequence as a random effect in the natural logarithmic transformed parameter; **90% CI based on un-transformed values

C_{min} for codeine fell slightly outside the BE range (105% to 129.4%), demonstrating that the codeine plasma levels following the ER formulation did not drop as substantially within the 12-hour sampling interval as did codeine plasma levels following IR administration. Consequently, the fluctuation index, defined as % swing between C_{max} and C_{min}, did decrease substantially for codeine, from 518.8% for the IR formulation to 382.5% for the ER formulation (*i.e.*, less fluctuation in the 12-hour codeine plasma levels for the ER compared to the IR formulation). There was less of a difference in fluctuation index for CPM, with a decrease from 38.7% for the IR formulation to 31% for the ER formulation.

Figure 2. Mean codeine (left) and CPM (right) plasma concentration-time course following multiple BID doses of 10 mL ER suspension and QID doses of 5 mL IR solution

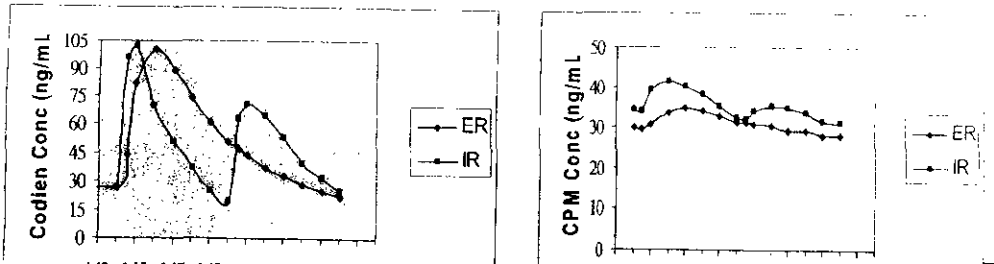


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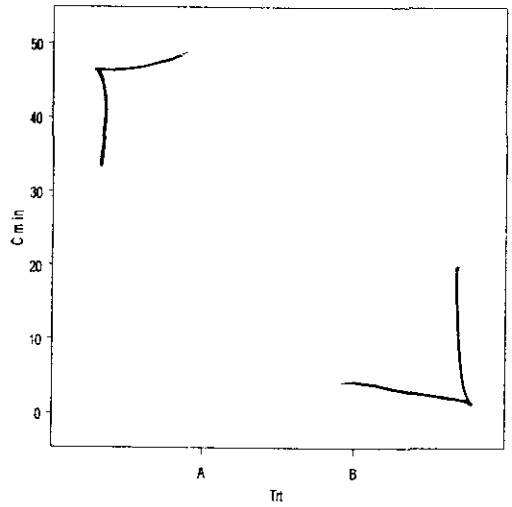
Figure 3. Individual codeine C_{min} values following multiple administrations of each treatments



The findings from this study are summarized as follows:

- Codeine in the proposed suspension is bioequivalent to that of the reference as 90% CI for the ratios of the PK parameters, AUC_{ss}, C_{max}, C (144) and C (156) contained within 80-125%, while C_{min} fell slightly outside the BE range (104.95% to 129.44%). However, this higher C_{min} is considered clinically not significant.
- CPM in the proposed suspension is bioequivalent to that of the reference as 90% CI for the ratios of the PK parameters including C_{min}.

2.3 General Biopharmaceutics

2.3.1. Was the to-be-marketed formulation used in the Pharmacokinetic studies?

Yes. The Codeprex ER suspension lot used in the bio studies was CL02123A, which utilized a —— coating level.

2.3.2. What is the effect of food on the BA of Codeine and CPM from the proposed formulation?

Study 2002-12 was an open-label, single dose, randomized, 2-way crossover study in 36 healthy male and female volunteers to determine the effect of a high-fat meal on the relative BA of a proposed formulation containing codeine 40 mg and CPM 8 mg under fed (Trt A) compared to that under the fasting condition

(Trt B). The summary of the PK parameters and statistical analysis results for the PK parameters of codeine and CPM are presented in Table 9. The mean concentration-time plots for codeine and CPM and individual Tmax value of CPM following each treatment are shown in Figures 4 and 5, respectively.

Table 9. Arithmetic Mean (SD) of COD and CPM PK parameters and statistical analysis following single dose of the treatments

			Codeine			CPM		
Parameter	**TRT**	**N**	**Mean (SD)**	**Ratio A/B**	**90% CI***	**Mean (SD)**	**Ratio A/B**	**90% CI***
C_{max}	A	36	70.9 (19.1)			7.5 (1.8)		
(ng/mL)	B	35	61.7 (18.5)	1.16	108.4-124.2	7.4 (1.6)	1.0	95.4-104.0
AUC_t	A	36	533.1 (160)			271.2 (103.7)		
(ng•hr/mL)	B	35	457.7 (116.4)	1.16	111-121.8	250.1 (75.8)	1.03	98.1-107.4
AUC_{inf}	A	36	561.8 (166.2)			323.8 (172.3)		
(ng•hr/mL)	B	35	500.2 (128.3)	1.12	107.4-117.4	293.7 (112.1)	1.01	95.8-105.8
T_{max}	A	36	2.42 (0.65)			9.06 (5.95)		
(hr)	B	35	2.56 (0.91)			6.3 (1.21)	*P*=0.004	
$T_{1/2}$	A	36	5.9 (1.2)			21.7 (8.7)		
(hr)	B	35	8 (2.9)			22.2 (5.8)		

A = Extended release suspension (fed)
B = Extended release suspension (fasted)
* The confidence intervals are obtained from an ANOVA model with treatment, period, sequence as fixed effects and subjects nested within sequence as a random effect in the natural logarithmic transformed parameter.

Figure 4. Mean codeine (left) and CPM (right) plasma concentration-time course following single dose of 10 mL ER suspension Under fasting condition and following high-fat breakfast

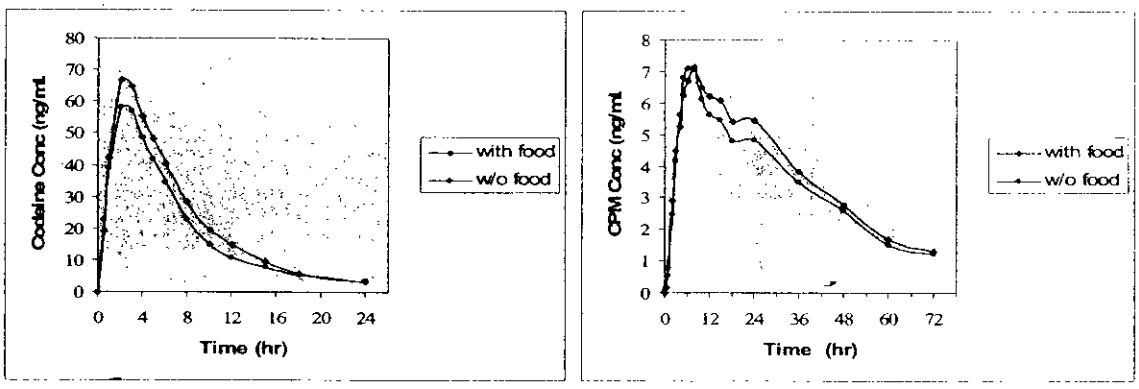


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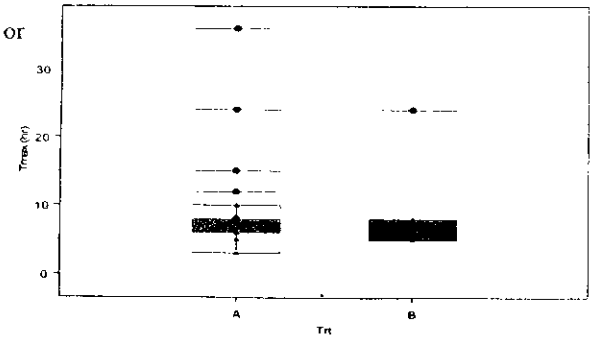
Figure 5. Median T_{max} of CPM with (trt A) or without (trt B) food



The following summarizes the findings from this study:

- High-fat meal had no effect on the bioavailability of codeine and CPM from Codeprex ER suspension, 90% CI for the ratios of AUC and C_{max} were within 80-125% BE range.
- Food caused a delay in T_{max} of CPM by 2.5 hrs, but this difference would not be expected to be of clinical relevance, particularly since the mean T_{max} of CPM under fed conditions (9.06 ± 5.95 hr) was similar to the mean T_{max} following 2 IR doses given 6 hours apart under fasting conditions (9.11 ± 0.88 hr), as reported in study COD03-01.

2.3.3. Are the dissolution method and specifications supported by the data?

A new manufacturing process for Codeprex ER Suspension has been developed to stabilize the *in-vitro* release rates observed for both codeine and CPM, and a full-scale production batch (CL-02123A) as well as 3 pilot scale batches were manufactured using the new process. Three PK studies were conducted employing lot CL-02123A. However, a consequence of the process changes has been a change in the *in-vitro* release rate profiles for both codeine and CPM. The sponsor proposed that the original dissolution method ——— for CPM (instead claiming IVIVC in the original NDA submission) and new one for codeine ——— . The new method ——— is developed to meet the criteria of *in-vitro* release rate of —— at l hour and —— at 12 hours in addition to change in manufacturing the product process.

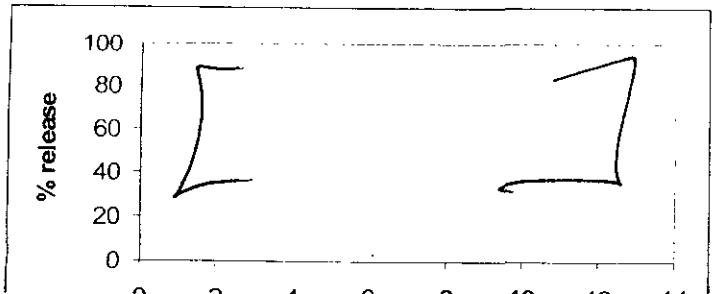
Codeine: The dissolution profiles of 4 batches obtained by the methods ——————— are shown in Table 10 and Figure 6.

Table 10. Codeine % released by two dissolution methods

Time (hr)	CL-02123A	CL-02115A	8047-189A	8047-190A
	Method ———			
1				
3				
6				
12				
	Method ———			
1				
3				
6				
12				
$f2^{*1}$				
$f2^{*2}$				

Similarity (f2) test: reference ——————— $f2^{*1}$ and $f2^{*2}$ by using 3 and 4 time points, respectively

Figure 6. % Codeine Release by two dissolution methods: Blue (upper) and red (lower) lines are by ——————— respectively.



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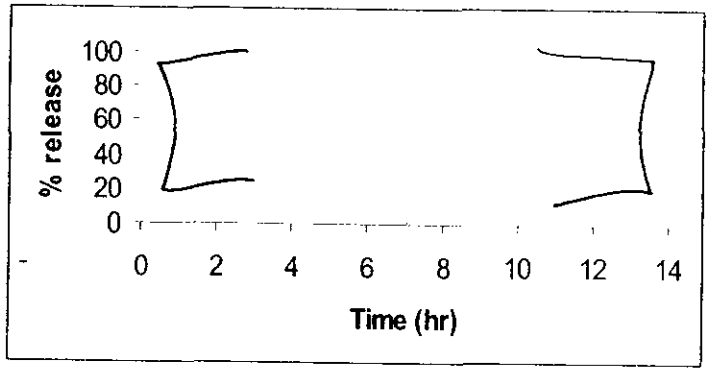
The dissolution profiles of codeine obtained by two methods are similar at 6 and 12 hr time-points, but the release was faster at 1 and 3 hr time-points by method —— compared to that by ——. Dissolution profiles obtained by —— (reference) are compared (f2 similarity) to those obtained by the method —— (test) for each batches. Although, the difference was shown at 1 and 3 hr sampling times, two methods provided the 'equivalent' *in vitro* dissolution profiles (Table 10, last 2 rows).

CPM: Dissolution profiles obtained by the method —— is presented in Table 11 and figure 7.

Table 11. CPM release rates (% released) by Method ——

Time (hr)	CL-02123A	CL-02115A	8047-189A	8047-190A
1				
3				
6				
12				

Figure 7. CPM release rates by dissolution method —— on 4 lots



Recommendation of Dissolution methods and Specifications:

Codeine: The method —— utilizes the 'replacement' medium with —— at each sampling times, *i.e.*, the method is designed to ——. Consequently, the method —— is inadequate. Thus, the sponsor is recommended to use the method —— for codeine as

the dissolution method. Regard to setting the dissolution specifications, the CMC team strongly suggested that it should be ~ of the mean release rate from the stability data that were obtained from the bio- and 3 pilot batches stored at room temperature (i.e., ——— RH) up to — months, rather than usual practice, i.e., — of the mean release rate obtained from the bio-batch at initial. The specifications are summarized in the table below.

Codeine (method by ~

Sampling time	CMC	Mean	Low-upper[3]
1 hr		44-64	
3 hr		65-85	
6 hr		76-96	
12 hr	%	NLT	

[1]based on the mean from bio- + 3 pilot lots (at ——— RH storage up to —months)
[2]based on the mean from bio-batch (at ——— RH initial)
[3]Low-upper: individual sample (bio- + 3 pilot lots at ——— RH storage)

In conclusion, the recommended the dissolution method and specifications for codeine is as follows (Table 12):

Table 12. Recommended dissolution method and specifications for Codeine

Method ~	
Apparatus	USP Apparatus II (paddle)
Media	
Speed of Rotation	~ rpm
Temperature:	
Specifications	
1 hr	
3 hr	
6 hr	
12 hr	

CPM: The sponsor proposed dissolution method, ——— is acceptable. However, the reviewing chemist (CMC team) suggested the same scenario as codeine. The options of specifications are shown in the table below.

Chlorpheniramine (method by ~

Sampling time	CMC	Mean	Low-upper[3]
1 hr		32-52	
3 hr		55-75	
6 hr		68-88	
12 hr		NLT	

[1]based on the mean from bio- + 3 pilot lots (at ——— RH storage up to — months)
[2]based on the mean from bio-batch (at ——— RH initial) (sponsor proposed)
[3]Low-upper: individual sample (bio- + 3 pilot lots at ——— RH storage)

In conclusion, the recommended the dissolution method (same as the sponsor proposed) and specifications for chlorpheniramine is as follows (Table 13):

Table 13. Method ——— and Specifications for CPM

Method ~	
Apparatus	USP Apparatus II (paddle)

Media	
Speed of Rotation	rpm
Temperature:	
Specifications	
1 hr	
3 hr	
6 hr	
12 hr	

2.4. Analytical Methodology

2.4.1 Was the suitability of the analytical method supported by the submitted information?

An LC/MS/MS method was employed for determination of the codeine and CPM plasma concentrations. Assay method has been validated for linearity, precision, recovery and stability over the concentration range for codeine and for CPM. The application of the validated method to analyze the samples from the present studies is acceptable. Also the accuracy and inter-day precision were acceptable for all the studies (Bias or %CV).

3. LABELING COMMENTS

- Under the pharmacokinetic section, the following description is removed.

- Under the "Food effect" section, it is recommended to withdraw the table, and modify the paragraphs as follows:

The bioavailability of Codeprex Extended-Release Suspension was not affected when administered after a high fat meal. In a two-way crossover study, pharmacokinetic parameters were evaluated in 36 healthy subjects and no differences between fed and fasted groups were for either Cmax or AUC for either codeine or chlorpheniramine. A statistically significant increase in T_{max} for chlorpheniramine from 6.3 hours to 9.1 hours was observed after a high fat meal; however this increase is unlikely to be clinically important.

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Proposed

11 page(s) of revised draft labeling has been redacted from this portion of the review.

Pharmacokinetic Results: The arithmetic means and standard deviations of the codeine and CPM PK parameters and the statistical comparisons for Treatment A and Treatment B are summarized in Table 1, and the mean plasma concentrations of Codeine and CPM are present in Figure 1.

