

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206323Orig1s000**

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

## CLINICAL PHARMACOLOGY REVIEW

NDA: 206323	Submission Date(s):
Brand Name	Unknown at the time of writing this review
Generic Name	Codeine/Chlorpheniramine ER Oral Tablets
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OCP Division	Clinical Pharmacology -2
OND division	Division of Pulmonary, Allergy and Rheumatology Products
Sponsor	Nexgen on behalf of Spriaso
Submission Type; Code	505 (b) (2) NDA; Standard
Formulation; Strength(s); Dose	40 mg codeine (54.3 mg codeine phosphate) and 8 mg chlorpheniramine maleate contained in 1 ER tablet every 12 hours, with or without food, not to exceed 2 doses (tablets) in 24 hours
Proposed Indication	Relief of cough (b) (4) common cold, (b) (4) upper (b) (4) respiratory allergies in adults (b) (4)

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## 1 Executive Summary

### 1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP 2), has reviewed the clinical pharmacology data included in NDA 206-323, and finds it approvable.

### 1.2 Phase IV Commitments

None.

### 1.3 Summary of Important Clinical Pharmacology Findings

#### 1.3.1 Background

NDA 206-323 was submitted by Nexgen Pharma on behalf of Spriaso LLC (Sponsor). In this application, Spriaso is seeking the marketing approval for a fixed-dose extended-release (ER) tablet containing 40 mg of codeine (as 54.3 mg codeine phosphate) and 8 mg of chlorpheniramine maleate to be dosed every 12 hours for a maximum of 2 doses. The rationale for the development of this product is simply patient convenience for the proposed indication, which is “for the temporary relief of cough (b) (4) common cold (b) (4) upper respiratory allergies (b) (4)”. (b) (4)

Currently, no other combination product containing codeine and chlorpheniramine is marketed. FDA previously approved two products containing these 2 components as listed below:

- Fisons Corporation previously marketed Pentuss extended release oral suspension (NDA 18-928 approved on 08/14/1985) containing 10 mg/5 mL of codeine and 4 mg/5 mL. This product was withdrawn from the market in 1996 for reasons unrelated to safety or efficacy.
- Celltech Pharmaceuticals received approval for Codeprex Pennkinetic extended release oral suspension (NDA 21-369 approved on 06/21/2004), containing codeine polistirex and chlorpheniramine polistirex equivalent to 20 mg codeine and 4 mg chlorpheniramine maleate respectively in each 5 mL of product. Codeprex was never marketed in the US and the sponsor eventually withdrew the NDA for reasons unrelated to safety and efficacy.

Spriaso has submitted this application through 505(b)(2) pathway and is relying on FDA’s safety and efficacy findings from:

- i. Previously approved Codeprex Pennkinetic extended release oral suspension, NDA 21-369
- ii. Over-The-Counter (OTC) monographs for codeine as an antitussive agent (21 CFR 341.14) and chlorpheniramine maleate as an antihistamine agent (21 CFR 341.12)

Codeine and chlorpheniramine maleate are OTC monograph listed drugs. Codeine is listed as an antitussive active ingredient in 21 CFR 341.14 and chlorpheniramine maleate is listed as antihistamine in 21 CFR 341.12. The recommended dose of Codeine is 10 to 20 mg every 4 to 6 hours, not to exceed 120 mg in 24 hours (21 CFR 341.74(d)(1)(ii)) and the recommended dose of chlorpheniramine maleate is 4 mg every 4 to 6 hours, not to exceed 24 mg in 24 hours (21 CFR 341.72(d)(3)).

The clinical development program in this application comprised of two pilot and two pivotal relative bioavailability/bioequivalence (BA/BE) studies which included comparison of systemic exposure of the 2 components in test vs. reference and evaluation of effect of food on the PK of the 2 components from the test product. No clinical safety/efficacy studies were conducted.

### 1.3.2 Results from Clinical Pharmacology Trials

As indicated before, the clinical development program in this application included data from two pivotal relative bioavailability/bioequivalence (BA/BE) studies. As no immediate (IR) or extended release (ER) codeine and chlorpheniramine combination products are currently marketed, the relative BA assessments were conducted using a codeine and chlorpheniramine combination IR tablet manufactured by the sponsor as the reference product. This issue was discussed during pre-submission meetings and was considered acceptable.

A summary of the results from the 2 pivotal BA/BE studies are provided below:

- Study **LPCN 1084-12-002**: A single-dose, crossover study evaluating relative BA of the ER tablet compared to the reference IR tablet and food effect on ER tablet indicated that the ER tablet yielded similar systemic exposures (AUC within BE limits of 80-125%) of codeine and chlorpheniramine as compared to that of the reference product. As expected, C<sub>max</sub> values for both codeine and chlorpheniramine were slightly lower from the ER product as compared to the IR products. Presence of a high-fat, high-calorie meal led to a 28% increase in C<sub>max</sub> and a 13% increase in the AUC for codeine and had no effect on chlorpheniramine PK. A BE analysis comparing codeine PK in ER fed vs. IR fasted conditions indicated that codeine PK from the ER tablet in fed conditions is similar to that of the IR tablet in fasted conditions. As such, the effect of food on the ER tablet is not considered relevant.
- Study **LPCN 1084-13-001**: A multiple-dose (7-day), 2-way crossover study evaluating relative BA of the ER tablet compared to the reference IR tablet indicated that the ER tablet yielded similar systemic exposures (AUC within BE limits of 80-125%) of codeine and chlorpheniramine as compared to that of the reference product on day 7 (steady-state). A visual comparison of the plasma profiles for codeine and chlorpheniramine from the ER tablet vs. the respective reference IR product indicated that plasma concentrations of codeine from the ER tablet were lower than that with the reference IR tablet between 6-12 hours of the dosing interval. However, the C<sub>min</sub> values for codeine obtained with the ER and IR tablets were similar indicating plasma concentrations of codeine with the ER

product do not fall below those obtained with the IR product throughout the dosing interval including the last 6 hours. An OSI inspection of the clinical and analytical portions of this study was deemed to be acceptable.

### **1.3.3 Overall Conclusion**

Overall, the sponsor has adequately bridged their ER fixed-dose combination tablet to the appropriate references and the information included in the NDA is acceptable from a clinical pharmacology perspective. At the time of writing this review, the labeling for this product has not been finalized and the reader is referred to the approved label for final labeling recommendations. It should be noted that the sponsor is seeking [REDACTED] (b) (4) [REDACTED] however the Agency is leaning towards approving this product for adults only, i.e., 18 years and up, as ER products containing opioids may not be suitable for use in children. The reader is referred to the approval letter for Agency's final recommendations.

