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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

505(b)(2) New Drug Application Clarification Memo

NDA 206323 Codeine Phosphate and Chlorpheniramine Extended Release Tablets

Nexgen/Spriaso LLC

This submission by the Nexgen/Spriaso LLC submitted August 22, 2014, is a 505(b)(2) New Drug Application (NDA 206323) for a fixed dose combination (FDC) extended release (ER) formulation containing codeine and chlorpheniramine. The Applicant bridged to FDA's safety and efficacy findings from two sources: 1) the basis of approval for reference product, CodeprexTM Pennkinetic® (NDA 021369) which was establishment of bioequivalence to immediate release codeine and chlorpheniramine; and 2) OTC monographs for codeine phosphate 21 CFR 341.14(a)(2)(ii) and chlorpheniramine maleate in 21 CFR 341.12(c) which establish what is considered safe and effective doses for the immediate release codeine and chlorpheniramine products.

The Applicant submitted studies that established bioequivalence to each component of the codeine/chlorpheniramine ER combination tablet to each of their respective reference drugs in a clinical pharmacology program that was the same as that used as the basis for approval that established the safety and efficacy of CodeprexTM. As no ER codeine and chlorpheniramine combination products were marketed in the US at the time of this NDA submission, the relative bioequivalence assessments were conducted using a codeine and chlorpheniramine combination immediate tablet manufactured by the Applicant as the reference product. This is considered acceptable for an immediate release product covered by the monograph.

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/s/

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CLINICAL REVIEW

Application Type	NDA
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Reviewer Name(s)	Xu Wang, M.D., Ph.D.
Review Completion Date	04/30/2015
Established Name	Codeine and chlorpheniramine
(Proposed) Trade Name	Codeine Phosphate and Chlorpheniramine Maleate ER Tablets
Therapeutic Class	Antitussive/antihistamine
Applicant	Nexgen Pharma on behalf of Spriaso LLC
Formulation(s)	Oral extended release tablet
Dosing Regimen	Codeine 40 mg/chlorpheniramine maleate 8 mg, 1 tablet every 12 hours, not to exceed 2 tablets in 24 hours
Indication(s)	Relief of cough and symptoms associated with upper respiratory allergies or a common cold
Intended Population(s)	Adults (b) (4)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends an “Approval” action for codeine phosphate and chlorpheniramine maleate extended release (ER) tablets. The development program for the proposed drug is a clinical pharmacology program. The proposed drug depends on the bioequivalence (BE) to the monograph drug codeine and chlorpheniramine maleate to support its efficacy and safety. No clinical efficacy and safety studies were conducted to support this application. The clinical pharmacology studies demonstrated that the BE between the proposed drug codeine phosphate and chlorpheniramine maleate ER tablets and the reference drug, codeine phosphate and chlorpheniramine maleate immediate release (IR) tablets, with a similar systemic exposures (AUC within BE limits of 80-125%) of codeine and chlorpheniramine maleate between the proposed drug and the reference drug. As expected for an ER formulation, C_{max} values for both codeine and chlorpheniramine were slightly lower from the ER tablets as compared to the IR tablets.

Codeine phosphate and chlorpheniramine maleate ER tablets contains 54.3 mg codeine phosphate equivalent to 40 mg of free codeine base and 8 mg of chlorpheniramine maleate per tablet. It is proposed as a fixed dose combination drug containing an antitussive and antihistamine. The indication is “relief of cough and symptoms associated with upper respiratory allergies or a common cold”. The proposed dose regimen is one tablet every 12 hours, not to exceed 2 tablets in 24 hours.