Figure 1. Mean plasma concentration-time profiles of Codeine (left) and CPM (right)

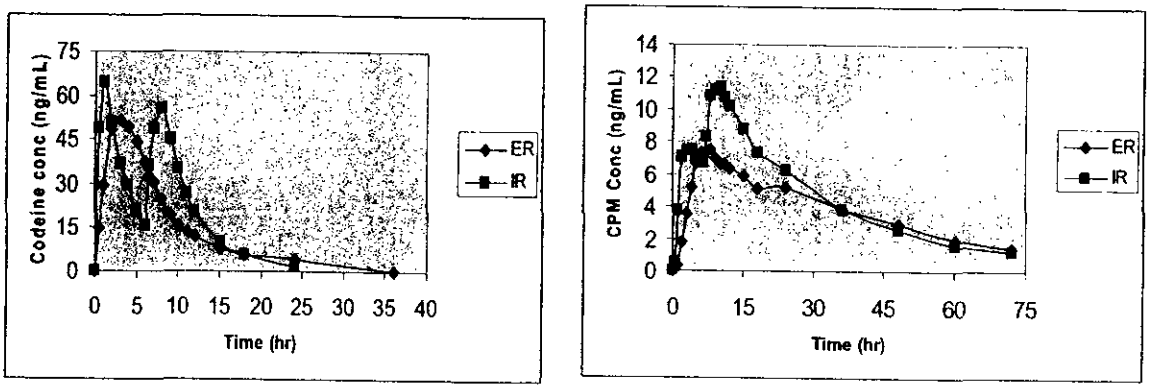


Table 1. Arithmetic Mean (SD) of codeine and CPM PK parameters and statistical analysis following single dose of the treatments

Parameter	TRT	N	Mean (SD)	Ratio ER/ IR	90% CI[a]	Mean (SD)[1]	Ratio ER/ IR	90% CI[a]
			Codeine			CPM		
C_{max} (ng/mL)	ER	20	53.9 (13.4)	0.79	73.0-85.5	7.9 (1.6)	0.65	61.9-67.7
	IR	19	67.3 (13.7)			11.9 (2.1)		
AUC_t (ng•hr/mL)	ER	20	448.6 (115)	0.83	78.7-86.7	272.3 (80.2)	0.81	77.6-85.5
	IR	19	531.9 (119)			329.8 (86)		
AUC_{inf} (ng•hr/mL)	ER	20	505.6 (129)	0.89	82.5-95	326.7 (126)	0.85	81.0-89.8
	IR	19	550. 3 (121)			378.9 (142)		
T_{max}[b] (hr)	ER	20	3.05 (0.9)		p=0.56	7.13 (1.4)		
	IR	19	2.66 (2.9)			9.11 (2.1)		
$T_{1/2}$ (hr)	ER	20	6.97 (2.5)			22.51 (8.6)		
	IR	19	3.46 (0.9)			21.58 (8.1)		

ER = Extended release suspension (test)
IR = Immediate release solution q6h x 2 (reference)
[a]The confidence intervals are obtained from an ANOVA model with treatment, period, sequence as fixed effects and subjects nested within sequence as a random effect in the natural logarithmic transformed parameter.
[b]Non parametric analysis

The 90% CI for AUC_t of codeine was not within the range of 80% to 125% while AUC_{inf} was. The sponsor stated that there were several limitations in comparing AUC_t between the ER formulation and IR formulation that could have affected this result: There was prolonged absorption for Treatment A as a result of the extended release formulation (flip-flop model for Trt A). The sampling times were the same, but the time of the last measurable concentration as well as the mean value of the last measurable concentration was different between Treatments A and B. Thus, the sponsor stated that the sampling strategy for evaluation of AUC_t was not optimized for both treatments. In this scenario, AUC_{inf} is a better comparator for the exposure following a single dose. The sponsor also stated that the area missed in Treatment A due to the sampling strategy was included in the AUC_{inf} by extrapolation to infinity. This

4.2. INDIVIDUAL STUDY REVIEWS

Protocol #COD03-01

Study Type: BE/single dose.

Title: A pharmacokenetic study to assess the oral bioavailability of an ER 10 ml Suspension of codeine 40 mg and CPM 8 mg Relative to an Immediate-Release 5 ml Solution of codeine 20 mg and CPM 4 mg.

Clinical Investigator: [redacted]
Analytical site: [redacted]

Objectives: To compare the relative bioavailability of a single dose of an ER 10 mL suspension of codeine 40 mg and CPM 8 mg relative to an immediate-release (IR) 5 ml solution of codeine 20 mg and CPM 4 mg administered every 6 hours for 2 consecutive doses, under fasting conditions.

Methodology: This was a single-dose, randomized, open-label, 2-way crossover study. A total of 20 subjects were enrolled in the study, and 19 subjects completed the study. Subjects randomized to receive the following treatments. There was a 7-day washout between doses.

- Treatment A (test): 10 mL syringe of Codeprex ER suspension (codeine 40 mg/CPM 8 mg/10 mL). Lot No.: CL-02123A, expiration date: Dec 2004.
- Treatment B (reference): 5 ml syringe of codeine/CPM IR solution (codeine 20 mg, CPM 4 mg/5 ml) every 6 hours for 2 consecutive doses, manufactured by Celltech lot No.: CL-031 33A, manufactured date: 09 April 2003

Criteria for Evaluation:
Blood sampling of PK analysis: predose, 0.5, 1, 2, 3, 4, 5, 6, 6.5, 7, 8, 9, 10, 11, 12, 15, 18, 24, 36, 48, 60, and 72 hours post dose. PK parameters (AUC_{0-t}, AUC_{0-inf}, AUCR (AUC_{0-t}/AUC_{0-inf}), Kel, $t_{1/2}$, C_{max}, and T_{max}) were computed.
Safety: Physical examination, clinical laboratory tests, vital signs, electrocardiogram, and adverse events.

Analytical Methodology

[redacted]

Statistical Methods (for PK): Descriptive statistics with plasma concentrations were presented. Analysis of variance (ANOVA) using a parametric (normal-theory) general linear model was applied to the untransformed AUC_{0-t}, AUC_{0-inf}, Kel and C_{max}, and to the logarithmic transformation of AUC_{0-t}, AUC_{0-inf} and C_{max}. T_{max} was analyzed using nonparametric analysis (Walsh Averages and appropriate quantile of the Wilcoxon Signed Rank Test Statistic). The 90% confidence intervals for the ratio of the test and reference means were calculated for the log transformed parameters. Ratios of means were expressed as a percentage of the reference least squares mean (LSM). Comparable bioavailability with

lessened the difference in the treatment means for AUC_{inf}. The same scenario/logic can be applied for chlorpheniramine.

Conclusion: Pharmacokinetic and statistical analyses of the data resulting from the administration of a single dose of 40 mg codeine/8 mg CPM ER suspension (Treatment A, test), compared to administration of 2 doses of 20 mg codeine/4 mg CPM IR solution 6 hours apart (Treatment B, reference), indicate that the test treatment met the criteria for comparable bioavailability to the reference treatment based on AUC_{inf}. Based on AUCt, the lower limit of the 90% confidence interval for the LSM ratio was less than 80% for both chlorpheniramine and codeine. C_{max} was also lower for the test formulation; however, this was expected since Treatment A is designed to provide slower drug release.

Protocol #CD00900

Study Type: BE/multiple dose.

Title: A pharmacokinetic study to assess the steady state bioavailability of an extended-release 10 ml suspension of codeine 40 mg/chlorpheniramifle maleate 8 mg relative to an immediate-release 5 ml solution of codeine 20 mg/chlorpheniramifle maleate 4 mg.

Clinical Investigator: [redacted]
Analytical site: [redacted]

Objectives: To assess the steady state BA of an ER 10 ml suspension of codeine 40 mg and CPM 8 mg relative to an immediate-release 5 ml solution of codeine 20 mg and CPM 4 mg following a multiple dose regimen.

Study Design and Method: This was a multiple-dose randomized open-label, 2-way crossover study. Subjects were randomized to receive following treatments. There was a 14-day washout between doses.

- Treatment A (test): 10 ml syringe of Codeprex ER suspension (codeine 40 mg/CPM 8 mg/10 mL) every 12 hours for 13 consecutive doses. Lot No. CL-02123A.
- Treatment B (reference): 5 ml syringe of IR solution (codeine 20 mg/CPM 4 mg/5 mL) every 6 hrs for 26 consecutive doses. Lot No. CL-02111A, manufactured by Celltech.

Criteria for Evaluation: PK parameters (AUC, C_{max}, C_{min}, T_{max}, CL, $t_{1/2}$) of guaifenesin and DM.

Blood sampling times: predose, and 96, 120, 144, 144.5, 145, 146, 147, 148, 149, 150, 150.5, 151, 152, 153, 154, 155, and 156 hours post dose. The PK of codeine and CPM were evaluated during the 144- through 156-hour interval for both the ER and IR formulations. AUC(144-156), Cmax, Tmax, Cmin, C(144), C(156), Cavg, Fluctuation Index, and Degree of Fluctuation were computed.

Analytical Methodology

[redacted]

Data Analysis: Descriptive statistics were reported for all pharmacokinetic parameters. Achievement of steady state was evaluated by regressing the 96-, 120-, and 144-hour codeine and CPM concentrations over time with respect to each treatment group. In addition, for chlorpheniramine, the 120, 144, and 156 hour concentrations were also regressed with respect to each treatment group. Achievement of steady state was evaluated based on the slope not being statistically different from zero.

A parametric (normal-theory) general linear model was applied to the logarithmic transformation of AUC(144-156), Cmax, and Cmin. The 90% confidence intervals for the ratio of the test and reference means were calculated for these log transformed parameters and for un-transformed AUC(144-156), C(144), and C(156). Fluctuation index and degree of fluctuation were evaluated for comparability between formulations. Comparable bioavailability of the formulations was declared with respect to

ln[AUC(144-156)] provided the 90% confidence interval of the ratio of the least-squares means for codeine and chlorpheniramine fell within the range of 80% to 125%.

Results:

Study Population: A total of 26 subjects (healthy 13 male and 13 female volunteers) were enrolled in the study, and 25 subjects included in the PK analyses. The subjects averaged 29 years of age with a range of 21-39 years. 2 subjects were Black, 6 subjects were Caucasian and 18 subjects were Hispanic.

Figure 1. Mean plasma concentration-time profiles of Codeine (left) and CPM (right)

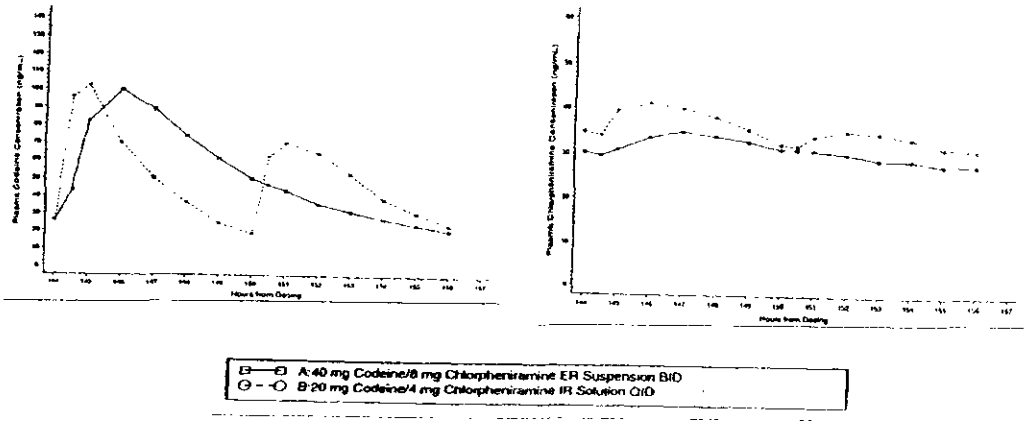


Table 1. Arithmetic Mean (SD) of codeine (COD) and CPM PK parameters and statistical analysis following multiple dose of the treatments

Parameter	TRT	N	Mean (SD)	Ratio ER/IR	90% CI*	Mean (SD)[1]	Ratio ER/IR	90% CI*
			Codeine			CPM		
C_{max} (ng/mL)	ER	24	100.5 (26.8)			35.8 (10.0)		
	IR	25	108.1 (33.8)	0.93	87.7-98.2	42.4 (15.4)	0.90	85.6-93.8
$AUC_{(144-156)}$ (ng•hr/mL)	ER		644.4 (182.7)			376.3 (106.2)		
	IR		617.4 (195.5)	1.04	99.2-108.9	429 (141.6)	0.92	88.7-95.9
C_{min} (ng/mL)	ER		21.4 (6.5)			27.7 (8.6)		
	IR		18.8 (8.4)	1.17	105-129.4	30.7 (10.2)	0.95	90.3-99.5
C (144)** (ng/mL)	ER		26 (8.4)			30.3 (9.6)		
	IR		26.1 (9.5)	0.99	89.8-107.9	34.7 (13.4)	0.94	88.8-99.2
C (156)** (ng/mL)	ER		21.8 (6.4)			28.1 (8.5)		
	IR		24.7 (9.4)	0.88	79.1-96.5	31.4 (10.7)	0.94	89.4-98.8
Cavg (ng/mL)	ER		53.7 (15.2)			31.3 (8.9)		
	IR		51.5 (16.3)			35.8 (11.8)		
T_{max} (hr)	ER		2.04 (0.2)			3.22 (0.9)		
	IR		1.1 (1.25)			3 (2.3)		
Fluct. Index (%)	ER		382.5 (104.6)			31.0 (12.2)		
	IR		518.8 (201.3)			38.7 (14.6)		
Degree of Fluct.	ER		1.48 (0.17)			0.27 (0.09)		
	IR		1.74 (0.33)			0.32 (0.11)		

ER = Extended release suspension IR = Immediate release solution

* The confidence intervals are obtained from an ANOVA model with treatment, period, sequence as fixed effects and subjects nested within sequence as a random effect in the natural logarithmic transformed parameter; 90% CI based on un-transformed values

C_{min} for COD fell slightly outside the BE range ( ), demonstrating that the COD plasma levels following the ER formulation did not drop as substantially within the 12-hour sampling

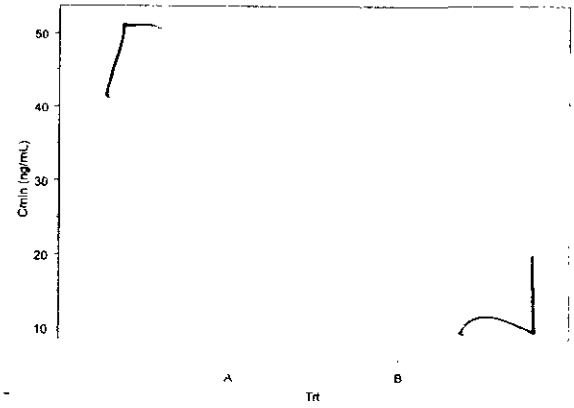
interval as did COD plasma levels following IR administration. Consequently, the fluctuation index, defined as % swing between C_{max} and C_{min}, did decrease substantially for COD, from 518.8% for the IR formulation to 382.5% for the ER formulation, indicating less variability in the 12-hour COD plasma levels for the ER compared to the IR formulation. There was less of a difference in fluctuation index for CPM, with a decrease from 38.7% for the IR formulation to 31% for the ER formulation.

Steady State: Achievement of steady state condition was tested by using the slope of regression of predose concentrations on 3 consecutive days. The results of regression analysis are shown in the table below;

Treatment	N	Mean Slope	p-Values
Codeine: Plasma concentrations at 96, 120 and 144 hours			
ER	24	-0.0899	0.003
IR	25	-0.0886	0.001
CPM: Plasma concentrations at 120, 144 and 156 hours			
ER	23	-0.00042	0.98
IR	25	-0.02175	0.32

The slope for codeine was negative, although statistically different than zero, indicating that plasma codeine concentrations were no longer increasing with multiple dosing. Thus codeine concentrations were considered to be at steady state by Hour 96. For CPM, the slope was negative and not statistically significant from zero. Thus CPM concentrations reached steady state by Hour 120.

Figure 2. Individual Codeine C_{min} values following multiple doses of the treatment



Conclusion:

The multiple twice daily administrations of 40 mg codeine/8 mg CPM ER suspension (Treatment A) and multiple 4 times a day administrations of 20 mg codeine/4 mg CPM IR solution (Treatment B) resulted in similar 12-hour extent of exposure to both codeine and CPM as determined during steady-state conditions on Day 7 of repeated dosing. The mean ratios for ln [AUC(144-156)] for the comparison of Treatment A to Treatment B were 103.9% for codeine and 92.2% for CPM. The 90% confidence interval for these comparisons, at 99.22% to 108.90% for codeine and 88.70% to 95.86% for CPM, were both within the 80% to 125% range required for the conclusion of comparable bioavailability between the 2 formulations.

Protocol #CD00800

Study Type: Food effect/single dose.

Title: Open-Label, Randomized, Crossover, Comparative, Bioavailabitity Study of an Extended-Release 10 mL Suspension of Codeine 40 mg/Chlorpheniramine Maleate 8 mg Given as a Single Dose After a High-Fat Meal or Under Fasting Conditions.

Clinical Investigator: [redacted]
Analytical site: [redacted]

Objectives: To compare the oral bioavailability of an extended-release 10 ml suspension of codeine 40 mg and chlorpheniramine maleate 8 mg after a single administration following a high-fat breakfast or under fasting conditions.