## 2 Question-Based Review (QBR)

### 2.1 General Attributes of the Drug and Drug Product

NDA 206-323 was submitted by Nexgen Pharma on behalf of Spriaso who developed the product. This application is a 505(b)(2) NDA for a fixed dose combination (FDC) extended release (ER) formulation containing codeine and chlorpheniramine, 40 mg/ 8 mg. The proposed indication for the FDC is "temporary relief of cough (b) (4) common cold (b) (4) upper respiratory allergies (b) (4)

The clinical development plan for the ER product is a bioequivalence based program, relying on the Agency's finding of safety and/or effectiveness as codeine and chlorpheniramine, identified as having established safety and efficacy under the OTC Monograph, including in combination with one another (21 CFR 341.40(d)). The OTC doses and indications for codeine and chlorpheniramine are indicated below:

For products containing codeine ingredients identified in § 341.14(a)(2):

- Adults and children 12 years of age and over: Oral dosage is 10 to 20 milligrams every 4 to 6 hours, not to exceed 120 milligrams in 24 hours, or as directed by a doctor.
- Children 6 to under 12 years of age: Oral dosage is 5 to 10 milligrams every 4 to 6 hours, not to exceed 60 milligrams in 24 hours, or as directed by a doctor.
- Temporary relief of cough in adults and children years 12 or older, as may occur with the common cold or inhaled irritants.

For products containing chlorpheniramine maleate identified in § 341.12(c).

- Adults and children 12 years of age and over: oral dosage is 4 milligrams every 4 to 6 hours, not to exceed 24 milligrams in 24 hours, or as directed by a doctor.
- Temporary relief of runny nose, sneezing, itching of the nose or throat and itchy watery eyes due to hay fever, other upper respiratory allergies, or allergic rhinitis.

The IND for this product (IND 106,992) was originally filed by Lipocine on October 14, 2009 and the sponsorship of the IND was transferred to Spriaso LLC on July 31, 2013. Lipocine held an End of Phase II meeting with the FDA on 4 October 2010. The pre-NDA meeting between Spriaso and the Agency was held on October 10, 2013.

#### 2.1.1 *What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?*

**Drug Substance:** The active ingredients in the ER tablet are codeine and chlorpheniramine. Codeine has been used widely in the United States for many years as a cough suppressant and for pain reliever. Chlorpheniramine is frequently used as an antihistamine.

**Drug Product:** The composition of the proposed ER tablet is shown in Table 4.

**Table 1: Composition of the Proposed Codeine-Chlorpheniramine Extended Release Tablets**

Ingredient	Function	mg/tablet	% w/w
Codeine Phosphate, USP <sup>1</sup>	Active	54.30	(b) (4)
Chlorpheniramine Maleate, USP	Active	8.00	(b) (4)
Magnesium Stearate, NF	(b) (4)	(b) (4)	(b) (4)
Colloidal Silicon Dioxide,	(b) (4)	(b) (4)	(b) (4)
(b) (4) Lactose Monohydrate	(b) (4)	(b) (4)	(b) (4)
Hypromellose	(b) (4)	(b) (4)	(b) (4)
Lactose Monohydrate, NF	(b) (4)	(b) (4)	(b) (4)
Microcrystalline Cellulose, (b) (4) NF	(b) (4)	(b) (4)	(b) (4)
Magnesium Stearate, NF	(b) (4)	(b) (4)	(b) (4)
Colloidal Silicon Dioxide, NF	(b) (4)	(b) (4)	(b) (4)
<b>Total Weight</b>		<b>200.00</b>	<b>100.00</b>

<sup>1</sup> 54.30 mg of Codeine Phosphate, USP is equivalent to 40.0 mg of Codeine

(b) (4)

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

There are currently no known marketed products containing a combination of codeine and chlorpheniramine as an ER formulation. Two similar products though, have been approved in the past:

- Fisons Corporation previously marketed Pentuss (NDA 18-928, approved on 08/14/1985) containing 10 mg/5 mL of codeine and 4 mg/5 mL of chlorpheniramine. It was, however, withdrawn from the market in 1996 for reasons unrelated to safety or efficacy (did not find a memo in DARRTS).
- Celltech Pharmaceuticals received approval for Codeprex Pennkinetic ER Suspension (NDA 21-369 approved on 06/21/2004), containing codeine polistirex and chlorpheniramine polistirex equivalent to 20 mg codeine and 4 mg chlorpheniramine maleate respectively in each 5 mL of product. Codeprex, although approved, was never marketed in the US and the sponsor eventually withdrew the NDA for reasons unrelated to safety and efficacy (memo in DARRTS dated 03/20/2007).

It should be noted that the OTC monograph for codeine as an antitussive active ingredient in 21 CFR 341.14 (shown below) indicates that codeine or codeine phosphate or codeine sulfate could be used interchangeably for this indication when used within the dosage limit set forth by 21 CFR 341.74 (d) which is 10 to 20 mg every 4 to 6 hours, not to exceed 120 mg in 24 hours.

**§ 341.14 Antitussive active ingredients.**

The active ingredients of the product consist of any of the following when used within the dosage limits and in the dosage forms established for each ingredient in § 341.74(d):

(a) *Oral antitussives*. (1) Chlophedianol hydrochloride.

(2) *Codeine ingredients*. The following ingredients may be used only in combination in accordance with § 290.2 and 21 CFR 1308.15(c).

(i) Codeine.

(ii) Codeine phosphate.

(iii) Codeine sulfate.

(3) Dextromethorphan.

(4) Dextromethorphan hydrobromide.

(5) Diphenhydramine citrate.

(6) Diphenhydramine hydrochloride.

(b) *Topical antitussives*. (1) Camphor.

(2) Menthol.

As such, sponsors can use either of the three entities, i.e, free base codeine (MW 300) or codeine phosphate (MW 406) or codeine sulfate (MW 750) to calculate a dose within the recommendations included in the OTC monograph. As such, the free base amount of codeine may be different in different formulations approved under the same OTC monograph. This issue was discussed at the midcycle meeting for this application. Agency's current guidelines for labeling indicate that sponsors should use the free base amount of any salt used as an active ingredient in the formulation in the label of the product. However, labeling for drugs that have been approved under the OTC monograph rule frequently include the salt as the active ingredient and not the free base as the OTC monograph allows sponsors to use the salt as the active ingredient. It was discussed, that sponsors of applications referencing OTC monographs for approval should be advised during the pre-submission phase, to use the free equivalent base to calculate the amount of active ingredient in their formulation per unit dosage form.

Note, that the ER tablet under review in this NDA contains 54.3 mg codeine phosphate representing 40 mg of free codeine base and 8 mg of chlorpheniramine maleate in each tablet. The OTC monograph of chlorpheniramine for the anti-histamine indication includes the maleate form only, and no other salts or derivatives are included (shown below):

**§ 341.12 Antihistamine active ingredients.**

The active ingredient of the product consists of any of the following when used within the dosage limits established for each ingredient:

- (a) Brompheniramine maleate.
- (b) Chlorcyclizine hydrochloride.
- (c) Chlorpheniramine maleate.
- (d) Dexbrompheniramine maleate.
- (e) Dexchlorpheniramine maleate.
- (f) Diphenhydramine citrate.
- (g) Diphenhydramine hydrochloride.
- (h) Doxylamine succinate.
- (i) Phenindamine tartrate.
- (j) Pheniramine maleate.
- (k) Pyrilamine maleate.
- (l) Thonzylamine hydrochloride.
- (m) Triprolidine hydrochloride.