It is noted that the Applicant is seeking approval for patients (b) (4)
The clinical pharmacology studies submitted in the application were conducted in subjects 18 years of age and older. The OTC monograph specifies that IR codeine and chlorpheniramine maleate can be used as an antitussive and antihistamine in pediatric patients 6 years of age and older [21 CFR 341.72, 241.74]. However, there are safety concerns for use of a long acting narcotic drug in children. There is no information regarding the exposure and safety of the proposed ER formulation in pediatric population. The recommendation is to approve the proposed drug for adults only, i.e., 18 years and up, and, as this is a new dosing presentation that triggers PREA, to require the Applicant to conduct PK and safety studies to assess the adequate dosage and safety profile of the proposed ER formulation in pediatric patients 6-17 years of age.

1.2 Risk Benefit Assessment

The overall risk benefit assessment supports codeine phosphate and chlorpheniramine maleate ER tablets for the indication of the relief of cough and symptoms associated with upper respiratory allergies or a common cold for patients 18 years of age and older.

This NDA is a 505(b)(2) application, and depending on the BE to the monograph drug codeine and chlorpheniramine maleate to support its efficacy and safety. No separate efficacy and safety studies were performed. The BE studies submitted in the NDA and the OTC monograph for codeine and chlorpheniramine all support the efficacy and safety of the proposed drug.

The 2 clinical pharmacology studies demonstrated that the BE between the proposed drug and the reference drug, IR codeine phosphate and chlorpheniramine maleate tablets, with a similar systemic exposures (AUC within the BE limits of 80-125%) of codeine and chlorpheniramine maleate. There were no unexpected adverse events occurred in the clinical pharmacology studies. There were no deaths and no serious adverse events. Dizziness, headache, and somnolence were the common adverse events. The data did not identify a new safety signal. With regard to the reported risk of respiratory depression and death associated with the use of codeine in children of ultra-rapid metabolizers of codeine, the proposed labeling reflects the important safety considerations in the a boxed warning and in the “Warnings and Precautions” section of the products’ full prescribing information.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The clinical review recommends no additional postmarketing risk evaluation and mitigation strategies at this time. If a signal of abuse, misuse, overdose and addiction is identified, further abuse liability assessment may need to be conducted.

1.4 Recommendations for Postmarket Requirements and Commitments

The clinical pharmacology studies to support this NDA were conducted in subjects 18 years of age and older. The intended patient population for the proposed drug is (b) (4). There is no information regarding the exposure and safety of the proposed ER formulation in pediatric population. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. The Applicant requested a waiver for pediatric studies below (b) (4) of age. In the negotiation for an initial pediatric study plan (iPSP), the Agency agreed to waive the pediatric studies in patients less than 6 years of age because opioids are contraindicated in children less than 6 years of age due to the risk of fatal respiratory depression. Although the OTC monograph specifies that IR codeine and chlorpheniramine can be used as an antitussive and antihistamine in pediatric patients 6 years of age and older, there are safety concerns for use of a long acting narcotic drug in children. With the recommendation from the Agency’s Pediatric Research Committee (PeRC) the Division required the Applicant to conduct

a PK study (b)(4) study in pediatric patients 6 to 17 years of age to evaluate the adequate dosage and the safety of the proposed drug in pediatric population.

2 Introduction and Regulatory Background

2.1 Product Information

The Applicant has developed an extended release tablet formulation of codeine phosphate and chlorpheniramine maleate. As a basis for the 505(b)(2) submission route, the Applicant cited monograph for codeine and chlorpheniramine to support the safety and efficacy of the proposed drug product.

Immediate release codeine phosphate is considered to be generally recognized as safe and effective (GRASE) as an orally active antitussive drug in the following age groups at the following oral doses [21 CFR 341.74]:

- Adults and children 12 years of age and older: 10 to 20 mg every 4 to 6 hours, not to exceed (NTE) 120 mg in 24 hours, or as directed by a doctor
- Children 6 to under 12 years of age: 5 to 10 mg every 4 to 6 hours, NTE 60 mg in 24 hours, or as directed by a doctor
- Children under 6 years of age: consult a doctor

Chlorpheniramine maleate is considered to be generally recognized as safe and effective (GRASE) as an expectorant in the following age groups at the following oral doses [21 CFR 341.72]:

- Adults and children 12 years of age and older: 4 mg every 4 to 6 hours, NTE 24 mg in 24 hours
- Children 6 to under 12 years of age: 2 mg every 4 to 6 hours, NTE 12 mg in 24 hours
- Children under 6 years of age: consult a doctor

The monograph considers the combination of any single monograph oral antitussive drug (such as codeine phosphate) with any single antihistamine (such as chlorpheniramine) to be a permitted combination [21 CFR 341.40(f)]. However, as an extended release formulation, a NDA approval is required for the proposed drug.