Methodology: This was a single-dose, fed versus fasted, randomized, open-label, 2-way crossover study. A total of 36 subjects were enrolled in the study and 35 subjects completed the study. Subjects randomized to receive the following treatments followed by 240 mL water.

- Treatment A (test): 10 mL syringe of Codeprex ER suspension (codeine 40 mg/CPM 8 mg/10 mL) following a high-fat breakfast. Batch no: CL-02123A
- Treatment B (reference): 10 mL syringe of Codeprex ER suspension (codeine 40 mg/CPM 8 mg/10 mL) following a 10-hour overnight fast. Batch no: CL-02123A

Criteria for Evaluation:

Blood sampling of PK analysis: predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 24, 36, 48, 60, and 72 hours postdose. PK parameters (AUC_{0-t}, AUC_{0-inf}, AUCR (AUC_{0-t}/AUC_{0-inf}), Kel, $t_{1/2}$, C_{max}, and T_{max}) were computed.
Safety: Physical examination, clinical laboratory tests, vital signs, electrocardiogram, and adverse events.

Analytical Methodology

[redacted]

Statistical Methods (for PK): Descriptive statistics with plasma concentrations were presented. A parametric (normal-theory) general linear model was applied to the untransformed AUC_{0-t}, AUC_{0-inf}, Kel and C_{max}, and to the logarithmic transformation of AUC_{0-t}, AUC_{0-inf} and C_{max}. T_{max} was analyzed using nonparametric analysis (Walsh Averages and appropriate quantile of the Wilcoxon Signed Rank Test Statistic). The 90% confidence intervals for the ratio of the test and reference means were calculated for the log transformed parameters. Ratio of means was expressed as a percentage of the least square means (LSM) for the fasted condition. Lack of food effect was evaluated based on the 90% confidence intervals for the ratio of LSM based on log-transformed C_{max}, AUC_{0-t} and AUC_{0-inf} (fed/fasted) falling within 80% to 125%.

Pharmacokinetic Results:

Study Population: Results from pharmacokinetic analysis of codeine were based on data from 36 subjects who completed Treatment A and 35 subjects who completed Treatment B. Results from pharmacokinetic analysis of CPM were based on data from 36 subjects in Treatment A and 33 subjects in Treatment B.

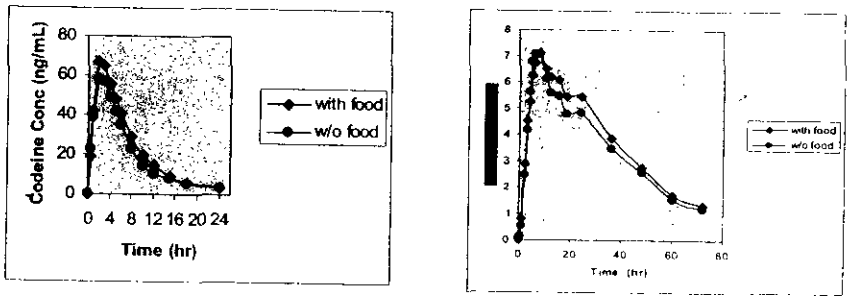
The arithmetic means and standard deviations of the codeine and CPM pharmacokinetic parameters and the statistical comparisons for Treatment A (fed) and Treatment B (fasted) are summarized in Table 1. Plasma profiles following the treatments and the individual Tmax of CPM are presented in Figure 1 and 2, respectively.

Table 1. Arithmetic Mean (SD) of COD and CPM PK parameters and statistical analysis following single dose of the treatments

Parameter	TRT	N	Mean (SD)	Ratio A/B	90% CI*	Mean (SD)	Ratio A/B	90% CI*
			Codeine			CPM		
C_{max} (ng/mL)	A	36	71 (19.1)	1.16	108.4-124.2	7.5 (1.8)	1.0	95.4-104.0
	B	35	61.7 (18.5)			7.4 (1.6)		
AUC_t (ng•hr/mL)	A	36	533.1 (160)	1.16	111-121.8	271.2 (103.7)	1.03	98.1-107.4
	B	35	457.7 (116.4)			250.1 (75.8)		
AUC_{inf} (ng•hr/mL)	A	36	561.8 (166.2)	1.12	107.4-117.4	323.8 (172.3)	1.01	95.8-105.8
	B	35	500.2 (128.3)			293.7 (112.1)		
T_{max} (hr)	A	36	2.42 (0.65)			9.06 (5.95)	*P*=0.004	
	B	35	2.56 (0.91)			6.3 (1.21)		
$T_{1/2}$ (hr)	A	36	5.9 (1.2)			21.7 (8.7)		
	B	35	8 (2.9)			22.2 (5.8)		

A = Extended release suspension (fed)
B = Extended release suspension (fasted)
* The confidence intervals are obtained from an ANOVA model with treatment, period, sequence as fixed effects and subjects nested within sequence as a random effect in the natural logarithmic transformed parameter.

Figure 1. Mean plasma concentrations of codeine (left) and CPM (right)



(trt A)

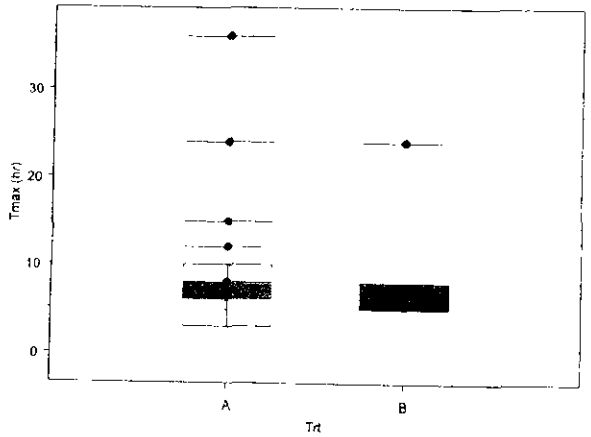


Figure 2. Median Tmax of CPM with or without (trt B) food

Conclusion: Pharmacokinetic and statistical analyses of the data resulting from the administration of a single dose of 40 mg codeine/8 mg CPM following a high-fat meal (Treatment A), compared to administration of the same formulation under fasting conditions (Treatment B) indicates that prandial status had no relevant effect on the rate and extent of exposure to codeine and CPM. The 90% CI for the comparison of ln-transformed C_{max}, AUC_{0-t} and AUC_{0-inf} were all within the acceptable range of 80% to 125% required for the conclusion of absence of any food effect on the plasma concentration-time profiles of both analytes. Food caused a delay in T_{max} of CPM by approximately 2.5 hours however there was a higher inter-subject variability compared to without food. Therefore, Codeplex ER suspension can be taken without regards to meals.

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Dissolution

There was a substantial decrease in release *in-vitro* of both the clinical and stability batches, which were submitted in original NDA, for codeine and chlorpheniramine (CPM) over time (as noted in the approvable letter). To address this concern, manufacturing process changes were implemented to produce a product that demonstrates stable release rates over time, and a suspension was produced via new manufacturing process (i.e., Lot CL-02123A - coated codeine polistirex with target polymer coating of —— The clinical studies were conducted employing lot CL-02123A.

However, a consequence of the process changes has been a change in the *in-vitro* release rate profiles for both codeine and CPM. The sponsor proposed that the original dissolution method —— for CPM (instead claiming IVIVC in the original NDA submission) and new one for codeine —— to meet the criteria of *in-vitro* release rate of ——

Codeine release: Proposed dissolution method —— and *in vitro* dissolution data obtained by this method as well as the proposed specifications are shown below;

Apparatus	USP Apparatus II (paddle)
Media	
Replacement medium:	
Speed of Rotation	
Temperature:	
Withdrawal Time	
Collection time	
% Released (range)	
Proposed Specifications	

Note: The medium —

CPM release: Proposed method, same method that was submitted in the original NDA —— , and *in vitro* dissolution data obtained by this method and the proposed specifications are shown below;

Apparatus	USP Apparatus II (paddle)
Media	
Speed of Rotation	
Temperature:	
Withdrawal Time	
Collection time	
% Released (range)	
Proposed Specifications	

Note: The medium —

The development of these two dissolution methods is summarized below.

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Development (Report No. R03056)

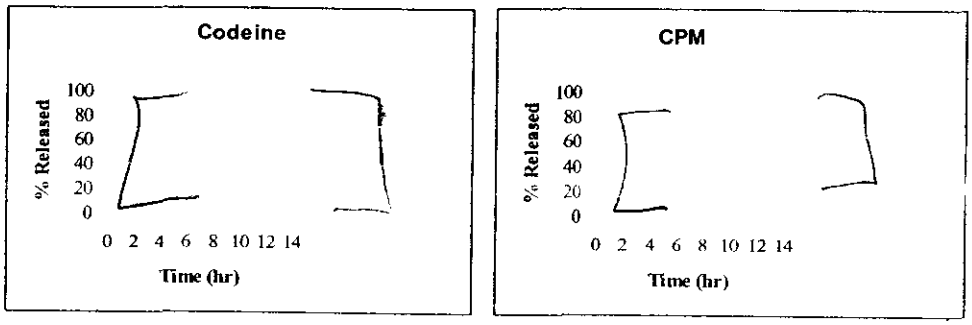
a. Evaluation of paddle rotation speed

The method [redacted] utilizes USP Apparatus II (paddles) at [redacted] An evaluation of [redacted] method at a lower rotation speed was performed, and the results are shown in Table 1 and presented graphically in Figure 1.

Table 1. Comparison of Codeine and CPM release rates at [redacted]

Time point (hr)	Codeine	Chlorpheniramine
1	[redacted]	
3		
6		
12		

Figure 1. Comparison of codeine and CPM release at [redacted]



The impact of using a lower paddle rotation speed of [redacted] on the release rate profiles of both codeine and CPM was minimal, with a small drop in release amounts at 1 and 3 hours. The sponsor stated that lower paddle rotation speeds [redacted]

b. Evaluation of Medium Composition

The nominal composition of the release rate medium in the method [redacted] The impact of each component of the medium on the release profiles was evaluated by varying the composition of the medium one component at a time and generating 12-hour profiles. Results of this study are shown in Tables 2a and 2b and presented graphically in Figure 2.

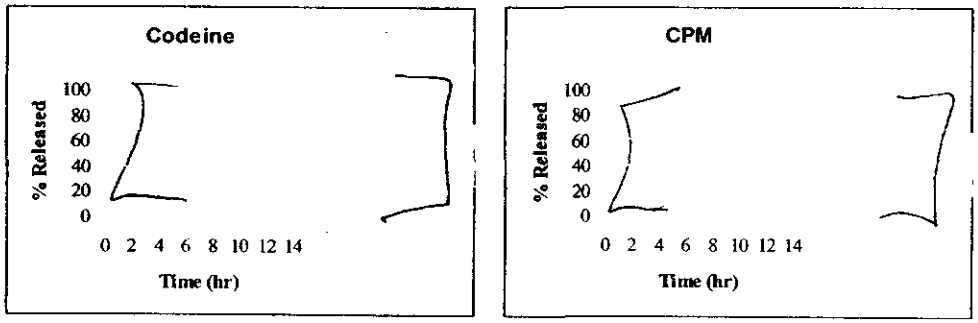
Table 2a. Comparison of **Codeine** Release Rates Using Various Media

Time point (hr)	Current medium [redacted]
1	
3	
6	
12	

Table 2b. Comparison of **Chlorpheniramine** Release Rates Using Various Media

Time point (hr)	Current medium
1	
3	
6	
12	

Figure 2. Comparison of codeine and CPM release by modified Medium



The greatest impact on the release rate of both codeine and CPM was obtained by lowering the amount of

c. Development of a New Release Rate Technique

A universal consequence of decreasing the 1-hour release rate values for codeine or CPM by changing the The sponsor stated that the release mechanism is based

To obtain release profiles that yield the desired characteristics of less than released at 1 hour and greater than at 12 hours, the sponsor developed a new release rate technique that utilizes medium

Three examples follow:

Starting Composition of Medium:
Sample Pull Volume:
Replacement Volume:
Replacement Medium Composition:

The results are summarized in Table 3.

Table 3: of Release Rate Media at Sampling Time-Points

Sampling Time-Point
1
3
6
12

Release profiles of codeine and CPM using the example techniques are shown in Tables 4 and 5 and presented graphically in Figure 3.

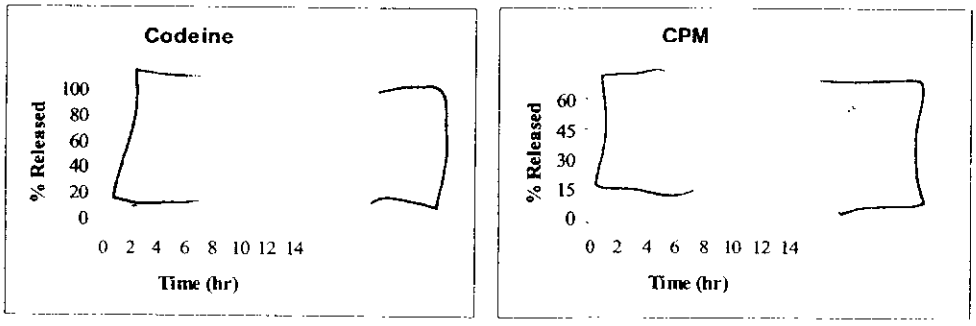
Table 4: Release Rates of Codeine Using Medium Replacement Techniques

Time point (hr)
1
3
6
12

Table 5: Release Rates of CPM Using Medium Replacement Techniques

Time point (hr)
1
3
6
12

Figure 3. Evaluation of ——— for medium replacement



Release rate profiles with the desired characteristics were achieved for codeine but not for CPM with the same method. The sponsor decided that since the method ——— yields suitable release rate profiles for CPM from Codeprex Suspension, no further development work was performed for a CPM release rate method.

d. Product Discrimination

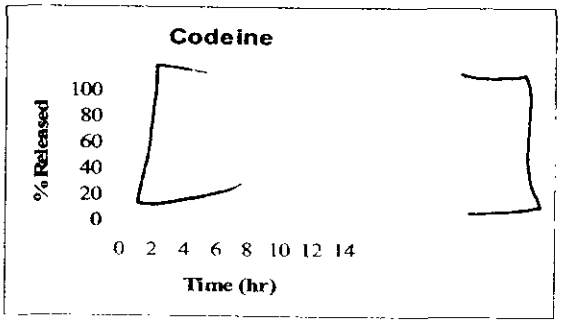
Discriminatory power of the method ——— was evaluated using Codeprex suspension made with coated codeine polistirex intermediate coated at levels of ——————— (the proposed target coating level is ———). Release rate method conditions were as follows:

Starting Composition of Medium:
Sample Pull Volume:
Replacement Volume:
Replacement Medium Composition:
Apparatus: II (paddles) at [redacted] RPM

Table 6: Coating Level Dependence of Release Rate of Codeine from Codeprex Suspension

Time point (hr)	[redacted]
1	
3	
6	
12	

Figure 4. Codeine release rates, Coating level dependence



Coating level discrimination is observed at each sampling time-point (1, 3, 6 and 12 hours) for the coating levels evaluated.

Conclusions:

- The new release rate method demonstrates [redacted] released at 1 hour for drug product made with intermediates coated at [redacted]
- Greater than [redacted] released at 12 hours is demonstrated for drug product made with intermediates coated at [redacted] (however, the proposed specification at 12 hrs is [redacted], therefore, [redacted] coating will fail to meet the criteria).
- Coating level discrimination at all sampling time-point (1, 3, 6 and 12 hours).
- The new release rate method is not suitable for the determination of CPM from Codeprex Suspension manufactured with the new process since it did not yield [redacted] released at 1 hour and greater than [redacted] CPM released at 12 hours (Table 5).

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The effects of paddle speed and dissolution medium pH on the release of codeine and CPM from Codeine/CPM Extended Release Suspension (CCERS) – Report No. R03266

The effect of pH: The effect of pH on the release of codeine and CPM from CCERS is shown in Table 7 and 8, respectively by comparing the release of codeine and CPM before and after methods modifications in dissolution media pH.

Table 7. Effect of dissolution medium pH on the release of Codeine from CCERS (using method

Time-Point	% Released – standard conditions	% Released – Modified,	% Released – Modified,
1			
3			
6			
12			

This data demonstrates that there is minimal effect of pH on the release of codeine from CCERS: this result is expected since the codeine molecule (pKa is essentially completely protonated at the pH values being evaluated.