[57 FR 58374, Dec. 9, 1992, as amended at 59 FR 4218, Jan. 28, 1994]

As no IR or ER codeine and chlorpheniramine combination products are currently marketed, the relative BA assessments were conducted using a codeine and chlorpheniramine combination IR tablet manufactured by the sponsor as the reference product. This issue was discussed during pre-submission meetings and was considered acceptable.

During the filing meeting, 2 review issues were determined and communicated to the sponsor, i.e., statistically relevant food effect on the codeine component of the ER tablet and lower plasma concentrations of codeine with the ER tablet vs. reference in the 6-12 hours period of the dosing interval. After completion of the review of the submitted data, both these issues are now considered addressed and there are no pending review issues from a clinical pharmacology perspective.

PREA is triggered by this application as the ER tablet formulation of codeine and chlorpheniramine is considered a new dosage form. The sponsor's pediatric study plan has not been discussed at the PeRC meeting at the time of writing this review. As noted before in the Executive Summary section, the sponsor is seeking [REDACTED] (b) (4) [REDACTED] however the Agency is leaning towards approving this product for adults only, i.e., 18 years and up, as ER products containing opioids may not be suitable for use in children. The reader is referred to the approval letter for Agency's final recommendations.

**2.1.3 What is the mechanism of action, proposed therapeutic indication and dosage recommendation for proposed product?**

**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. Chlorpheniramine is an antihistamine (H1-receptor antagonist) and also possesses anticholinergic and sedative activity.

**Proposed Indication:** Indicated for the relief of cough [REDACTED] (b) (4) common cold, [REDACTED] (b) (4) upper respiratory allergies in adults 18 years of age and older.

**Dosage:** One tablet every 12 hours, with or without food, not to exceed 2 doses in 24 hours.

**2.1.4 *Is any OSI (Office of Scientific Investigation) inspection requested for any of the clinical studies?***

Yes. The OSI inspection was requested for multiple dose steady state relative bioavailability study (Study LPCN 1084-13-001). The clinical site and analytical sites were QPS Bio-Kinetic, Springfield, MO and [REDACTED] (b) (4) respectively. The OSI review team recommended accepting the data of this relative bioavailability study. The reader is referred to the OSI memo in DARRTS dated 12/04/2014 for further details.

**2.2 General Clinical Pharmacology**

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

This NDA application is a 505(b)(2) application where the sponsor is relying on the Agency's previous findings of efficacy and safety from the reference product, Codeprex Pennkinetic (NDA 21-369), and the monograph for Combination Cough, Cold and Bronchodilator Drug Products for their fixed dose ER product containing codeine and chlorpheniramine.

The clinical development program for is therefore comprised of PK studies intended to establish relative bioavailability between the ER tablet and the reference, and evaluate the effect of food on the ER product. At the present time, as there is no IR or ER codeine and chlorpheniramine combination product currently marketed (via an NDA), the PK studies employed a codeine and chlorpheniramine combination IR tablet manufactured by the sponsor for investigational purpose only.

Two pivotal clinical studies were conducted to support the development and registration of the ER tablet (test):

- LPCN 1084-12-002: a single-dose, crossover study evaluating relative BA of the ER tablet (Lot 100097) compared to the reference IR tablet (Lot 100106) and food effect on ER tablet

- LPCN 1084-13-001: a multiple-dose, 2-way crossover study evaluating relative BA of the ER tablet (Lot 100097) compared to the reference IR tablet (Lot 100106)

### ***2.2.2 Are the active moieties in the plasma appropriately identified and measured?***

Yes. The reader is referred to section 2.6 for details on the bioanalytical method.

### ***2.2.3 Is the systemic exposure after single administration of the test product comparable to that after the administration of the reference product?***

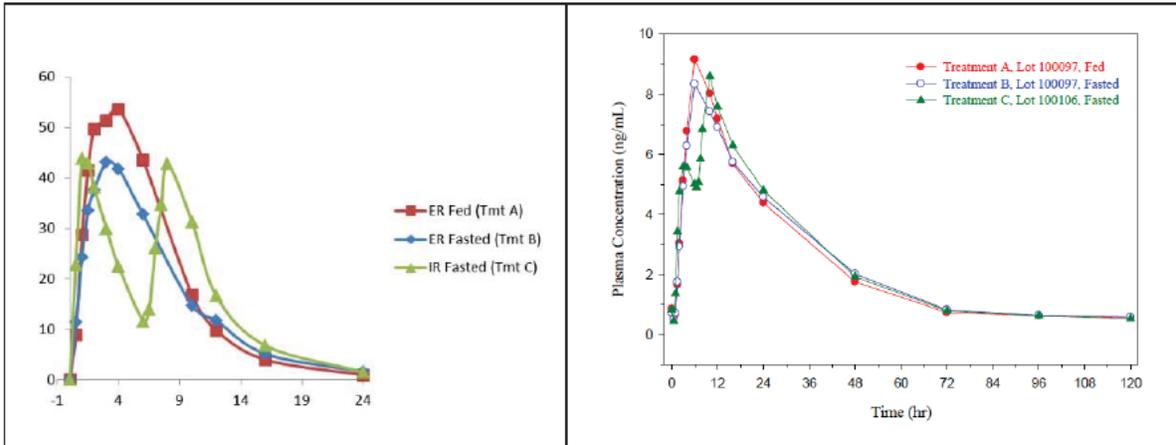
Yes, the systemic exposures (AUC) of both, codeine and chlorpheniramine from the ER product at single dose were found to be comparable to the reference IR product.

Study LPCN 1084-12-002 evaluated the oral bioavailability of a single dose of the ER tablet (40 mg codeine and 8 mg chlorpheniramine maleate) vs. 20 mg codeine IR tablet and 4 mg chlorpheniramine maleate IR tablet administered every 6 hours for a total of 2 doses of the reference products.

Study LPCN 1084-12-002 was a single-center, open-label, single-dose, three-treatment, three-period, crossover design during which 24 healthy adult male and female subjects were assigned to receive the ER tablet under fed and fasting conditions and two doses each of the two IR tablets in a randomized sequence. Each subject received each of three treatments once.

Mean codeine and chlorpheniramine plasma concentration-time profiles are shown in Figure 1. Mean and statistical analysis of the PK parameters for codeine and chlorpheniramine are shown in Table 2. Mean PK parameters obtained with the ER tablet are shown in Table 3.

**Figure 1: Mean Codeine (Left) and Chlorpheniramine (Right) Plasma Concentration-Time Profile of ER Tablet (40 g Codeine and 8 mg Chlorpheniramine Maleate as Treatment B) and Two Doses (Q6h) of Reference Product (20 mg Codeine and 4 mg Chlorpheniramine Maleate IR Tablet as Treatment C) Following Single Dose Administration (Study LPCN 1084-12-002)**



**Table 2: Geometric Mean, Ratios of Geometric Means and the 90% Confidence Intervals for the PK Parameters of Codeine and Chlorpheniramine of ER Tablet (40 g Codeine and 8 mg Chlorpheniramine Maleate) and Two Doses (Q6h) of Reference Product (20 mg Codeine and 4 mg Chlorpheniramine Maleate IR Tablet) Following Single Dose Administration in Fasting Conditions (Study LPCN 1084-12-002)**

Parameter	Codeine			90% Confidence Interval
	Geometric Mean		%Ratio	
	Test	Ref		
AUC <sub>last</sub> (ng·h/mL)	361	385	94	(88.60-99.38)
AUC <sub>inf</sub> (ng·h/mL)	371	395	94	(88.66-99.72)
C <sub>max</sub> (ng/mL)	44	52	85	(77.30-93.49)
Parameter	Chlorpheniramine			90% Confidence Interval
	Geometric Mean		%Ratio	
	Test	Ref		
AUC <sub>last</sub> (ng·h/mL)	284	284	100	(96.33-104.13)
AUC <sub>inf</sub> (ng·h/mL)	298	297	100	(96.49-104.34)
C <sub>max</sub> (ng/mL)	8.7	9.2	94.8	(88.35-101.80)

Source: Study Report for LPCN 1084-12-002

**Table 3: Summary (Mean ± SD) of PK Parameters for Codeine and Chlorpheniramine after Administration of ER Tablet (40 g Codeine and 8 mg Chlorpheniramine Maleate) in Fasting Conditions In Study LPCN 1084-12-002**

	<b>Codeine</b>	<b>Chlorpheniramine</b>
Cmax	45.565 +/- 11	8.95 +/- 2.5
AUCt	372 +/- 94	298 +/- 126
AUCinf	383 +/- 99	312 +/- 137
Thalf	4.29 +/- 1	21.3 +/- 7.2

Source: Study Report for LPCN 1084-12-002

*Reviewer's Comments: In this study, systemic exposure of both, codeine and chlorpheniramine from the ER product were found to be comparable to the reference IR product. The 90% confidence intervals for the geometric mean ratio for AUClast and AUCinf for both the components with the ER product were within the 80-125% bioequivalence limits when compared to the IR product. The ER product yielded lower Cmax values for codeine and chlorpheniramine as compared to the reference IR product. The 90% confidence intervals for the geometric mean ratio for Cmax for codeine with the ER product fell outside of the 80-125% bioequivalence limits at the lower end as indicated in Table 2. This is expected from an ER product, as typically, it is designed to reduce the sharp peaks observed with the IR product, and provides slower drug release as compared to the IR product. As such, lower codeine Cmax with the ER product is not of a concern.*

**2.2.4 Is the systemic exposure after multiple administrations (steady-state) of the test product comparable to that after the administration of the reference product?**

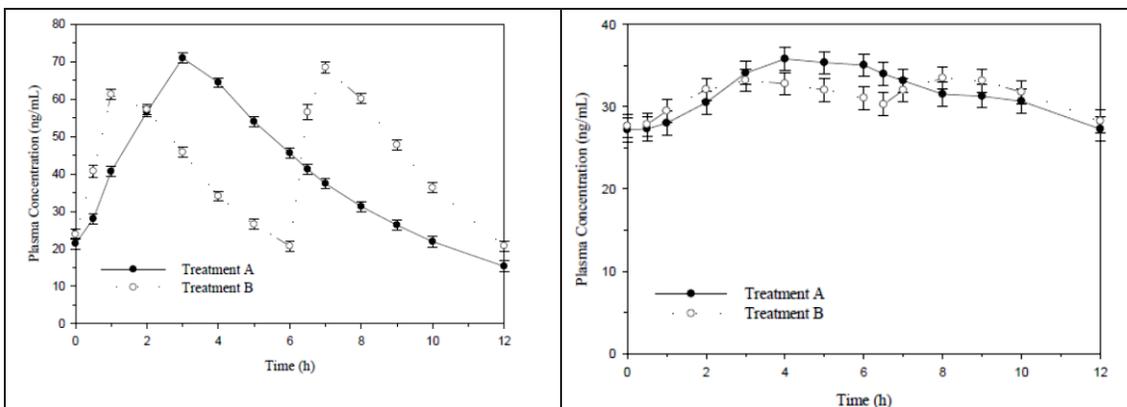
Yes, the systemic exposures (AUC) of both, codeine and chlorpheniramine from the ER product at steady state were found to be comparable to the reference IR product.

Study LPCN 1084-13-001 evaluated the oral bioavailability of the ER tablet vs. reference IR tablet at steady-state after oral administration. Subjects received the two treatments in a randomized sequence, with a minimum of 7 days washout period between the treatments.

Study LPCN 1084-13-001 was an open-label, randomized, multiple-dose, 2-way crossover comparative bioavailability study during which 38 healthy adult male and female subjects were assigned to receive the ER tablet (40 mg codeine and 8 mg chlorpheniramine) twice a day under fasting conditions and 4 doses of the reference IR tablet (20 mg codeine and 4 mg chlorpheniramine) in a randomized sequence for 6.5 days. Each subject received each of three treatments once.

Steady state mean codeine and chlorpheniramine plasma concentration-time profiles are shown in Figure 2. Mean and statistical analysis of the PK parameters for codeine and chlorpheniramine are shown in Table 4. Mean PK parameters obtained with the ER and IR tablets are shown in Table 5. Box plots comparing Cmin codeine concentrations from ER and IR tablets are shown in Figure 3.

**Figure 2: Mean Codeine (Left) and Chlorpheniramine (Right) Plasma Concentration-Time Profile Following Multiple Dose Administration of ER Tablet and Reference IR Tablet Under Fasting Condition for 6.5 Days ( Study LPCN 1084-13-001)**



**Table 4: Geometric Mean, Ratios of Geometric Means and the 90% Confidence Intervals for the PK Parameters of Codeine and Chlorpheniramine Following Multiple Dose Administration of ER Tablet and Reference IR Tablet in Fasting Condition for 6.5 Days (Study LPCN 1084-13-001)**

	Least-squares Geometric Means		Least-squares Means Ratio (%) (Treatment A / Treatment B)	90% CI Ratio
	Treatment A	Treatment B		
<b>Codeine</b>				
C <sub>max</sub> , ng/mL	71.5	84.2	85.0	(78.91, 91.46)
AUC <sub>12</sub> , h·ng/mL	487	523	93.1	(89.42, 97.03)
<b>Chlorpheniramine</b>				
C <sub>max</sub> , ng/mL	36.9	35.2	105	(100.39, 109.33)
AUC <sub>12</sub> , h·ng/mL	382	376	102	(97.46, 105.78)