Table 8. Effect of dissolution medium pH on the release of CPM from CCERS (using method

Time-Point	% Released – standard conditions	% Released – Modified,	% Released – Modified,
1			
3			
6			
12			

There is a difference in the release of CPM from CCERS over the pH range being studied: this observation is not unexpected as the CPM molecule has two pKa values (pKa and pKa . Thus, the amount of CPM release from CCERS is increased under conditions of elevated pH ( ) when compared to standard conditions (pH

The effect of paddle speed: The effect of paddle speed on the release of codeine and CPM from CCERS is shown in Table 9 and 10, respectively by comparing the release of codeine and CPM before and after methods modifications in paddle speed.

Table 9. Effect of paddle speed on the release of Codeine from CCERS (using method

Time point	% release at RPM	% release at RPM	% release at RPM
Mean at 1 hr (SD)	12 (0.7)	40 (0.9)	45 (0.5)
RSD	5.8	2.3	1.1
Range			
Mean at 3 hr (SD)	33 (5.0)	68 (3.1)	70 (0.4)
RSD	15.2	4.6	0.6
Range			
Mean at 6 hr (SD)	64 (11.2)	82 (3.5)	84 (0.3)
RSD	17.5	4.3	0.4
Range			
Mean at 12 hr (SD)	90 (2.1)	91 (1.4)	91 (0.3)
RSD	2.3	1.5	0.3
Range			

Table 10. Effect of paddle speed on the release of CPM from CCERS (using method ———)

Time point	% release at — RPM	% release at — RPM	% release at — RPM
Mean at 1 hr (SD)	9 (1.9)	40 (2.3)	47 (0.4)
RSD	21.1	5.8	0.9
Range			
Mean at 3 hr (SD)	25 (3.3)	62 (2.8)	69 (0.5)
RSD	13.2	4.5	0.7
Range			
Mean at 6 hr (SD)	51 (8.1)	77 (3.1)	82 (0.5)
RSD	15.9	4.0	0.6
Range			
Mean at 12 hr (SD)	80 (4.7)	89 (1.9)	91 (0.6)
RSD	5.9	2.1	0.7
Range			

There is a major difference in the release profile in both cases when a — RPM paddle speed is used compared to ——— RPM paddle speeds. Also, while the profiles for — RPM are similar to those for — RPM, the dissolution tests run at — RPM gave results with a % release range with less variability (lower % RSD) across the 6 vessels than those samples run at — RPM.

Conclusions:

- pH has little effect on the release of codeine from CCERS, but do have a effect on the release of CPM.
- This data demonstrates that a — RPM paddle speed is the most appropriate for codeine and CPM release.

Note: All of the above experiments were carried out using CCERS lot 00032-12 (% coating was not provided).

Dissolution profiles with the bio- and stability batches:

A full-scale production batch (CL-02123A) was manufactured using the new process for use in clinical studies as well as 3 pilot scale batches (CL-02115, 8047-189A and 8047-190A). Codeine and CPM dissolution profiles of these batches are shown in Tables 11-12 and presented graphically in Figures 5-6, respectively. Note that codeine release profiles were obtained by the methods ———

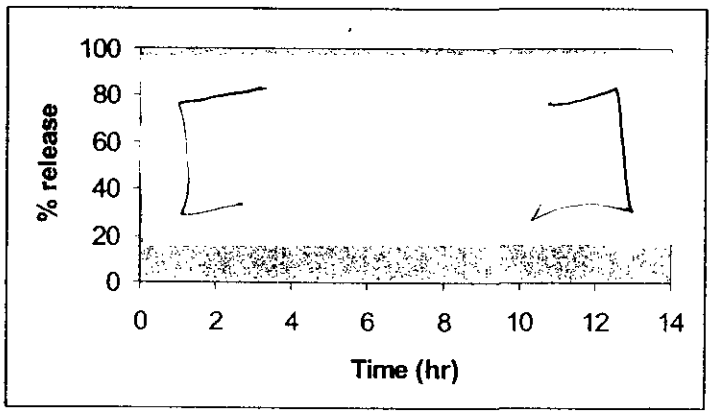
Table 11. Codeine % released by two dissolution methods

Time (hr)	CL-02123A	CL-02115A	8047-189A	8047-190A	Average	Total-range
	Method —					
1					55	
3					75	
6					86	
12					92	
	Method —					
1					41	
3					67	
6					81	
12					90	
f2[a]					*50.4*	
f2[b]					*53.4*	

Similarity (f2) test: reference ——— f2[a] and f2[b] obtained by 3 and 4 time points, respectively

Figure 5. % Codeine Release by two dissolution methods: Blue (upper) and red (lower) lines

are by ——————— , respectively.

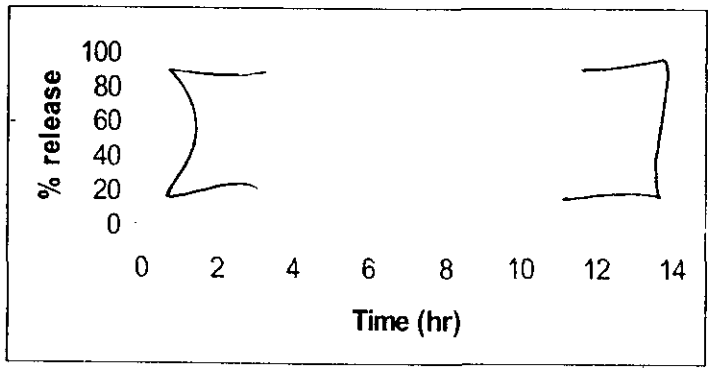


The dissolution profiles of codeine obtained by two methods are similar at 6 and 12 hr time-points, but the release was faster at 1 and 3 hr time-points by method —— compared to that by ——. Dissolution profiles obtained by —— (reference) are compared (f2 similarity) to those obtained by the method —— (test) for each batches. Although, the difference was shown at 1 and 3 hr sampling times, two methods provided the 'equivalent' *in vitro* dissolution profiles (Table 11, last 2 rows).

Table 12. CPM release rates (% released) by Method ——

Time (hr)	CL-02123A	CL-02115A	8047-189A	8047-190A	Average	Overall-ranges
1					43	
3					65	
6					79	
12					88	

Figure 6. CPM release rates by dissolution method —— on 4 lots



Dissolution methods for codeine, ——————— Codeine release at 1 hr was ——, by ——, while that was —— by ———, thus, the dissolution profiles generated by ——— appears to

be superior because the profile meets the criteria of release rate of —— at 1 hour. However, the method ——— uses the replacement of medium with ——— (Tables 3-4) at each sampling times, *i.e.*, the method is designed to ——— Consequently, the method ——— is inadequate. Note that the media composition of ———

Recommended Dissolution methods and Specifications:

Codeine: The sponsor is recommended to use the method ——— as the dissolution method. Regard to setting the dissolution specifications, the CMC team strongly suggested that it should be —— of the mean release rate from the stability data that were obtained from the bio- and 3 pilot batches stored at room temperature (i.e., —— /—— RH) up to —— months, rather than usual practice, i.e., —— of the mean release rate obtained from the bio-batch at initial. The specifications are summarized in the table below.

Codeine (method by ———)

Sampling time	CMC ———	Mean ———	Low-upper[3]
1 hr		44-64	
3 hr		65-85	
6 hr		76-96	
12 hr			

[1]based on the mean from bio- + 3 pilot lots (at ——— RH storage up to —— months)
[2]based on the mean from bio-batch (at ——— RH initial)
[3]Low-upper: individual sample (bio- + 3 pilot lots at ——— RH storage)

In conclusion, the recommended the dissolution method and specifications for codeine is as follows (Table 12):

Table 12. Recommended dissolution method and specifications for Codeine

Method ———	
Apparatus	USP Apparatus II (paddle)
Media	
Speed of Rotation	— rpm
Temperature:	———
Specifications	
1 hr	——
3 hr	———
6 hr	———
12 hr	———

CPM: The sponsor proposed dissolution method, ——— is acceptable. However, the reviewing chemist (CMC team) suggested the same scenario as codeine. The options of specifications are shown in the table below.

Chlorpheniramine (method by ———)

Sampling time	CMC ———	Mean ———	Low-upper[3]
1 hr		32-52	——
3 hr		55-75	———

6 hr		68-88	
12 hr	NLT	NLT	

[1]based on the mean from bio- + 3 pilot lots (at , RH storage up to months)
[2]based on the mean from bio-batch (at RH initial) (sponsor proposed)
[3]Low-upper: individual sample (bio- + 3 pilot lots at RH storage)

In conclusion, the recommended the dissolution method (same as the sponsor proposed) and specifications for chlorpheniramine is as follows (Table 13):

Table 13. Method and Specifications for CPM

Method	
Apparatus	USP Apparatus II (paddle)
Media	
Speed of Rotation	rpm
Temperature:	
Specifications	
1 hr	
3 hr	
6 hr	
12 hr	NLT

Stability: The batches manufactured using the new process (*i.e.*, bio- and 3 pilot scale batches) were placed in to a stability program, at RH for months and accelerated conditions of RH for months. The results were acceptable.

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4.3. OCPB FILING/REVIEW FORM: None (Re-submission of the original NDA)

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/s/

Shinja Kim
6/16/04 09:38:38 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
6/17/04 08:37:58 AM
BIOPHARMACEUTICS
I concur

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-369	**Submission Date:** September 25, 2003
Name: Codeprex™ Extended-release suspension	**Sponsor:** Celltech Pharmace. Inc., NY
Type of Submission: Type B MR	**Reviewer:** Shinja R. Kim, Ph.D.

Background:

The sponsor, Celltech Pharmaceuticals Inc, received the FDA approvable letter to the NDA 21-369 on February 13, 2002, with the contingency for the sponsor to address the deficiencies listed in the letter. The sponsor responded to the FDA approvable letter on April 25, 2003, and requested a meeting.

To address the deficiencies, the sponsor reformulated Codeprex Extended-Release Suspension, and conducted three PK studies with the batch that was manufactured using the new formulation (CL02123A). For chlorpheniramine from batch CL02123A, the sponsor proposed dissolution specification utilizing original dissolution method, ——— (instead claiming IVIVC in the original NDA submission). However, the sponsor proposed a new dissolution method and specification (——— for codeine from batch CL02123A. Therefore, the CPB made the comment for the sponsor at the meeting regarding the new method, ——— and the sponsor responded in the present submission as follows (discussed CPB related only):

Biopharmaceutics:

Please provide dissolution data using the new method ——— on bio- and/or stability batches, which were utilized to show stability for codeine in the original NDA submission.

Response: The information is provided in Tab 2/Report R03177.1 in the submission package, and they are summarized in the Attachment to this review.

Note: Labeling for the CPB section will be updated from the previous version submitted in the original NDA, such as, replacing the data from original NDA with the data from the recently conducted PK studies.

Comment: The sponsor provided the requested data and the planned labeling revision is reasonable. This data will be reviewed when the sponsor provides complete response to the approval letter.

Recommendation: The Office of Clinical Pharmacology and Biopharmaceutics has reviewed this submission and the above comment was conveyed to the sponsor via teleconference.

Shinja R. Kim, Ph.D., DPE II

Emmanuel Fadiran, Ph.D., Team Leader

Attachment

[redacted] is the new release rate method for codeine that utilizes alternate simulated [redacted]

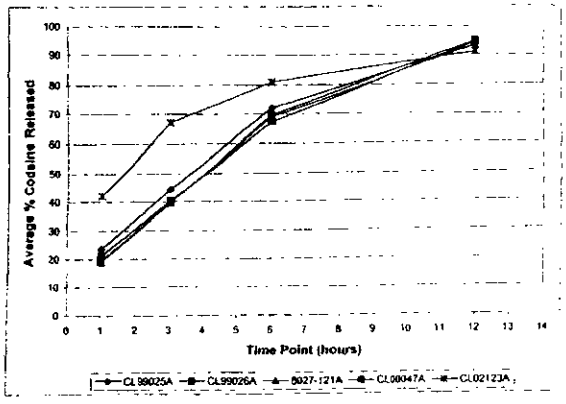
The dissolution test employing [redacted] method was performed using 5 batches of Codeprex ER Suspension. Batches CL99025A, CL99026A, 8027-121A, and CL00047A were manufactured using the original process (i.e., old formulation) submitted in NDA 21-369. These batches were the clinical and the three stability batches. The 5th batch, CL02123A was manufactured using the current process (i.e., new formulation). According to the sponsor, this batch was tested at the time of manufacture with the new and old release rate methods for codeine.

Each lot of Codeprex ER Suspension was stored at [redacted] conditions since their manufacture.

Results: Comparing the release rate profiles (n=6) of the five lots of Codeprex ER Suspension using [redacted] are summarized in the table and figure below.

Time point (hr)	Average % Codeine Released				
	CL99025A	CL99026A	8027-121A	CL00047A	CL02123A
1	24	19	19	21	42
3	44	40	40	40	67
6	72	70	69	67	81
12	93	95	93	94	91

Comparison of Average % Codeine Released results in [redacted]



Conclusions: The release rate profile of the Codeprex ER Suspension lot manufactured using the current process showed faster % released for codeine as compared to the profile of the lots manufactured using the original process. The dissolution profiles generated by [redacted] showed discrimination between Codeprex ER Suspension lots manufactured by the current and original processes. The results generated from testing of lots manufactured using the original process

would fail to meet the proposed release rate specifications intended for lots manufactured in accordance with the current process.

Discussion: Batch CL02123A tested in this experiment was [redacted] old, while other batches were [redacted] old. Thus, release profile of this batch at [redacted] is not known (*i.e.*, stability of batch CL02123A at [redacted] is not known). However, % released with the batch CL02123A at 1 and 3 hour time-points were quite faster compared to other 4 batches at those time-points. Therefore, using new dissolution method for codeine is reasonable.

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/s/

Shinja Kim
12/10/03 01:10:14 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
12/10/03 01:20:57 PM
BIOPHARMACEUTICS
I concur

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-369
Brand Name	Codeprex (tentative)
Drug Class	Codeine: Opiate antitussive
	Chlorpheniramine: Antihistamine
Drug Substances	Codeine and Chlorpheniramine
Dosage form and strengths	Extended release suspension;
	Combination product of codeine 40 mg/10 ml and chlorpheniramine 8 mg/10 ml
	The pink to purple pink colored, cherry cream flavored suspension will be available in 480 ml bottles
Dosing regimen	Adults and adolescents, ages 12 and older: Two teaspoonfuls (10 ml) every 12 hours; do not exceed four teaspoonfuls in 24 hours
	Children ages 6 to under 12 : One teaspoonful (5 ml) every 12 hours; do not exceed two teaspoonfuls in 24 hours
	Not recommended for patients under 6 years of age
Indication	Relief of symptoms of the common cold, allergies, or following exposure to airborne irritants
Sponsor	Celltech Pharmaceuticals Inc. (formerly known as Medeva Pharmaceuticals, Ind.)
Type of submission	4S (New combination)
Date of submission	4/13/2001(N-000)
	6/19/2001 (000 BP)
	8/3/2001 (N000 BZ)
	8/24/2001 (N000BZ)
Medical Division	HFD-570
	(Division of Pulmonary and Allergic Drug Products)
Reviewer	Young Moon Choi, Ph.D.
Team Leader	Emmanuel Fadiran, Ph.D.
OCPB division	OCPB/DPE-2 (HFD-870)

Executive Summary

Celltech Pharmaceuticals is seeking for an approval of an extended release suspension, a new combination drug product of codeine and chlorpeniramine. Without any data from clinical safety and efficacy trials, the approval of this NDA mainly relies on an assessment of the pharmacokinetic data relative to an immediate release solution (i.e., IR solution). This is possible because an antihistamine (chlorpheniramine maleate) and antitussive (codeine) combination product is listed under the Tentative Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antihistaminic Combination Drug Products.

The sponsor has adequately described the pharmacokinetics of the two active ingredients, codeine and chlropheniramine. The systemic exposures of the codeine and chlopheniramine are acceptable after multiple dose of the proposed extended release, combination suspension. Food does not affect the pharmacokinetics of codeine and chlorpheniramine following administration of the proposed extended release product.

The sponsor claims that a Level A IVIVC was established for chlopheniramine but this was not appropriately validated and therefore cannot be used for setting dissolution specification at this time.

It should be noted that there were substantial reductions of release rate for both bio- and stability batches for codeine and chlorpheniramine, i.e., [redacted] reduction in dissolution at 3 hour and 6 hour, respectively, after [redacted] months. If the level A IVIVC correlation for chlorpheniramine is validated, it may be used to predict in vivo performance of the product with reduced release rate, but there is no data that ensures the in vivo performance of the batch with a significantly reduced release profile for codeine. Therefore, at present, the maximum shelf-life should be shorter than [redacted] months depending on storage condition.

Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II has reviewed the NDA 21-369. It has been found that the submission is acceptable from a pharmacokinetic perspective, provided the sponsor gives adequate responses to the agency's comments on the dissolution specification and labeling.