**Table 5: Summary (Mean ± SD) of PK Parameters for Codeine and Chlorpheniramine Following Multiple Dose Administrations of ER Tablet and Reference IR Tablet in Fasting Condition for 6.5 Days (Study LPCN 1084-13-001)**

Treatment	Treatment A Extended-Release Tablet (N=38)		Treatment B Immediate-Release Tablet (N=37) <sup>b</sup>	
	Mean	SD	Mean	SD
<b>Codeine</b>				
C <sub>max</sub> , ng/mL	73.703	18.743	88.317	29.629
C <sub>min</sub> , ng/mL	16.475	6.648	19.976	6.488
C <sub>avg</sub> , ng/mL	42.1	11.9	45.0	12.0
AUC <sub>12</sub> , h·ng/mL	505	143	541	144
F1 (%)	139	25.5	151	36.1
T <sub>max</sub> , ha	3.00 (2.00-5.00)		6.50 (0.50-9.00)	
<b>Chlorpheniramine</b>				
C <sub>max</sub> , ng/mL	38.791	12.944	37.250	12.368
C <sub>min</sub> , ng/mL	27.823	10.444	28.278	9.692
C <sub>avg</sub> , ng/mL	33.7	12.1	33.2	11.1
AUC <sub>12</sub> , h·ng/mL	405	145	398	133
F1 (%)	33.9	7.73	27.4	6.00
T <sub>max</sub> , ha	5.00 (3.00-7.00)		7.00 (2.00-10.00)	

SD: Standard Deviation

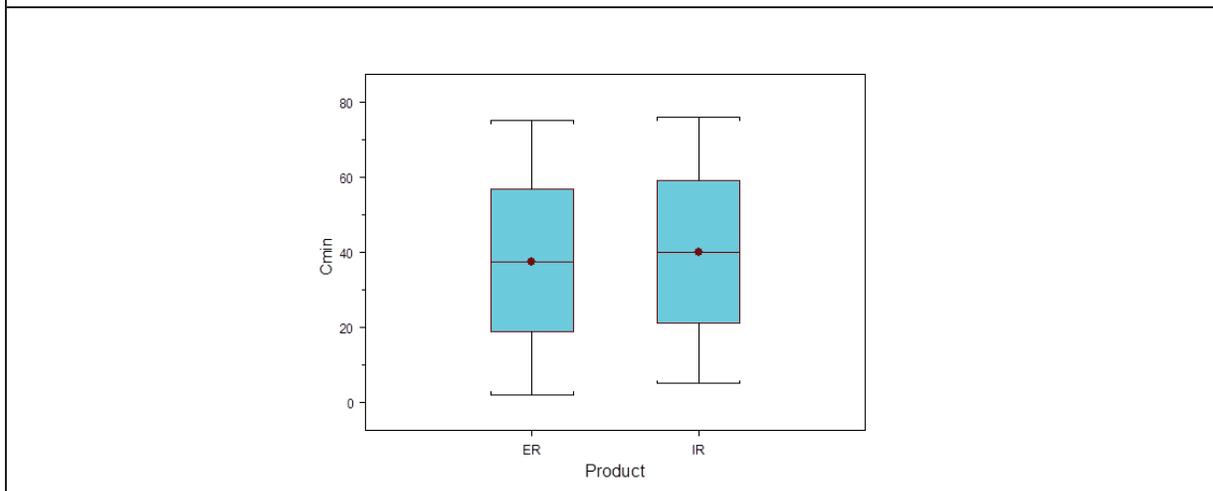
<sup>a</sup>: median (range), time after last morning dose (on Day 7).

<sup>b</sup>: N=37, Subject 031 was withdrawn from the study during the study period 2.

Treatment A: one (1) codeine 40 mg (as codeine phosphate)/chlorpheniramine maleate 8 mg extended-release tablet (Lot 100097) two times a day, 12 hours apart, for 6.5 days;

Treatment B: one (1) codeine 20 mg (as codeine phosphate)/chlorpheniramine maleate 4 mg immediate-release tablet (Lot 100106) four times a day, 6 hours apart, for 6.5 days

**Figure 3: Box Plots Comparing Codeine Cmin Concentrations Following Multiple Dose Administrations of ER Tablet and Reference IR Tablet in Fasting Condition for 6.5 Days (Study LPCN 1084-13-001)**



*Reviewer's Comments: In this study, systemic exposure of both, codeine and chlorpheniramine from the ER product at steady state were found to be comparable to the reference IR product. The 90% confidence intervals for the geometric mean ratio for AUC<sub>last</sub> and AUC<sub>inf</sub> for both the components with the ER product were within the 80-125% bioequivalence limits when compared to the IR product. The ER product yielded lower C<sub>max</sub> values for codeine and chlorpheniramine as compared to the reference IR products. The 90% confidence intervals for the geometric mean ratio for C<sub>max</sub> for codeine with the ER product fell outside of the 80-125% bioequivalence limits at the lower end as indicated in Table 4. At steady state, AUC were bioequivalent between the ER and IR product. From Figure 3, it is observed that mean plasma concentrations for codeine from the ER tablet were lower than that with the reference IR tablet between 6-12 hours of the dosing interval. However, a comparison of the mean C<sub>min</sub> values for codeine obtained with the ER and IR tablets (Table 5 and Figure 3) indicated that the values were comparable implying that the plasma concentrations of codeine with the ER product do not fall below those obtained with the IR product throughout the dosing interval including the last 6 hours. An OSI inspection of the clinical and analytical portions of this study was deemed to be acceptable.*

## **2.3 General Biopharmaceutics**

### **2.3.1 *Is the to-be-marketed formulation used in the pharmacokinetic studies?***

Yes, the sponsor used proposed to-be-marketed formulation in the pivotal bioavailability and food effect studies.

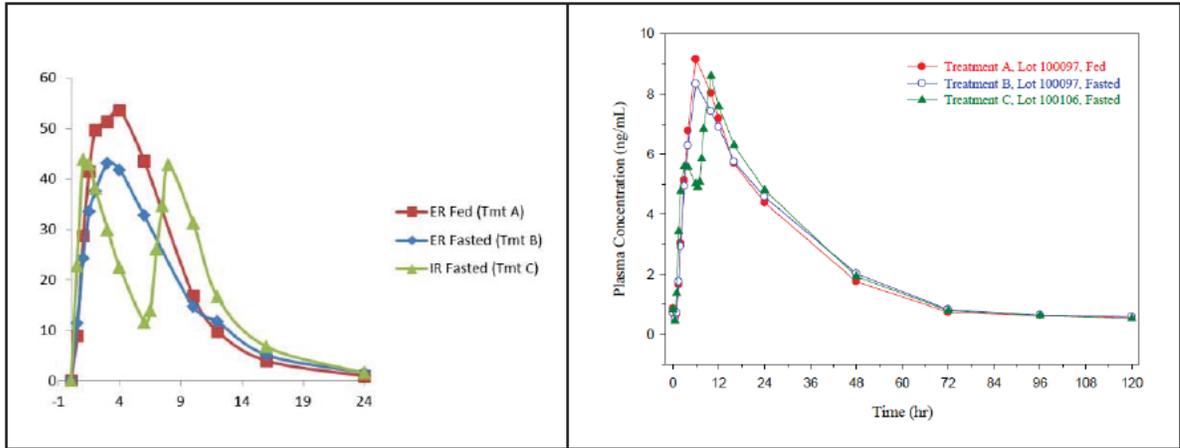
### **2.3.2 *What is the effect of food on the bioavailability of codeine and chlorpheniramine from the ER product?***

Effect of a high-fat, high-calorie meal on the ER tablet was evaluated in the single dose relative BA study, Study LPCN 1084-12-002. The presence of food led to a 28% increase in C<sub>max</sub> and a 13% increase in the AUC for codeine and had no effect on chlorpheniramine PK. A BE analysis comparing codeine PK in ER fed vs. IR fasted conditions indicated that codeine PK from the ER tablet in fed conditions is similar to that of the IR tablet in fasted conditions. As such, the effect of food on the ER tablet is not considered relevant.

Study LPCN 1084-12-002 (same study as discussed before for single dose relative BA) evaluated the effect of presence of a high-fat, high-calorie meal on a single dose of the ER tablet in which 24 healthy adult male and female subjects were assigned to receive the ER tablet under fed and fasting conditions.

Mean codeine and chlorpheniramine plasma concentration-time profiles are shown in Figure 4. Mean and statistical analysis of the PK parameters for codeine and chlorpheniramine are shown in Table 6.

**Figure 4: Mean Codeine (Left) and Chlorpheniramine (Right) Plasma Concentration-Time Profile Following Administration of Test Product Under Fed (Treatment A) and Fasting Conditions (Treatment B)**



**Table 6: Geometric Mean, Ratios of Geometric Means and the 90% Confidence Intervals for the PK Parameters of Codeine and Chlorpheniramine Following Single Dose Administration Under Fed and Fasted Condition**

Parameter	Codeine			90% Confidence Interval
	Geometric Mean		%Ratio	
	Fed	Fasted		
$AUC_{inf}$ (ng·h/mL)	421	371	113	(107.08-120.20)
$C_{max}$ (ng/mL)	56.6	44.2	128	(116.45-140.84)
Parameter	Chlorpheniramine			90% Confidence Interval
	Geometric Mean		%Ratio	
	Fed	Fasted		
$AUC_{inf}$ (ng·h/mL)	287	298	96.3	(92.67-100.15)
$C_{max}$ (ng/mL)	9.5	8.7	109	(101.93-117.34)

Source: Study LPCN 1084-12-002

**Table 7: Mean ( $\pm$ SD) PK Data of ER Tablet Administered under Fed and the IR Tablet under Fasting Conditions (Study LPCN 1084-12-002)**

Parameter	Codeine			90% Confidence Interval
	PK (Mean $\pm$ SD)		%Ratio	
	ER Fed	IR Fasted		
$AUC_{inf}$ (ng·h/mL)	457 $\pm$ 130	430 $\pm$ 115	1.06	97.4 – 114.8
$C_{max}$ (ng/mL)	58.9 $\pm$ 19.5	54.1 $\pm$ 16.4	1.08	98.1 – 118.7

*Reviewer’s Comment: The presence of food led to a 28% increase in  $C_{max}$  and a 13% increase in the  $AUC_{inf}$  for codeine and had no effect on chlorpheniramine PK (Table 6). A BE analysis comparing codeine PK in ER fed vs. IR fasted conditions (Table 7) indicated that codeine PK from the ER tablet in fed conditions is similar to that of the IR tablet in fasted conditions, i.e.,  $C_{max}$  and  $AUC_{inf}$  values of codeine from ER tablet are within BE limits of 80-125% of the reference. As such, the effect of food on the ER tablet is not considered relevant.*

### **2.3.3 What is the dose dumping potential of the proposed ER product?**

In vitro dissolution data indicate that increasing levels of ethanol lead to slightly decreasing release for both codeine and chlorpheniramine (Dr. Craig Bertha’s filing review in DARRTS dated 09/08/2014). For further details please refer to the final Biopharmaceutics review.

## **2.4 Analytical**

### **2.4.1 How are the active moieties identified and measured in the plasma/serum?**

Quantitation of plasma codeine and chlorpheniramine concentrations were determined using validated liquid chromatography with tandem mass spectrometry (LC/MS/MS).

### **2.4.2 What bioanalytical methods are used to assess concentrations?**

Codeine and chlorpheniramine concentrations were determined in human plasma samples by Bio-Kinetic Clinical Applications according to the method entitled “Validation of a Method for the Determination of Chlorpheniramine, Codeine, and Guaifenesin in Human Plasma by LC-MS/MS.” Data were acquired and processed using the proprietary software application Analyst® (Version 1.6.1) as summarized below in Tables 8 and 9. The assay validation criteria met the FDA guidance “Bioanalytical Method Validation” recommendations, and were therefore acceptable.

**Table 8: Assay Validation Results for Codeine**

Report Title	Validation of a Method for the Determination of Chlorpheniramine, Codeine, and Guaifenesin in Human Plasma by LC-MS/MS
Study Number	QPS 42-1202
Analyte Name	Codeine
Internal Standard (IS)	Codeine- <i>d</i> <sub>3</sub>
Analytical Method Type	LC-MS/MS
Extraction Method	Solid Phase
Sample Volume	200 µL
QC Concentrations	0.3, 0.9, 12, 150, and 240 ng/mL
Standard Curve Concentrations	0.3, 0.6, 3, 9, 30, 90, 270, and 300 ng/mL
Lower Limit Of Quantitation	0.3 ng/mL
Upper Limit Of Quantitation	300 ng/mL
Average Recovery of Analyte (%)	98.0
Average Recovery of Internal Standard (%)	NA <sup>a</sup>
LLOQ QC Intraday Precision Range (%CV)	7.5 to 9.1
LLOQ QC Intraday Accuracy Range (%RE)	-5.7 to 6.3
Analytical QC Intraday Precision Range (%CV)	0.9 to 8.1
Analytical QC Intraday Accuracy Range (%RE)	-5.0 to 5.4
LLOQ QC Interday Precision (%CV)	9.8
LLOQ QC Interday Accuracy (%RE)	2.3
Analytical QC Interday Precision Range (%CV)	2.1 to 6.0
Analytical QC Interday Accuracy Range (%RE)	-4.1 to 4.2
Stock Solution Stability in Methanol	Refer to COA <sup>b</sup> at -20°C 23 Hours at Room Temperature
Reinjection Reproducibility in Processed Samples	118 Hours at 4°C
Benchmark Stability in Plasma	24 Hours at Room Temperature
Freeze/Thaw Stability in Plasma	5 Cycles at -20°C 5 Cycles at -70°C
Long-term Storage Stability in Plasma	71 Days at -20°C and -70°C
Dilution Integrity	750 ng/mL diluted 20-fold
Selectivity	≤ 20.0% LLOQ for analyte; ≤ 5.0% for IS

<sup>a</sup> Not applicable since a stable isotope labeled internal standard was used. The results are expected to be similar to those of the unlabeled analyte.