It is also recommended that for a longer shelf-life, the sponsor needs to provide data that ensures the sameness of in vivo performance of a batch with a significantly reduced release profile, especially for codeine.

If a new formulation is developed to improve stability, comparative bioavailability / bioequivalence studies may be needed based on the level of the formulation change.

Comments to the sponsor

1. Recommendation for chlorpheniramine dissolution and in vitro –in vivo correlation (IVIVC)

It is recommended that the food effect study data be used for external validation of the IVIVC. If IVIVC is validated with this analysis, then [redacted]

2. Recommended dissolution method/specification for codeine

Method: USP Apparatus II (Paddle), [redacted] rpm

Medium: [redacted]

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Time	Biobatch (Lot CL00047A) Average (range), n=12	Sponsor's proposal	Agency's recommendation
1	33 ( ) %	[redacted]	[redacted]
3	62 ( ) %		
6	82 ( ) %		
12	93 ( ) %		
24	94 ( ) %		-

3. It is recommended that for obtaining a longer shelf-life, the sponsor needs to provide data to ensure the sameness of in vivo performance for a batch with a significantly reduced release profile, especially for codeine for the newly requested/proposed shelf-life.

4. If a new formulation is developed to improve stability, comparative bioavailability/ bioequivalence studies may be needed depending on the level of the formulation change.

Young Moon Choi, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence

Emmanuel Fadiran, Ph.D.
Team Leader
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

II. Table of contents

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III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Celltech Pharmaceuticals is seeking for an approval for an extended release suspension, a new combination drug product of codeine and chlorpheniramine.

The proposed dosage regimen is within the monograph for OTC antitussive and antihistamine drug product. However, the proposed drug formulation has higher strength of codeine (4 mg/ml) than the limit (2.2 mg/ml) allowing exemption from prescription requirement. Therefore, the sponsor is seeking this product as prescription drug categorized as a Schedule III controlled substance.

Without any clinical safety and efficacy trial, this NDA relies mainly on an assessment of the following pharmacokinetic data relative to an appropriate reference standard.

- A multiple dose PK study: This was a comparative BA study with an immediate release solution (IR) formulation at steady state (Study COD-02002)
- A single dose food effect study (Study COD02001)
- Single dose PK study with three experimental ER formulations i.e., [redacted] dissolution formulations. This study is used to establish IVIVC. (Study 1109/99)

Comparative Bioavailability of ER to IR

The sponsor adequately described the pharmacokinetics of active ingredients. The systemic exposures of the codeine and chlopheniramine were described after multiple dose of the proposed extended release, combination suspension:

For chlorpheniramine, AUCss, Cmax, and Cmin after multiple dose of ER were considered comparable to those after multiple dose of IR solution. It is noted that the 90% CI for the AUC and Cmax were below 100 % indicating that the bioavailability of the combination ER product is less than those of the IR solution.

Table I. Mean (SD) chlorpheniramine pharmacokinetic parameters (Study COD-02002)

	ER [1] N=22	IR [2] N=22	Ratio (%) ER/IR	90 % CI [3]	
				Low (%)	High (%)
Cmax (ng/ml)	35.46 (13.92)	40.25 (14.902)	87.8	83.4	92.3
AUCss (ng.hr/ml)	365.90 (142.30)	421.33 (146.232)	85.8	82.5	89.2
Cmin (ng/ml)	28.29 (12.05)	31.16 (12.068)	90.2	84.9	95.83
Fluctuation [4]	0.25 (0.157)	0.26 (0.100)	90.9	76.9	107.5
Tmax Median (range)	6.2 (1.0-9.0)	3.0 (0.5 5.0)	-	-	-

[1] Extended release suspension

[2] immediate release solution

[3] The confidence intervals are obtained from an ANOVA model with treatment, period, sequence as fixed effects and subjects nested within sequence as a random effect in the natural logarithmic transformed parameter.

[4] Difference between Cmax and Cmin divided by Cavg; Cavg represents average plasma concentration during dosing interval

For codeine, while AUCss was comparable, Cmax was lower, and Cmin was higher after multiple dose of the ER than that achieved with equivalent doses of the reference IR solution (Table II). This systemic exposure profile of codeine after administration of extended suspension is considered acceptable based on the OTC monograph. OTC monograph indicates that a dosage regimen of codein10 mg very 6 hours (i.e., a half of the dose used in the

present study) is effective. Therefore, the reviewing medical officer is of the opinion that Cmax achieved 88% of the 20 mg Codeine every 6 hours is acceptable.

Table II. Mean (SD) codeine pharmacokinetic parameters (Study COD 02002)

	ER[1] N=22	IR[2] N=22	Ratio (%) ER/IR	90 % CI[3]	
				Low (%)	High (%)
Cmax (ng/ml)	62.02 (16.163)	88.48 (25.074)	69.9	64.9	75.3
AUC0-inf (ng.hr/ml)	554.03 (152.686)	602.95 (138.956)	90.9	86.2	95.8
Cmin (ng/ml)	31.87 (9.731)	22.24 96.084)	141.9	132.6	151.9
Fluctuation[4]	0.67 (0.171)	1.26 (0.261)	52.0	48.3	56.0
Tmax (hr) Median (range)			-	-	-

[1] Extended release suspension

[2] Immediate release solution

[3] The confidence intervals are obtained from an ANOVA model with treatment, period, sequence as fixed effects and subjects nested within sequence as a random effect in the natural logarithmic transformed parameter.

[4] Difference between Cmax and Cmin divided by Cavg; Cavg represents average plasma concentration during dosing interval

Food effect

Food did not affect the systemic exposure of both chlorpheniramine (Table III) and codeine (Table IV).

Table III. Mean (SD) chlorpheniramine pharmacokinetic parameters (Study COD 02001)

	Fed (n=18)	Fasted (n=18)	Ratio (%) Fed/Fast	90 % CI *	
				Low (%)	High (%)
Cmax (ng/ml)	6.30 (1.191)	6.68 (1.477)	94.35	88.46	100.63
AUC0-inf (ng.hr/ml)	368.60 (126.338)	376.04 (172.539)	99.58	91.45	108.43
AUC0-last (ng.hr/ml)	275.58 (85.991)	266.08 (89.226)	103.17	97.53	109.14
T1/2 (hr)	29.55 (8583)	32.91 (13.707)	-	-	-
Tmax Median (range)	15.00 (5.00 – 18.00)	8.00 (5.00 – 18.00)	-	-	-

* The confidence intervals are obtained from an ANOVA model with food condition, period, sequence as fixed effects and subjects nested within sequence as a random effect in the natural logarithmic transformed parameter. Food effect is absent if the ratio and 90 % confidence interval falls within the 80-125 % limits.

Table IV. Mean (SD) codeine pharmacokinetic parameters (Study COD02001)

	Fed (n=18)	Fasted (n=18)	Ratio (%) Fed/Fast	90 % CI *	
				Low (%)	High (%)
Cmax (ng/ml)	32.48 (8.970)	28.91 (9.463)	112.71	101.92	124.64

AUC0-inf (ng.hr/ml)	495.70 (144.086)	468.67(150.509)	104.83	99.04	110.95
AUC0-last (ng.hr/ml)	408.53 (118.012)	361.61(114.440)	112.73	104.17	122.00
T1/2 (hr)	8.92 (1.483)	11.55 (4.024)	-	-	-
Tmax Median (range)	4.50 (2.00 – 5.00)	5.00 (2.00 – 8.00)	-	-	-

* The confidence intervals are obtained from an ANOVA model with food condition, period, sequence as fixed effects and subjects nested within sequence as a random effect in the natural logarithmic transformed parameter. Food effect is absent if the ratio and 90 % confidence interval falls within the 80-125 % limits.

Dissolution method development and IVIVC

For chlorpheniramine

The sponsor claimed that a Level A IVIVC was established for chlopheniramine based on two formulations coating and coating). However, the sponsor's proposed dissolution specification determined by is not acceptable, since the formulations are not bioequivalent (Cmax of the formulations used in the IVIVC study is different by more than 20 %).

Recommendation for chlorpheniramine dissolution and IVIVC

It is recommended that the food effect study data should be used for external validation of the IVIVC. If the IVIVC is validated in that external analysis, then calculate the plasma concentration time profile using convolution or other appropriate modeling techniques and determine the dissolution specification that will result in a maximal difference of 20 % in Cmax and AUC (i.e., + and – 10 % of the Cmax or AUC of the biobatch).

Table V. IVIVC validation summary for chlorpheniramine

					AUC(0-72)			
	Pred (ng/mL)	Obs. (ng/mL)	ratio	|%PE| (%)	Pred (ng/mL)	Obs. (ng/mL)	ratio	|%PE| (%)
Internal validation								
A	6.854	[redacted]	1.055	5.530	233.042	[redacted]	0.913	8.658
C	4.194		0.946	5.440	209.481		0.958	4.216
mean	5.524	5.465	1.000	5.485	221.262	236.917	0.936	6.437
External validation								
B	6.742	[redacted]	1.049	4.942	234.448	[redacted]	0.931	6.891

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For Codeine

An IVIVC was not established for codeine. Furthermore, the fast and slow release formulations were not bioequivalent (There was more than a 20 % difference in Cmax). Therefore, the dissolution specification for codeine is recommended based on the dissolution data of the biobatch (CL00047A).

Recommended dissolution method/specification for codeine

Method: USP Apparatus II (Paddle), [redacted] rpm

Medium: [redacted]

Time (hr)	Biobatch (Lot CL00047A) Average (range); n=12	Sponsor's proposal	Agency's recommendation
1	33 [redacted] %	[redacted]	
3	62 [redacted] %		
6	82 [redacted] %		
12	93 [redacted] %		
24	94 [redacted] %		

Table VI. IVIVC Validation summary for codeine

treatment	C_{max}				AUC(0-24)			
	Pred. (ng/mL)	Obs. (ng/mL)	ratio	|%PE| (%)	Pred (ng/mL)	Obs. (ng/mL)	ratio	|%PE| (%)
A	35.247	[redacted]	1.069	6.877	310.717	[redacted]	0.860	13.987

B	31.225	[redacted]	1.131	13.135	313.633	[redacted]	0.923	7.672
C	18.417	[redacted]	0.820	17.995	248.290	[redacted]	0.824	17.637
mean	28.296	27.679	1.007	12.669	290.880	334.133	0.869	13.099

Stability concern

It should be noted that there were substantial reductions in release rate of both bio- and stability batches for codeine and chlorpheniramine (e.g., more than [redacted] reduction in dissolution at 3 hour and 6 hour, after [redacted] months stored at [redacted]. While the level A IVIVC correlation established for chlorpheniramine may allow one to predict in vivo performance, no data ensures the in vivo performance of the batch with a significantly reduced release profile for codeine. Therefore, at present, the shelf-life needs to be shorter than [redacted] months depending on storage conditions.

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Chlorpheniramine Release at the Time of Release (0 month storage time):

Lot #		26A	121A	34A	25A	43A	47A	43A	47A	35A
% Coating										
Purpose		Stability	Stability /IVIVC*	IVIVC	Stability	Similar to Clinical	Clinical	Similar to Clinical	Clinical	IVIVC
	RR	%Rlz	%Rlz	%Rlz	%Rlz	%Rlz	%Rlz	%Rlz	%Rlz	%Rlz
Initial (0M)	1 Hr									
	3 Hr									
	6 Hr									
	12 Hr									
	24 Hr									

* for ivivc study purpose, stored for ——— to reduce release rate

Decrease in Chlorpheniramine release pooled by storage conditions at all release time points

Lot #		26A	121A	34A	25A	43A	47A	43A	47A	35A
% Coating										
Storage	RR	%Dcrz	%Dcrz	%Dcrz	%Dcrz	%Dcrz	%Dcrz	%Dcrz	%Dcrz	%Dcrz
	1 Hr									
	3 Hr									
	6 Hr									
	12 Hr									
	24 Hr									
	1 Hr									
	3 Hr									
	6 Hr									
	12 Hr									
	24 Hr									
	1 Hr									
	3 Hr									
	6 Hr									
	12 Hr									
	24 Hr									

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Codeine Release at the Time of Release (0 month storage time):

Lot #		26A	121A	34A	25A	43A	47A	43A	47A	35A
% Coating										
Purpose		Stability	Stability /IVIVC *	IVIVC	Stability	Similar to Clinical	Clinical	Similar to Clinical	Clinical	IVIVC
	RR	%Rlz	%Rlz	%Rlz	%Rlz	%Rlz	%Rlz	%Rlz	%Rlz	%Rlz
Initial (0M)	1 Hr									
	3 Hr									
	6 Hr									
	12 Hr									
	24 Hr									

* for ivivc study purpose, stored for _____ to reduce release rate

Decrease in Codeine release pooled by storage conditions at all release time points

Lot #		26A	121A	34A	25A	43A	47A	43A	47A	35A
% Coating										
Storage	RR	%Dcrz	%Dcrz	%Dcrz	%Dcrz	%Dcrz	%Dcrz	%Dcrz	%Dcrz	%Dcrz
	1 Hr									
	3 Hr									
	6 Hr									
	12 Hr									
	24 Hr									
	1 Hr									
	3 Hr									
	6 Hr									
	12 Hr									
	24 Hr									
	1 Hr									
	3 Hr									
	6 Hr									
	12 Hr									
	24 Hr									

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IV. Question Based Review

Based on the nature of the submission, the present review was focused on following questions/issues:

Q: What is the composition of the extended release product?

Proposed product

Ingredients	mg/10ml
Dye, D&C Red #33 Certified	
Microcrystalline cellulose and carboxyethylcellulose sodium, NF	
Sucrose, NF	
Glycerin, USP	
Propylen glycol, USP	
Methyparaben, NF	
Propylparaben, NF	
Xanthan Gum, NF	
Citric acid (anhydrous), USP	
Edetate Disodium, USP	
Flavor, Artificial Cherry Cream	
Polysorbate 80, NF	
Coated codeine polistirex	Input quantities vary slightly based on assay resin bound codeine. The total amount of coated codeine polistirex is equivalent to 40 mg of codeine base. The calculation is based on the following equation: Coated codeine polistirex = (40 mg) x (100) / (% assay)
Chlorpheniramine maleate, USP	8.0
Water, Purified, USP	

Q : Is the reference formulation acceptable ?

Reference standard

An appropriate immediate release liquid combination product to serve as a reference was not commercially available. Therefore, immediate release (solution) formulation that complies with the OTC monograph was prepared by the sponsor. The reference product used in the development program consisted of 40 mg codeine and 8 mg of chlopheniramine maleate per 10 ml to be administered as 5 ml dose. This reference standard is different from the to-be-marketed suspension in polystirex resin, ethylcellulose coating, and the suspending agents.

Q: Is the study design for comparative PK study acceptable?

To compare the steady state bioavailability of an extended release suspension of codeine 40 mg and chlorpheniramine maleate 8 mg relative to an immediate-release solution of codeine 20 mg and chlorpheniramine maleate 4 mg following a multiple dose regimen, a multiple dose, randomized, open label, two way crossover study was conducted.

Twenty seven subjects were entered and 22 subjects were evaluable since five subjects withdrew during the first treatment period: Four withdrew due to an adverse event (3 from ER), and one voluntarily withdrew.

Treatment:

Treatment A: 10 ml extended-release suspension containing 40 mg codeine and 8 mg chlorpheniramine maleate dosed every 12 hours for 6.5 days.

Treatment B: 5 ml immediate-release solution containing 20 mg codeine and 4 mg chlorpheniramine maleate (Medeva America) dosed every 6 hours for 6.5 days

Q: Are the pharmacokinetic and statistical analyses acceptable?

Statistical analyses were performed on the natural logarithmic transformed pharmacokinetic parameters for codeine and chlorpheniramine using Winnonlin. The analysis of variance model (ANOVA) for a crossover design, included effects for treatment, period, sequence, and subject within sequence. This model was used to assess the differences between each parameter. The two one-sided tests procedure was tested at the 5 % level by conducting 90 % confidence interval for natural log transformed Cmax, Cmin, and AUC for dosing interval at steady state. Cmin was assumed the concentration at 156 hours after first dose. Based on the 96, 144, and 156 hour data, this is acceptable (see graph).

For chlorpheniramine, AUCss, Cmax, and Cmin after multiple dose of ER were considered comparable to those after multiple dose of IR solution.