<sup>b</sup> Compound received in an ampoule, see COA for expiration date and storage conditions.

**Table 9: Assay Validation Results for Chlorpheniramine**

Report Title	Validation of a Method for the Determination of Chlorpheniramine, Codeine, and Guaifenesin in Human Plasma by LC-MS/MS
Study Number	QPS 42-1202
Analyte Name	Chlorpheniramine
Internal Standard (IS)	Chlorpheniramine- <i>d</i> <sub>6</sub>
Analytical Method Type	LC-MS/MS
Extraction Method	Solid Phase
Sample Volume	200 µL
QC Concentrations	0.1, 0.3, 4, 50, and 80 ng/mL
Standard Curve Concentrations	0.1, 0.2, 1, 3, 10, 30, 90, and 100 ng/mL
Lower Limit Of Quantitation	0.1 ng/mL
Upper Limit Of Quantitation	100 ng/mL
Average Recovery of Analyte (%)	112.1
Average Recovery of Internal Standard (%)	NA <sup>a</sup>
LLOQ QC Intraday Precision Range (%CV)	7.0 to 11.3
LLOQ QC Intraday Accuracy Range (%RE)	-3.0 to 14.0
Analytical QC Intraday Precision Range (%CV)	0.5 to 5.1
Analytical QC Intraday Accuracy Range (%RE)	-6.5 to 12.2
LLOQ QC Interday Precision (%CV)	11.3
LLOQ QC Interday Accuracy (%RE)	6.0
Analytical QC Interday Precision Range (%CV)	2.1 to 5.7
Analytical QC Interday Accuracy Range (%RE)	-4.5 to 9.1
Stock Solution Stability in Methanol	162 Days at -20°C 23 Hours at Room Temperature
Reinjection Reproducibility in Processed Samples	118 Hours at 4°C
Benchtop Stability in Plasma	24 Hours at Room Temperature
Freeze/Thaw Stability in Plasma	5 Cycles at -20°C 5 Cycles at -70°C
Long-term Storage Stability in Plasma	71 Days at -20°C and -70°C
Dilution Integrity	250 ng/mL diluted 20-fold
Selectivity	≤ 20.0% LLOQ for analyte; ≤ 5.0% for IS

<sup>a</sup> Not applicable since a stable isotope labeled internal standard was used. The results are expected to be similar to those of the unlabeled analyte.

### **3 DETAILED LABELING RECOMMENDATION**

At the time of writing this review, the labeling discussion is ongoing and the reader is referred to the final approved label for the final labeling recommendations.

4 APPENDIX

4.1 OCP FILING MEMO

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

<b>Office of Clinical Pharmacology</b>				
<i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA/BLA Number	NDA 206323		Proposed Brand Name	-
OCP Division (I, II, III, IV, V)	II		Generic Name	Codeine and chlorpheniramine
Medical Division	DPARP		Drug Class	
OCP Reviewer	Sheetal Agarwal, Ph.D., RAC		Proposed Indication(s)	
OCP Team Leader	Satjit Brar, PharmD., Ph.D.		Dosage Form	40 mg codeine and 8 mg chlorpheniramine in an ER tablet formulation
Other discipline reviewers	-		Dosing Regimen	BID
Date of Submission	Aug 22, 2014		Route of Administration	Oral
Estimated Due Date of OCP Review	May 18, 2015 (primary review)		Sponsor	Nexgen (Agent) on behalf of Spriso
Medical Division Due Date	June 1, 2015 (CDTL date)		Priority Classification	S
PDUFA Due Date	June 22, 2015			
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies to be reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
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:				

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
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<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD -</b>				
Phase 2:				
Phase 3:				
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	X	3	3	2 relative BA/BE studies (single and multiple dose comparing the test ER product to immediate release reference products developed by the sponsor) and 1 bioanalytical report
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>	X	1	1	Food effect assessment with ER product is incorporated into the single dose relative BA/BE study, however a separate study evaluating food effect on the reference IR product may need to be reviewed
<b>Bio-waiver request</b>				
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		4	4	

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

	Content Parameter	Yes	No	N/A	Comment
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist

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

2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			x	
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**  
YES

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist

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

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

The NDA is fileable.

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

The following comment should be conveyed to the sponsor in the 74-day filing letter:

Your food effect study (1084-12-002) indicates that presence of a high-fat, high-calorie meal leads to 28% increase in C<sub>max</sub> of codeine from your ER product. Considering the safety risks associated with codeine, the increase in systemic exposure of codeine in the presence of food, is a potential review issue. The totality of evidence will be considered in evaluating the risk-benefit profile of your product for the proposed indication and for the proposed population.

The rationale for this comment can be found below under Reviewer's notes.

### Background and regulatory history:

NDA 206-323 was submitted by Nexgen Pharma on behalf of SPRIASO who developed the product. This application is a 505(b)(2) NDA for a fixed dose combination (FDC) extended release (ER) formulation containing codeine and chlorpheniramine, 40 mg/ 8 mg. The proposed indication for the FDC is "temporary relief of cough (b) (4) common cold (b) (4) upper respiratory allergies (b) (4)

This application is a bioequivalence based program, relying on the Agency's finding of safety and/or effectiveness as codeine and chlorpheniramine, identified as having established safety and efficacy under the OTC Monograph, including in combination with one another (21 CFR 341.40(d)). The OTC doses and indications for codeine and chlorpheniramine are indicated below:

For products containing codeine ingredients identified in § 341.14(a)(2):

- Adults and children 12 years of age and over: Oral dosage is 10 to 20 milligrams every 4 to 6 hours, not to exceed 120 milligrams in 24 hours, or as directed by a doctor.
- Children 6 to under 12 years of age: Oral dosage is 5 to 10 milligrams every 4 to 6 hours, not to exceed 60 milligrams in 24 hours, or as directed by a doctor.
- Temporary relief of cough in adults and children years 12 or older, as may occur with the common cold or inhaled irritants.

For products containing chlorpheniramine maleate identified in § 341.12(c).

- Adults and children 12 years of age and over: oral dosage is 4 milligrams every 4 to 6 hours, not to exceed 24 milligrams in 24 hours, or as directed by a doctor.
- Temporary relief of runny nose, sneezing, itching of the nose or throat and itchy watery eyes due to hay fever, other upper respiratory allergies, or allergic rhinitis.

The IND for the present NDA (IND 106,992) was originally filed by Lipocine on October 14, 2009 and the sponsorship of the IND was transferred to Spriaso LLC on July 31, 2013. Lipocine held an End of Phase II meeting with the FDA on 4 October 2010. The pre-NDA meeting between SPRIASO and the Agency was held on October 10, 2013.

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

There are currently no known marketed products containing a combination of codeine and chlorpheniramine as an ER formulation. Two similar products though, have been approved in the past:

- Fisons Corporation previously marketed Pentuss (NDA 18-928, approved on 08/14/1985 based on DARRTS) containing 10 mg/5 mL of codeine and 4 mg/5 mL of chlorpheniramine. It was, however, withdrawn from the market in 1996 for reasons unrelated to safety or efficacy (did not find a memo in DARRTS).
- Celltech Pharmaceuticals received approval for Codeprex Pennkinetic ER Suspension (NDA 21-369 approved on 06/21/2004), containing codeine polistirex and chlorpheniramine polistirex equivalent to 20 mg codeine and 4 mg chlorpheniramine maleate respectively in each 5 mL of product. Codeprex, although approved, was never marketed in the US and the sponsor eventually withdrew the NDA for reasons unrelated to safety and efficacy (memo in DARRTS dated 03/20/2007).

### Reviewer's notes:

The sponsor used the Codeprex NDA as a model NDA for their product which was deemed acceptable by the Agency as noted from the pre-NDA meeting minutes for this product. Codeprex NDA included 3 assessments, single and multiple dose relative BA assessments of the test ER product vs. reference IR products as well as a food effect assessment. As such, the sponsor also included these 3 assessments in their NDA; no dedicated clinical safety/efficacy studies were conducted.

Codeprex NDA was approved in its second cycle based on the results that the ER formulation components had similar AUC values as compared to the reference IR products in both single and multiple dose relative BA/BE studies as well as there was no significant food effect on the ER formulation (Clinical Pharmacology review dated 6/17/2004). In the case of Spriaso's ER product, the AUC values for codeine and chlorpheniramine seem similar to those from the reference IR products, however, the C<sub>max</sub> of codeine was observed to be 28% higher in the presence of food as compared to the C<sub>max</sub> under fasted conditions. The OTC monograph for codeine (immediate-release) for the cough indication indicates that codeine products can be taken without regard to meals, indicating that presence of food is not expected to significantly alter codeine PK. As such, altered PK parameters in the presence of food with the sponsor's ER product, present a review issue considering the safety risks associated with the drug, codeine. The sponsor argues that this increase in presence of food is not clinically relevant due to the following reasons:

1. The maximum dose of codeine administration possible based on the recommendation in the OTC monograph for an IR product is higher than the dose of the sponsor's product (designated LPCN1084) as shown in the table below:

Drug	OTC Dose <sup>1</sup>	Min. Possible Dose Every 12 Hours	Max. Possible Dose Every 12 Hours	Selected LPCN 1084 IR and ER Dose
Codeine	10 to 20 mg every 4 to 6 hours – not to exceed 120 mg in 24 hours	20 mg	60 mg	40 mg
Chlorpheniramine	4 mg every 4 to 6 hours – not to exceed 24 mg in 24 hours	8 mg	12 mg	8 mg

<sup>1</sup> OTC Monograph dose recommended for adults and children >12 years of age.

As such, the sponsor argues that the C<sub>max</sub> increase (28%) in the presence of food with their ER product containing 40 mg codeine, would be lower than the possible C<sub>max</sub> with highest recommended dose of codeine under the OTC monograph (60 mg).

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist

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

2. A BE analyses conducted comparing sponsor's ER product under fed conditions with reference IR under fasted conditions indicates that C<sub>max</sub> and AUC values of the sponsor's product under fed conditions are similar to those of the reference IR product under fasted conditions.

This reviewer sent an information request to the sponsor (dated 9/12/2014 in DARRTS) asking them to submit PK simulations using observed or predicted PK data with codeine IR products supporting their point 1. In addition, a second information request was sent out (dated 10/20/2014 in DARRTS) as a follow-up to the first information request as well as requesting additional BE analyses using different PK parameters compared to what the sponsor employed in their original BE analyses. The response to the second information request is expected by 11/07/2014.

Besides the impact of the observed food effect, there is no other potential review issue that has been identified by this reviewer, so far. The sponsor has submitted 2 pilot studies, 2 relative BA/BE studies (including food effect assessment in the single dose relative BA/BE study), as well as bioanalytical validation reports. One of the pilot studies includes food effect assessment on the reference IR product, which may be reviewed if pertinent to review decision for the sponsor's ER product. One point to note is that the reference IR products (codeine IR tablets and chlorpheniramine IR tablets) were manufactured by the sponsor for use in their studies, and are for investigative purposes only, this was discussed during the pre-NDA meetings and was deemed acceptable.

### Administrative notes:

A study inspection request will be made for the multiple-dose relative BA/BE study LPCN 1084-13-001, titled "An Open-Label, Randomized, Multiple-Dose, 2-Way Crossover Comparative Bioavailability Study of Codeine Phosphate/Chlorpheniramine Maleate Extended-Release Tablet with Immediate-Release Tablet in Healthy Subjects."

An agreed upon pediatric study plan (PSP) was not submitted at the time of NDA submission, this is being worked upon by the sponsor and the clinical team. An iPSP was discussed with the Agency (letter in DARRTS dated 07/05/2014).

In addition, it is to be noted that a second NDA 207-768 (submitted on 06/30/2014, about 2 months before Spriso's NDA was submitted) that is also seeking marketing approval of a FDC ER product (oral suspension) containing 40 mg codeine and 8 mg chlorpheniramine (Sponsor: Tris Pharma) is also under review by the same division.

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist

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/s/  
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SHEETAL S AGARWAL  
03/04/2015

SATJIT S BRAR  
03/05/2015

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

**Office of Clinical Pharmacology**

*New Drug Application Filing and Review Form*

General Information About the Submission

	Information		Information
NDA/BLA Number	NDA 206323	Proposed Brand Name	-
OCP Division (I, II, III, IV, V)	II	Generic Name	Codeine and chlorpheniramine
Medical Division	DPARP	Drug Class	
OCP Reviewer	Sheetal Agarwal, Ph.D., RAC	Proposed Indication(s)	
OCP Team Leader	Satjit Brar, PharmD., Ph.D.	Dosage Form	40 mg codeine and 8 mg chlorpheniramine in an ER tablet formulation
Other discipline reviewers	-	Dosing Regimen	BID
Date of Submission	Aug 22, 2014	Route of Administration	Oral
Estimated Due Date of OCP Review	May 18, 2015 (primary review)	Sponsor	Nexgen (Agent) on behalf of Spriaso
Medical Division Due Date	June 1, 2015 (CDTL date)	Priority Classification	S
PDUFA Due Date	June 22, 2015		

*Clin. Pharm. and Biopharm. Information*

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

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SHEETAL S AGARWAL  
10/21/2014

SATJIT S BRAR  
10/21/2014