Table I. Mean (SD) chlorpheniramine pharmacokinetic parameters (Study COD-02002)

	ER [1] N=22	IR [2] N=22	Ratio (%) ER/IR	90 % CI [3] Low (%)	High (%)
Cmax (ng/ml)	35.46 (13.92)	40.25 (14.902)	87.8	83.4	92.3
AUCss (ng.hr/ml)	365.90 (142.30)	421.33 (146.232)	85.8	82.5	89.2
Cmin (ng/ml)	28.29 (12.05)	31.16 (12.068)	90.2	84.9	95.83
Fluctuation [4]	0.25 (0.157)	0.26 (0.100)	90.9	76.9	107.5
Tmax Median (range)	6.2 (1.0-9.0)	3.0 (0.5 5.0)	-	-	-

[1] Extended release suspension

[2] Immediate release solution

[3] The confidence intervals are obtained from an ANOVA model with treatment, period, sequence as fixed effects and subjects nested within sequence as a random effect in the natural logarithmic transformed parameter.

[4] Difference between Cmax and Cmin divided by Cavg; Cavg represents average plasma concentration during dosing interval

For codeine, while AUCss was comparable, Cmax was lower, and Cmin was higher after multiple dose of the ER than that achieved with equivalent doses of the reference IR solution (Table II). This systemic exposure profile of

codeine after administration of extended suspension is considered acceptable based on the monograph. OTC monograph indicates that a dosage regimen of codein10 mg very 6 hours (i.e., a half of the dose used in the present study) is effective. Therefore, the reviewing medical officer is of the opinion that Cmax achieved 88% of the 20 mg Codeine every 6 hours is acceptable.

Table II. Mean (SD) codeine pharmacokinetic parameters (Study COD 02002)

	ER[1] N=22	IR[2] N=22	Ratio (%) ERR	90 % CI[3]	
				Low (%)	High (%)
Cmax (ng/ml)	62.02 (16.163)	88.48 (25.074)	69.9	64.9	75.3
AUC0-inf (ng.hr/ml)	554.03 (152.686)	602.95 (138.956)	90.9	86.2	95.8
Cmin (ng/ml)	31.87 (9.731)	22.24 96.084)	141.9	132.6	151.9
Fluctuation[4]	0.67 (0.171)	1.26 (0.261)	52.0	48.3	56.0
Tmax (hr) Median (range)			-	-	-

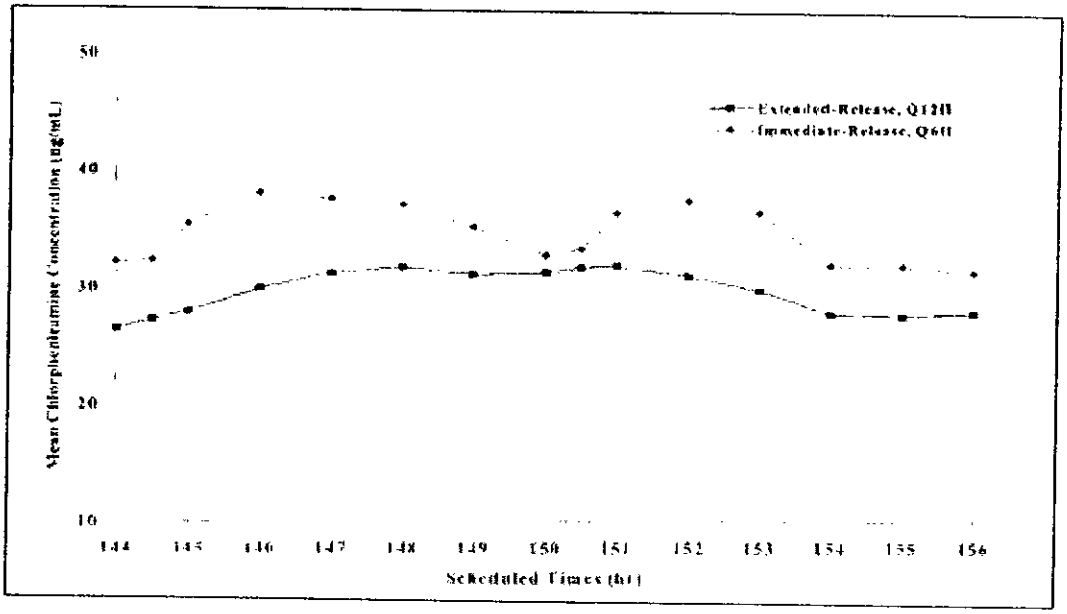
[1] Extended release suspension

[2] Immediate release solution

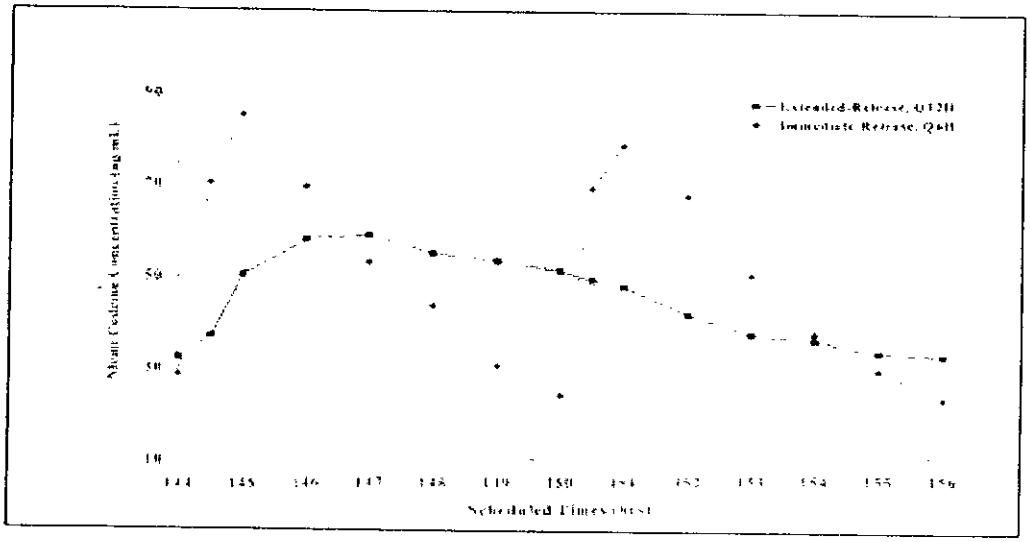
[3] The confidence intervals are obtained from an ANOVA model with treatment, period, sequence as fixed effects and subjects nested within sequence as a random effect in the natural logarithmic transformed parameter.

[4] Difference between Cmax and Cmin divided by Cavg; Cavg represents average plasma concentration during dosing interval

Chlorpheniramine



Codeine



Q: What is the food effect on the bioavailability of the drug from the dosage form?

A single dose, two-way crossover bioavailability study was performed to investigate the food effect in 19 healthy subjects.

Total 18 subjects were evaluated since one subject withdrew during the first period due to an adverse effect.

For both codeine and chlorpheniramine, no food effect was observed.

Table III. Mean (SD) chlorpheniramine pharmacokinetic parameters

	Fed (n=18)	Fasted (n=18)	Ratio (%) Fed/Fast	90 % CI *	
				Low (%)	High (%)
Cmax (ng/ml)	6.30 (1.191)	6.68 (1.477)	94.35	88.46	100.63
AUC0-inf (ng.hr/ml)	368.60 (126.338)	376.04 (172.539)	99.58	91.45	108.43
AUC0-last (ng.hr/ml)	275.58 (85.991)	266.08 (89.226)	103.17	97.53	109.14
T1/2 (hr)	29.55 (8583)	32.91 (13.707)	-	-	-
Tmax Median (range)	15.00 (5.00 – 18.00)	8.00 (5.00 – 18.00)	-	-	-

* The confidence intervals are obtained from an ANOVA model with food condition, period, sequence as fixed effects and subjects nested within sequence as a random effect in the natural logarithmic transformed parameter. Food effect is absent if the ratio and 90 % confidence interval falls within the 80-125 % limits.

Table IV. Mean (SD) codeine pharmacokinetic parameters

	Fed (n=18)	Fasted (n=18)	Ratio (%) Fed/Fast	90 % CI *	
				Low (%)	High (%)
Cmax (ng/ml)	32.48 (8.970)	28.91 (9.463)	112.71	101.92	124.64
AUC0-inf (ng.hr/ml)	495.70 (144.086)	468.67(150.509)	104.83	99.04	110.95
AUC0-last (ng.hr/ml)	408.53 (118.012)	361.61(114.440)	112.73	104.17	122.00
T1/2 (hr)	8.92 (1.483)	11.55 (4.024)	-	-	-
Tmax Median (range)	4.50 (2.00 – 5.00)	5.00 (2.00 – 8.00)	-	-	-

* The confidence intervals are obtained from an ANOVA model with food condition, period, sequence as fixed effects and subjects nested within sequence as a random effect in the natural logarithmic transformed parameter. Food effect is absent if the ratio and 90 % confidence interval falls within the 80-125 % limits.

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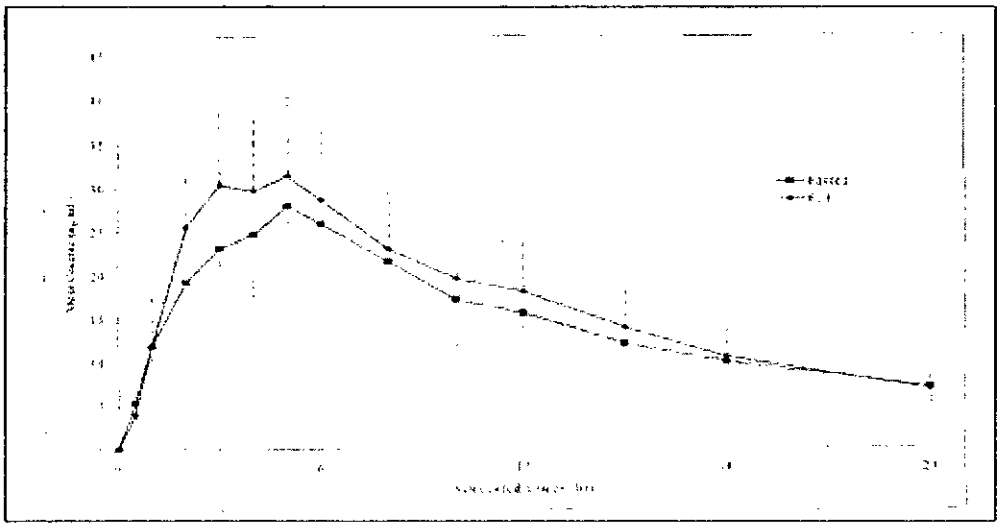
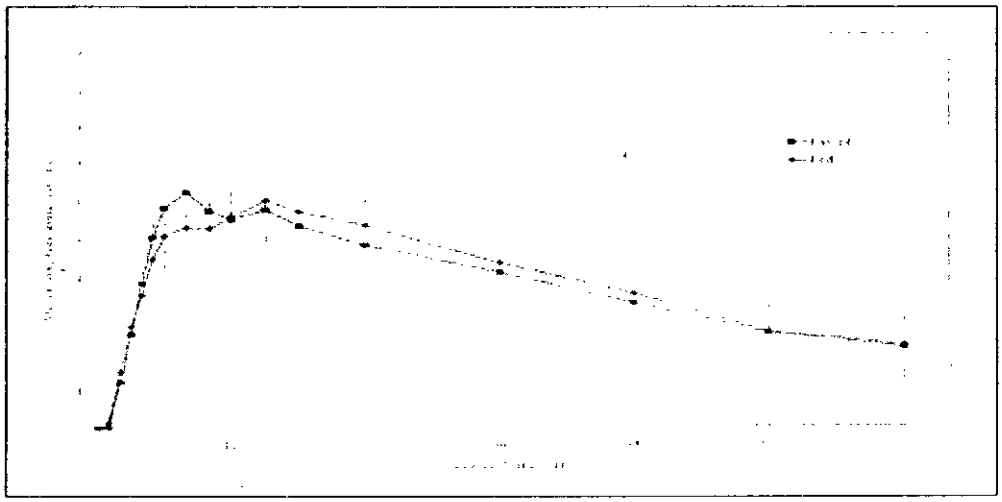
Mean (SD) codeine plasma concentration –time profile following administration of a 10 ml extended release suspension of codeine/chlorpheniramine maleate under fasted and fed conditions



Mean (SD) chlorpheniramine plasma concentration–time profile following administration of a 10 ml extended release suspension of codeine/chlorpheniramine maleate under fasted and fed conditions



Attachment B

4 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Mean, minimum, maximum, %CV, and geometric mean of pharmacokinetic parameters for COD following the administration of an ER suspensions with a [redacted] polymer coating containing 40 mg COD and 8 mg CPM in 10 mL and a reference solution containing 20 mg COD and 4 mg CPM in 5 mL dosed as two doses separated by 6 hours

Treatment		C_{max} (ng/mL)	C_{24} (ng/mL)	C_{12} (ng/mL)	T_{max} (h)	λ_z (1/h)	AUC_{last} (ng·h/mL)	AUC_{0-inf} (ng·h/mL)	AUC_{0-12} (ng·h/mL)
A: [redacted] polymer coating	Mean	35.926			3.632	0.08	361.245	426.575	267.87
	Min								
	Max								
	CV%	22.6			34.6	29.6	23.3	21.8	22.4
	G.Mean	35.092			3.416	0.077	353.675	418.204	262.51
B: [redacted] polymer coating	Mean	29.858			3.579	0.064	339.696	447.489	238.52
	Min								
	Max								
	CV%	22.7			32.7	25.9	22.5	24.3	22
	G.Mean	29.174			3.397	0.061	332.141	435.464	233.28
C: [redacted] polymer coating	Mean	23.063			5.053	0.048	301.459	480.625	190.95
	Min								
	Max								
	CV%	21.5			17.7	34	23.4	29.7	20.7
	G.Mean	22.57			4.965	0.045	294.483	463.477	187.33
D: reference solution	Mean	54.784			3.132	0.215	421.738	437.272	359.39
	Min								
	Max								
	CV%	22.3			95.3	15.9	22	21.7	18.5
	G.Mean	53.569			1.897	0.213	412.535	427.994	353.62

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Summary of Bioequivalence Analysis Results: Pharmacokinetic Parameter Ratios and 90% Confidence Intervals for COD

Comparison	Parameter	Ratio	90% Confidence Limits	
			lower	Upper
[redacted] polymer coating suspension vs. reference solution	AUC_{0-inf}	97.03	90.65	103.86
	AUC_{last}	85.65	81.48	90.04
	AUC_{0-12}	74.15	70.21	78.3
	C_{max}	65.47	61.07	70.19
	C_{24}	223.47	197.12	253.33
	C_{12}	88.01	81.85	94.64
	T_{max}	115.89	85.66	146.11
[redacted] polymer coating suspension vs. reference solution	AUC_{0-inf}	101.1	94.44	108.21
	AUC_{last}	80.16	76.25	84.26
	AUC_{0-12}	65.54	62.06	69.22
	C_{max}	54.02	50.39	57.92
	C_{24}	280.59	247.33	318.33
	C_{12}	89.95	83.65	96.72
	T_{max}	116.16	85.93	146.38
[redacted] polymer coating suspension vs. reference solution	AUC_{0-inf}	107.71	100.62	115.29
	AUC_{last}	71.42	67.94	75.08
	AUC_{0-12}	53	50.19	55.97
	C_{max}	42.14	39.3	45.18
	C_{24}	341.29	301.06	386.91
	C_{12}	88.62	82.42	95.29
	T_{max}	161.41	131.18	191.63

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Summary of Bioequivalence Analysis Results: Pharmacokinetic Parameter Ratios and 90% Confidence Intervals for COD

Comparison	Parameter	Ratio	90% Confidence Limits	
			lower	Upper
[redacted] polymer coating suspension vs. high polymer coating suspension	AUC_{0-inf}	90.09	84.16	96.43
	AUC_{last}	119.92	114.08	126.06
	AUC_{0-12}	139.91	132.48	147.75
	C_{max}	155.37	144.92	166.57
	C_{24}	65.48	60.95	70.33
	C_{12}	99.31	92.36	106.79
	T_{max}	57.29	53.07	90.52
[redacted] polymer coating suspension vs. high polymer coating suspension	AUC_{0-inf}	93.86	87.69	100.47
	AUC_{last}	112.23	106.76	117.98
	AUC_{0-12}	123.67	117.11	130.6
	C_{max}	128.2	119.58	137.44
	C_{24}	82.21	76.54	88.31
	C_{12}	101.5	94.4	109.14
	T_{max}	57.45	53.24	90.69
[redacted] polymer coating suspension vs. medium polymer coating suspension	AUC_{0-inf}	95.98	89.66	102.74
	AUC_{last}	106.86	101.65	112.33
	AUC_{0-12}	113.13	107.12	119.47
	C_{max}	121.19	113.04	129.93
	C_{24}	79.64	74.14	85.55
	C_{12}	97.85	91	105.21
	T_{max}	99.77	73.75	125.79

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Mean, minimum, maximum, %CV, and geometric mean of pharmacokinetic parameters CPM following the administration of an ER Suspension with a [redacted] polymer coating containing 40 mg COD and 8 mg CPM in 10 mL and a reference solution containing 20 mg COD and 4 mg CPM in 5 mL dosed as two doses separated by 6 hours

Treatment		C_{max} (ng/mL)	C_{24} (ng/mL)	C_{12} (ng/mL)	T_{max} (h)	λ_z (1/h)	AUC_{last} (ng·h/mL)	AUC_{0-inf} (ng·h/mL)	AUC_{0-12} (ng·h/mL)
A: [redacted] polymer coating	Mean	6.691	4.855	5.714	7.342	0.029	250.827	330.42	51.89
	Min	[redacted]							
	Max								
	CV%	26.6	[redacted]		36.1	23.7	50.1	66.8	27.8
	G.Mean	6.491			7.082	0.028	227.147	288.951	50.1
B: [redacted] polymer coating	Mean	6.701			8.132	0.029	248.429	318.685	52.86
	Min	[redacted]							
	Max								
	CV%	28.5			51.1	22.6	49.5	54.3	32.7
	G.Mean	6.479			7.569	0.028	225.899	286.6	50.56
C: [redacted] polymer coating	Mean	4.934			12	0.024	214.259	306.78	35.24
	Min	[redacted]							
	Max								
	CV%	30.7			70.4	26.3	46.7	53.1	32.9
	G.Mean	4.761			10.167	0.023	195.728	277.768	33.9
D: a reference solution	Mean	10.288			8.526	0.036	284.309	344.181	83.56
	Min	[redacted]							
	Max								
	CV%	28.3			13.2	28.5	47.4	56.7	28.7
	G.Mean	9.977			8.466	0.034	260.671	307.81	80.93

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Summary of Bioequivalence Analysis Results: Pharmacokinetic Parameter Ratios and 90% Confidence Intervals for CPM

Comparison	Parameter	Ratio	90% Confidence Limits	
			lower	Upper
[redacted] polymer coating suspension vs. reference solution	AUC_{0-inf}	93.85	87.87	100.25
	AUC_{last}	87.11	81.49	93.12
	AUC_{0-12}	61.9	58.02	66.03
	C_{max}	64.98	61.02	69.21
	C_{24}	89.59	84.11	95.43
	C_{12}	64.38	60.74	68.24
	T_{max}	86.47	59.43	113.51
[redacted] polymer coating suspension vs. reference solution	AUC_{0-inf}	93.08	87.15	99.42
	AUC_{last}	86.29	80.72	92.24
	AUC_{0-12}	62.14	58.25	66.29
	C_{max}	64.66	60.71	68.87
	C_{24}	89.79	84.3	95.63
	C_{12}	64.29	60.66	68.13
	T_{max}	94.25	67.21	121.3
[redacted] polymer coating suspension vs. reference solution	AUC_{0-inf}	90.37	84.61	96.53
	AUC_{last}	75.06	70.21	80.23
	AUC_{0-12}	41.93	39.31	44.73
	C_{max}	47.68	44.77	50.79
	C_{24}	78.61	73.8	83.73
	C_{12}	48.56	45.81	51.47
	T_{max}	139.54	112.5	166.58

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Summary of Bioequivalence Analysis Results: Pharmacokinetic Parameter Ratios and 90% Confidence Intervals for CPM (continuation).

Comparison	Parameter	Ratio	90% Confidence Limits	
			lower	upper
[redacted] polymer coating suspension vs. high polymer coating suspension	AUC_{0-inf}	103.85	97.23	110.93
	AUC_{last}	116.06	108.58	124.07
	AUC_{0-12}	147.6	138.37	157.46
	C_{max}	136.28	127.95	145.14
	C_{24}	113.97	107	121.39
	C_{12}	132.59	125.23	140.38
	T_{max}	61.97	42.59	81.34
[redacted] polymer coating suspension vs. high polymer coating suspension	AUC_{0-inf}	103	96.43	110.02
	AUC_{last}	114.96	107.55	122.89
	AUC_{0-12}	148.19	138.91	158.08
	C_{max}	135.6	127.32	144.42
	C_{24}	114.22	107.23	121.66
	C_{12}	132.39	125.05	140.17
	T_{max}	67.55	48.17	86.92
[redacted] polymer coating suspension vs. medium polymer coating suspension	AUC_{0-inf}	100.83	94.4	107.7
	AUC_{last}	100.96	94.44	107.92
	AUC_{0-12}	99.61	93.37	106.26
	C_{max}	100.5	94.36	107.03
	C_{24}	99.78	93.68	106.28
	C_{12}	100.15	94.59	106.03
	T_{max}	91.74	63.05	120.43

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Analytical Section

Q: What bioanalytical methods are used to assess concentrations?

An LC/MS/MS method was employed for determination of the codeine and chlorpheniramine plasma concentrations. Assay method has been validated for linearity , precision, recovery and stability over the concentration range ——— ng/ml for codeine and ——— ng/ml for chlorpheniramine.

Codeine and its internal standard codeine-d3 were extracted from alkalinized human plasma with

Chlorpheniramine and its internal standard ——— were extracted from alkalinized human plasma with

No major interference peaks were found for the compounds of interest or the internal standard.

The application of the above method to analyze the samples from the present study is acceptable.

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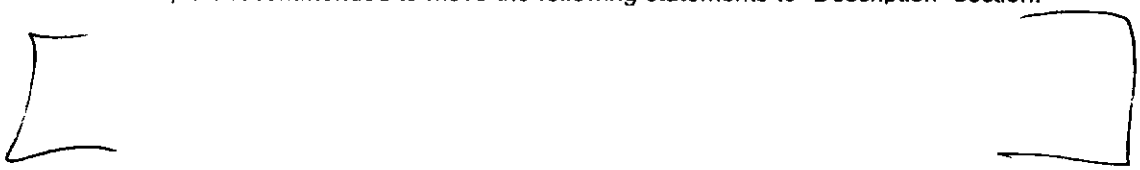
V. Detailed labeling recommendation

1. Under the pharmacokinetic section, the following description is more relevant to characteristics of formulation. Therefore, it is recommended to move the following statements to "Description" section.



2. Under the "Food effect" section, it is recommended to withdraw the table.

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15 page(s) of revised draft labeling has been redacted from this portion of the review.

IVIVC summary

TITLE: Development and validation of an in vitro – in vivo correlation for codeine/ chlorpheniramine extended-release suspensions

INTRODUCTION: An open label, four treatment, four period crossover study (protocol # 1109/00) with a seven day washout between dosing days was conducted. Twenty (20) healthy male volunteers between the age of 21 and 40 years were enrolled in the study. A total daily oral dose of 40 mg codeine (COD) and 8 mg chlorpheniramine (CPM) was administered at each treatment period. The following medication was used: extended-release suspensions containing 40 mg COD and 8 mg CPM in 10 mL, batch # CL99035A ~ polymer coating, Treatment A), batch # CL99034A ~ polymer coating, Treatment B), batch # 8027-121A ~ polymer coating, Treatment C); reference solution containing 20 mg codeine and 4 mg chlorpheniramine in 5 mL (Treatment D). The extended release suspensions were administered as a single dose. The reference solution was administered as two 20 mg COD and 4 mg CPM doses separated by 6 hours. The data from this study were used to develop and validate an *in vitro / in vivo* correlation (IVIVC) for the extended release COD/CPM suspensions.

OBJECTIVES: To develop and validate an IVIVC for codeine/chlorpheniramine extended-release suspensions.

RESULTS:

CONCLUSIONS

Data Source

The plasma concentration-time data for COD and CPM was obtained from a 4-way crossover study in 20 healthy volunteers. Extended release suspensions were administered as a single oral dose following an overnight fast. The reference solution was administered as two oral doses separated by 6 hours following an overnight fast. 19 volunteers completed all four treatment periods and received the following treatments:

- A: 40 mg COD and 8 mg CPM suspension; Batch # CL99035A – polymer coating
- B: 40 mg COD and 8 mg CPM suspension; Batch # CL99034A – polymer coating
- C: 40 mg COD and 8 mg CPM suspension; Batch # 8027-121A - polymer coating
- D: 20 mg COD and 4 mg CPM solution, two doses separated by 6 hours.

The in vitro dissolution data used for the IVIVC was obtained from USP Apparatus II (paddles) at RPM with the suspension dissolved in The sampling times for the batches were 1, 3, 6, 12, and 24 hours.

Blood samples were collected at 0.0 hour (predose) and 0.5, 1, 2, 3, 5, 6, 6.5, 7, 8,10, 12, 18, 24, 36, 48, 60, and 72 hours after drug administration. Plasma harvested from the blood samples collected at 0.0, 0.5, 1, 2, 3, 5, 6, 6.5, 7, 8,10, 12, 18, and 24 hours post-dose was used for the assay of codeine plasma concentrations. These samples were also assayed for chlorpheniramine maleate plasma concentrations as well as samples collected at 36, 48, 60, and 72 hours post-dose.

Concerns on IVIVC data

The FDA guidance states that "the release rate, as measured by percent dissolved, for each formulation studied, should differ adequately (e.g., by 10%). This should result in vivo profiles that show a comparable difference, for example, a 10% difference in the pharmacokinetic parameters of interest (C_{max} and AUC) between each formulation." A preliminary inspection of the *in vitro* data indicated that there was an insufficient difference between the Treatment A and Treatment B suspensions.

Modeling approach

The analysis was approached by application of the following IVIVC models:

Model 1.

Model 2.

Modeling was performed separately for COD and CPM.

Model 1: The linear model applied to the mean concentration time data

The Level A IVIVC Model 1 is constructed using approaches [2,3]. This model may be described in terms of a integral equation of the form:

Attachment C

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Model 2: The linear [redacted] model applied to the individual concentration time courses

[redacted]

IVIVC Model Validation

The IVIVC model should be evaluated to demonstrate the ability of the model to predict in vivo drug concentrations. Evaluation of internal predictability is based on the initial data used to define the IVIVC model. Evaluation of external predictability is based on additional test data sets. The FDA criteria for assessing IVIVC model predictability are based on comparing the IVIVC model-predicted C_{max} and AUC values with the observed values .

Computations differ for mean based Model 1 and individual Model 2.

For the mean based Model 1, the predicted C_{max} and AUC values are obtained from the fitted mean concentration-time data. Predicted concentrations are computed

[redacted]

For the individual based Model 2, individual predicted and observed C_{max} and AUC are computed. The geometric mean values of each treatment are used as the predicted and observed C_{max} and AUC for each treatment. The geometric means are used because the combination of the IVIVC model and in vitro dissolution data is used as a surrogate for in vivo bioequivalence assessment. The approaches to bioequivalence assessment currently recommended by the FDA are based on comparison of the geometric mean parameter values (or the means of the log transformed values).

Following the FDA guidance on IVIVC development and evaluation, the percent prediction error is estimated for each treatment according to:

$$\%PE = 100\left(\frac{P_{observed} - P_{predicted}}{P_{observed}}\right),$$

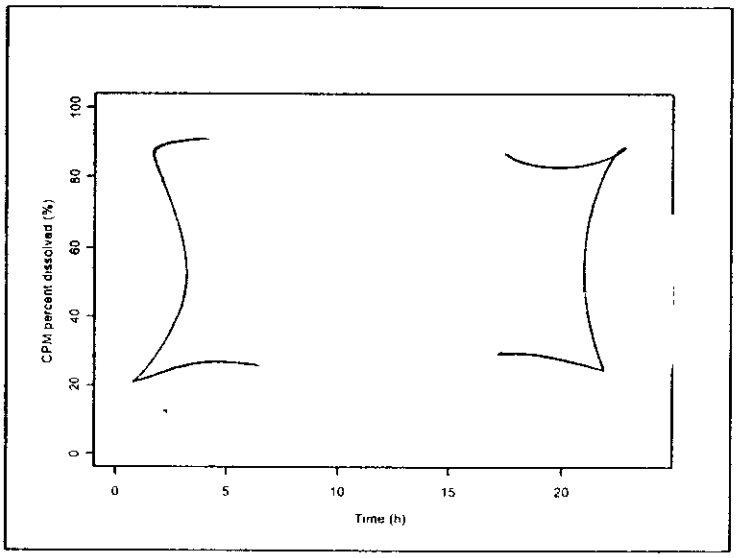
where $P_{observed}$ and $P_{predicted}$ are the observed and predicted C_{max} or AUC values [2]. The term "mean absolute percent prediction error" (MAPPE) refers to the mean of the absolute values of the treatments' %PE. The individual prediction error estimates are calculated using the same equation, but $P_{observed}$ and $P_{predicted}$ represent the individual parameter estimates.

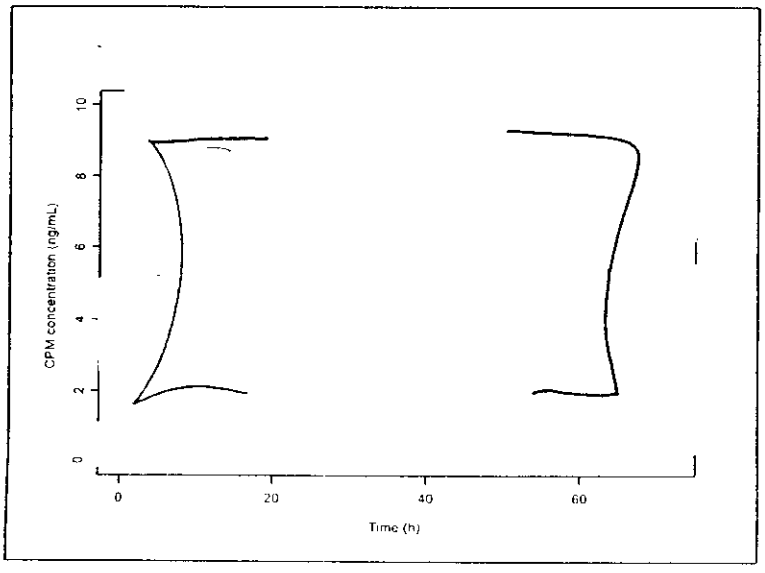
The FDA criteria for internal validation of an IVIVC model state that for C_{max} and AUC, the absolute %PE for each formulation should not exceed 15%, and MAPPE should not exceed 10%. For external validation, |%PE| < 10% for C_{max} and AUC establishes external predictability of an IVIVC, |%PE| between 10 – 20 % indicates inconclusive predictability, and |%PE| greater than 20% indicates inadequate predictability.

As was mentioned earlier, the difference between CPM dissolution profiles for Treatment A and Treatment B suspensions may be insufficient. In this situation, for each CPM model studied, the following two analyses were carried out:

1. IVIVC modeling using all three ER formulation, with internal predictability evaluation of the model.
2. IVIVC modeling using Treatment–A and Treatment C, internal validation of the resulting model supplemented by the external validation of the model by the data for Treatment B.

Dissolution (upper panel) and plasma concentration (lower panel) profile of chlorpehniramine. Two fast release formulations are virtually identical in vitro and in vivo performnace.





The validation statistics for Model 1 (the model based on the data for all four treatments) is shown in the following table. Maximum absolute prediction error (|%PE|) was 6.8% for C_{max} and 7.5% for AUC, with mean absolute prediction error (MAPPE) equal to 4.5% for C_{max} and 5.6% for AUC. These characteristics are well within the FDA internal validation limits (|%PE| < 15% for C_{max} and AUC for each formulation, and MAPPE < 10% for C_{max} and AUC).

Model 1 (fitted to the mean IR and ER CPM data): validation summary

Treatment	C_{max}				AUC(0-72)			
	Pred. (ng/mL)	Obs. (ng/mL)	ratio	|%PE| (%)	Pred. (ng/mL)	Obs. (ng/mL)	ratio	|%PE| (%)
A	6.732		1.036	3.648	235.899		0.925	7.538
B	6.622		1.031	3.068	237.254		0.942	5.776
C	4.134		0.932	6.791	211.334		0.966	3.369
mean	5.829	5.785	1.000	4.502	228.162	241.877	0.944	5.561

Model 1AC: Treatment B data was excluded from the modeling and used for external validation

As was discussed, in vitro and in vivo performance of Treatments A and B is very similar. Therefore, the decision was made to exclude treatment B from the model building procedure, and use it later for model validation purposes. Model 1 was fitted to the data for Treatment A, Treatment C, and Treatment D, excluding the Treatment B data. It was called Model 1AC to distinguish it from the model that uses all the available data.

The internal and external validation statistics for Model 1AC (fitted to the data for Treatment A, Treatment C, Treatment D and externally validated with the data for Treatment B) is shown in **Error! Reference source not found.**. Maximum internal |%PE| was 5.5% for C_{max} and 8.7% for AUC, with MAPPE equal to 5.5% for C_{max} and 6.4% for AUC. The prediction errors for external Treatment B were 4.9% for C_{max} and 6.9% for AUC. All the characteristics are well within the FDA internal validation limits (|%PE| < 15%) and the external validation limits (|%PE| < 10%).

Model 1AC (fitted to the mean IR, Treatment A and Treatment C ER CPM data): validation summary

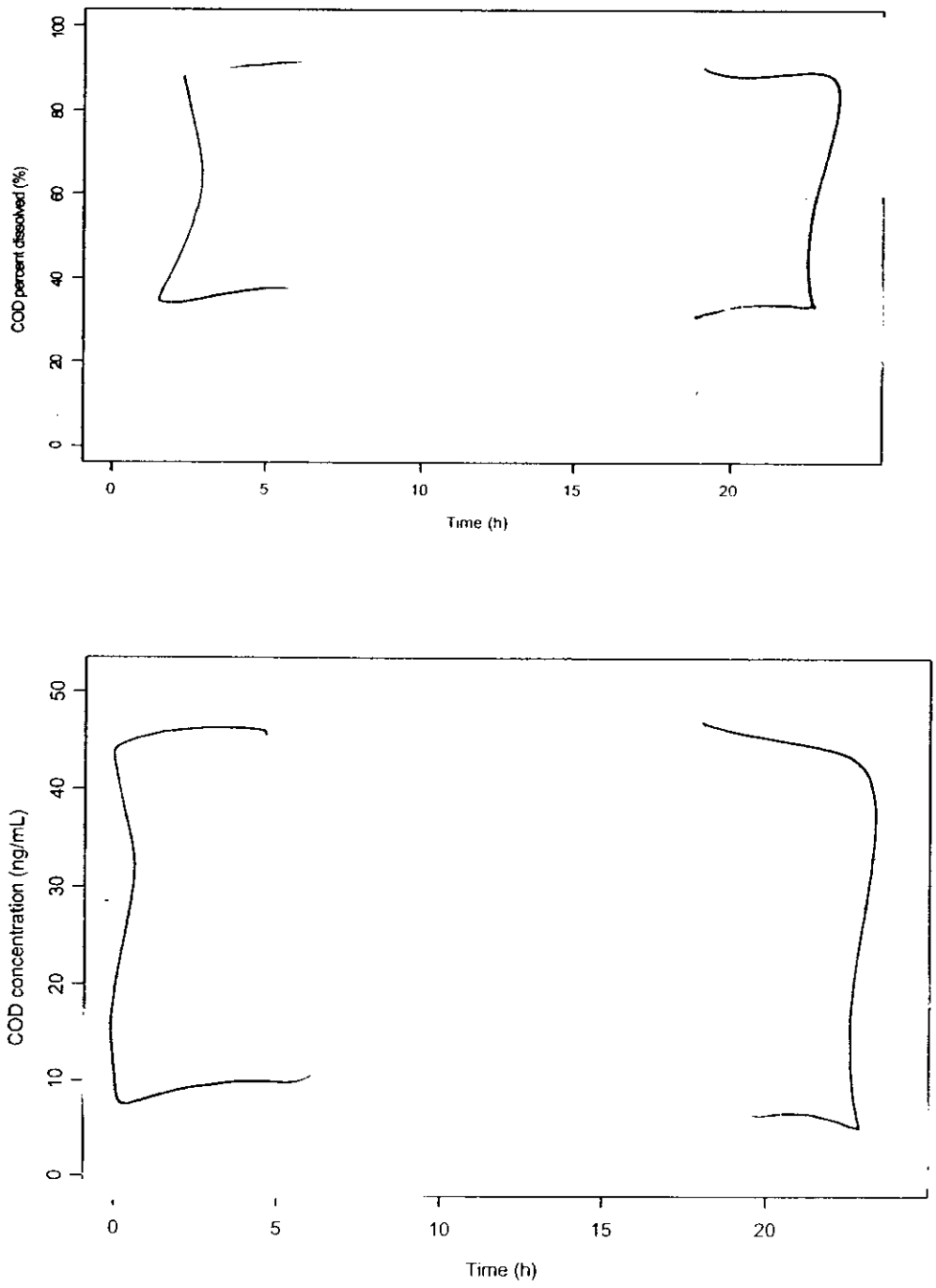
Treatment	C_{max}				AUC(0-72)			
	Pred. (ng/mL)	Obs. (ng/mL)	ratio	|%PE| (%)	Pred (ng/mL)	Obs. (ng/mL)	ratio	|%PE| (%)
Internal validation								
A	6.854		1.055	5.530	233.042		0.913	8.658
C	4.194		0.946	5.440	209.481		0.958	4.216
mean	5.524	5.465	1.000	5.485	221.262	236.917	0.936	6.437
External validation								
B	6.742		1.049	4.942	234.448		0.931	6.891

Model 2: The linear convolution-based (one-stage) model applied to the individual CPM data

The initial estimates of the individual impulse response functions were obtained by fitting the concentration time course for the IR formulation . Model 2 was fitted to the CPM plasma concentrations from the IR and all

three ER lots. The result is illustrated in **Error! Reference source not found. - Error! Reference source not found.**

Dissolution data (upper panel) and plasma concentration (lower panel) of codeine



Model 1: Internal validation

Validation statistics for Model 1 is shown in **Error! Reference source not found.**. Maximum |%PE| was 18.0% for C_{max} and 17.6% for AUC, with MAPPE equal to 12.7% for C_{max} and 13.1% for AUC. These characteristics exceed the FDA internal validation limits (|%PE| < 15% for C_{max} and AUC for each formulation, and MAPPE < 10% for C_{max} and AUC).

Model 1 (fitted to the mean IR and ER COD data): validation summary

treatment	C_{max}				AUC(0-24)			
	Pred. (ng/mL)	Obs. (ng/mL)	ratio	|%PE| (%)	Pred (ng/mL)	Obs. (ng/mL)	ratio	|%PE| (%)
A	35.247		1.069	6.877	310.717		0.860	13.987
B	31.225		1.131	13.135	313.633		0.923	7.672
C	18.417		0.820	17.995	248.290		0.824	17.637
mean	28.296	27.679	1.007	12.669	290.880	334.133	0.869	13.099

Model 2: The linear ——— model applied to the individual COD data

The initial estimates of the individual impulse response functions were obtained by fitting the concentration time course for the IR formulation (see Appendix 1).

Model 2 was fitted to the COD plasma concentrations from the IR and all three ER lots. The result is illustrated in **Error! Reference source not found.-Error! Reference source not found.**. Lines represent the predicted concentration time courses and points represent the observed concentrations.

Model 2: Internal validation

The predicted (fitted) COD plasma concentrations from Model 2 follow the observed data. The bioequivalence metrics C_{max} and AUC(0-24 h) for the individual observed and fitted values are presented Appendix 1. The geometric means of C_{max} and AUC(0-24 h) for each treatment are presented in **Error! Reference source not found.**. Maximum |%PE| was 18.1% for C_{max} and 13.4% for AUC, with MAPPE equal to 10.0% for C_{max} and 9.8% for AUC. All the characteristics are within the FDA internal validation limits except |%PE| = 18.1% for C_{max} for Treatment C. This exceeds the maximum allowable error by 3.1%.

Model 2 (fitted to the individual IR and ER COD data): validation summary

treatment	C_{max}				AUC(0-24)			
	Pred. (ng/mL)	Obs. (ng/mL)	ratio	|%PE| (%)	Pred (ng/mL)	Obs. (ng/mL)	ratio	|%PE| (%)
A	35.561		1.013	1.337	312.537		0.884	11.631
B	32.262		1.106	10.584	317.196		0.955	4.500
C	18.484		0.819	18.102	255.064	— —	0.866	13.386
mean	28.769	28.945	0.979	10.007	294.932	326.766	0.902	9.839

The parameters of the polyexponential approximation of the impulse response function represent the impulse response of the mean subject to the unit dose of the drug. The unit dose of the ER dose for this study was 8 mg for CPM and 40 mg for COD. The impulse response function represents the subject response on administration of the unit ER dose (8 mg of CPM and 40 mg of COD) of IR formulation.

In vivo dissolution data was in the form of the percent dissolved. Therefore, 100% dissolution corresponds to the unit (8 mg of CPM and 40 mg of COD) dose. Moreover, the impulse response function is a response on the administration of the unit dose of the IR drug. The model parameters a_1 and a_2 reflect this scaling.

The only model parameters that differed significantly between Model 1 and Model 1AC, and between Model 2 and Model 2AC were a_i parameters of the impulse response functions. The reason for this difference was that several exponential terms in polyexponential approximations of these impulse response functions had similar powers. This created the over-parameterized approximation where the shapes of the resulting curves were similar although the parameters of the approximation were different. The exponential terms that described the terminal phase of the concentration-time courses were similar in all three models. Since the goal was to find the approximation that describes the observed data, the over-parameterization was acceptable.

Parameters of the polyexponential impulse response functions for CPM fitted to the mean IR data

subject	a (ng/mL/unit)	α (1/h)	t_0 (1/h)
mean	27.983	0.491	0.529
mean	10.451	0.035	0.529
mean	32.475	0.460	0.529
mean	-70.910	0.627	0.529

Model 1 (fitted to the mean IR and ER CPM data): the parameters of the polyexponential impulse response functions

subject	a (ng/mL/unit)	α (1/h)	t_0 (1/h)
mean	542.903	0.560	0.423
mean	9.362	0.026	0.423
mean	890.432	0.559	0.423
mean	-1442.698	0.567	0.423

Model 1 (fitted to the mean IR and ER CPM data): the IVIVC model parameters

subject	a_1(unit)	a_2 (unit/100%)	B_1 (h)	b_2
mean	-0.0391	0.0081	0.3804	0.5386

Model 1AC (fitted to the mean IR, Treatment A and Treatment C ER CPM data): the parameters of the polyexponential impulse response functions

subject	a (ng/mL/unit)	α (1/h)	t_0 (1/h)
mean	1119.776	0.546	0.424
mean	9.377	0.027	0.424
mean	719.358	0.546	0.424
mean	-1848.512	0.551	0.424

Model 1AC (fitted to the mean IR, Treatment A and Treatment C ER CPM data): the IVIVC model parameters

subject	a_1(unit)	a_2 (unit/100%)	B_1 (h)	b_2
mean	-0.0432	0.0081	0.3965	0.5498

The parameters of the polyexponential impulse response functions for COD fitted to the mean IR data

subject	a (ng/mL/unit)	α (1/h)	t_0 (1/h)
mean	117.486	0.272	0.266
mean	-117.486	4.645	0.266

Model 1 (fitted to the mean IR and ER COD data): the parameters of the polyexponential impulse response functions

subject	a (ng/mL/unit)	α (1/h)	t_0 (1/h)

mean	119.603	0.273	0.208
mean	-119.603	3.598	0.208

Model 1 (fitted to the mean IR and ER COD data): the IVIVC model parameters

Subject	a_1 (unit)	a_2 (unit/100%)	b_1 (h)	b_2
mean	0.0571	0.0074	0.0228	0.5072

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Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA or IND Number	**N21-369**	**Brand Name**	**[redacted] (Tenatative)**
OCPB Division	**DPE-2**	**Generic Name**	**Codeine/chlorphenirami ne**
Medical Division	**HFD-570 (Division of Pulmonary and Allergic Drug Products)**	**Drug Class**	**Antituissive / antihistamine**
OCPB Reviewer	**Young Moon Choi, Ph.D.**	**Indication(s)**	**Treatment of cough and upper respiratory symptoms associated with allergy or cold**
OCPB Team Leader	**Emmanuel Fadiran, Ph.D.**	**Dosage Form**	**Extended release Suspension (Polistirex resin); combination product of Codeine 40 mg/10 ml and chlorpheniramine 8 mg/10 ml.**
		Dosing Regimen **(Note:** *The proposed dosage regimen is within the monograph for OTC antitussive and antihistamine drug product. However, the proposed drug formulation has higher strength than the limit (2.2 mg/ml) allowing exemption for codein from prescription requirement. Therefore, the sponsor are seeking this product as prescription drug categorized as a Schedule III controlled substance.***)**	Adults and adolescents, ages 12 and older: **Two teaspoonfuls (10 ml) every 12 hours; do not exceed four teaspoonfuls in 24 hours** **Children ages 6 to under 12 : One teaspoonful (5 ml) every 12 hours; do not exceed two teaspoonfuls in 24 hours** **Not recommended for patients under 6 years of age**
Date of Submission	**4/13/2001** **(Filing due on 6/12/2001)**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**1/13/2002**	**Sponsor**	**Celltech Pharmaceuticals Inc. (formerly known as Medeva Pharmaceuticals, Ind.)**
PDUFA Due Date	**2/13/2002**	**Priority Classification**	

Clin. Pharmaco. and Biopharm. Information

	"✔" if included at filing	Number of study submitted	Number of study reviewed	Comments

STUDY TYPE				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, prove of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				

II. Biopharmaceutics		3		The sponsor submitted three study reports: (1) study 1109/99, an IVIVC study. Single dose PK study with three ER formulations with different dissolution characteristics release) This study is used to select to-be-marketed formulaiton for pivotal study. (2) Study COD-02002, a multi dose, comparative BA study with solution IR formulation. (3) Study COD02001, a single dose food effect study
Absolute bioavailability:				
Relative bioavailability -	✔			
solution as reference:	✔			
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	✔			It should be noted that the sponsor submitted comparative BA study, however, calculated 90% confidence interval for geometric ratio of the mean values of PK parameters, as per agency's request. It is also noted that the single dose study was not performed with to-be-marketed formulation.
replicate design; single / multi dose:				
Food-drug interaction studies:	✔			
Dissolution:	✔			It is noted that the sponsor submitted average dissolution data with extent of variation. The individual dissolution data will be requested.
(IVIVC):	✔			**The sponsor stated that the electronic data set as a review aid has been submitted, however, this reviewer could not find the data. The sponsor was asked about the missing electronic data. It is noted that the data is not an archive electronic file, but a review aid.**
Bio-wavier request based on BCS				
BCS study				

III. Other				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Filability and QBR comments				
	"✔" if yes	Comments		
Application filable ?	✔	**The application is able to be review. Please see other comments for discussion points (may be potential review issues).**		
Comments sent to firm ?		For dissolution specification, the sponsor needs to provide individual dissolution data of biobatch and stability batches.		
QBR questions (key issues to be considered)	• **Is the systemic exposure of the extended release formulation comparable to the appropriate reference product?** • **Is the level A IVIVC acceptable?** • **Is there any drug interaction?** • **Is there any food effect?**			
Other comments or information not included above	Discussion points (may be potential review issue, but not a filing issue) are: **1. Clinical importance of C12 and AUC12 after single dose:** The sponsor stated that for chloropheniramine, only AUCinf met BE criteria. AUC12 and C12 did not meet BE criteria. However, after the multiple dose, AUCτ and Cmin met BE criteria for chlorheniramine. The sponsor stated that for codein, AUC inf and C12 met BE criteria. However, after the multiple dose, only AUCτ met BE criteria. It should be noted that the Cmax is lower and Cmin is higher than the IR product for codein. It should be noted that the single dose study has not been performed with to-be-marketed formulation. Instead the sponsor performed three different formulations, i.e., ——— dissolution formulations. **2. IVIVC:** It should be noted that, based on the sponsor's statement, an IVIVC (level A) has been established for chlorpheniramine. For codein, the IVIVC has not been established. This is important for dissolution specification. **3. Drug interaction on PK parameters:** The sponsor did not perform drug interaction study after single dose using to-be-marketed formulation. However, this point may not be an issue, because AUCτ after multiple dose of the to-be-marketed ER formulation appeared to meet BE criteria with IR (solution) formulation. Furthermore, AUCinf values for tow active ingredients after single dose of three ER formulations with different dissolution rate appeared to meet BE criteria. **4. Biopharmaceutical Site Investigation will be consulted to DSI for the pivotal multiple dose study, Study COD-02002.** **5. The IVIVC data need to be consulted to Pharmacometric scientists.**			

Primary reviewer Signature and Date	**Young Moon Choi, Ph.D.**
Secondary reviewer Signature and Date	**Emmanuel Fadiran, Ph.D.**

CC: NDA 21-369, HFD-850(Lee), HFD-570(Yu), HFD-870(Fadiran, Malinowski), CDR

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

/s/

Young-Moon Choi
1/28/02 04:49:24 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
1/29/02 11:44:43 AM
BIOPHARMACEUTICS
I concur