2.2 Tables of Currently Available Treatments for Proposed Indications

For the proposed indication, multiple cold and cough products are currently available, both prescribed and OTC. Based on the OTC monograph 21 CFR 341, the following ingredients are approved for this indication, and 21 CFR 341.40 permits various combinations of the listed active ingredients. Table 1 lists the active ingredients described in 21 CFR 341 for antihistamine and antitussive drugs. 21 CFR 341.40 permits various combinations of the listed active ingredients.

Table 1. 21 CFR 341 Antihistamine and Antitussive Drugs for OTC Human Use

CFR 341.12 Antihistamine	<ul style="list-style-type: none"> (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
CFR 341.12 Antitussive	<ul style="list-style-type: none"> (a) Oral antitussives <ul style="list-style-type: none"> (1) Chlophedianol hydrochloride (2) Codeine ingredients <ul style="list-style-type: none"> (i) Codeine (ii) Codeine phosphate (iii) Codeine sulfate (3) Dexamethorphan (4) Dextromehorphan hydrobromide (5) Diphenhydramine citrate (6) Diphenhydramine hydrochloride (b) Topical antitussives <ul style="list-style-type: none"> (1) Camphor (2) Menthol

In the past 3 decades, two extended-release combination drugs containing codeine and chlorpheniramine maleate have been approved in the US. (1) Pentuss (NDA 018928, approved on 08/14/1985) contained codeine 10mg and 4mg chlorpheniramine maleate per 5mL. Pentuss was withdrawn from the market in 1996 for reasons unrelated to safety or efficacy. (2) Codeprex™ Pennkinetic® (NDA 021369) contained codeine 20mg and 4mg chlorpheniramine maleate per 5mL. Codeprex was never marketed in the US, and eventually the NDA was withdrawn for reasons unrelated to safety and efficacy (memo dated 03/20/2007). Recently, the FDA approved a codeine polistirex and chlorpheniramine polistirex extended release oral suspension (TUZISTRA XR NDA 207-768, approved 4/30/2015).

2.3 Availability of Proposed Active Ingredient in the United States

Codeine is currently approved in the United States in syrup as an antitussive in combination with bromodiphenhydramine (NDA 88-626), with promethazine (NDA 88-763, NDA 40-451, NDA 40-650, NDA 88-875, NDA 89647), with promethazine and phenylephrine (NDA 40-660), with pseudoephedrine and triprolidine (NDA 88-704, NDA 88-833), and in an extended release suspension in combination with chlorpheniramine

(NDA 21-369). In addition, codeine is approved in the United States in tablet and capsule formulations as analgesic medications at higher doses than antitussives.

Chlorpheniramine is available as a non-prescription monograph drug, being considered to be generally recognized as safe and effective (GRASE) at the OTC monograph dose for the temporary relief of allergy symptoms. A large number of antihistamines (both over the counter and prescription) are available on the market. Examples include diphenhydramine, loratadine, desloratadine, and fexofenadine. Also antihistamines are available as combination products with a variety of cough and cold preparations.

2.4 Important Safety Issues with Consideration to Related Drugs

Both codeine and chlorpheniramine have a long history for human use, and there are numerous publicly available nonclinical and clinical study reports regarding the 2 drugs. Therefore, the safety of codeine and chlorpheniramine has been well established.

Respiratory depression is a particular concern when codeine is used as an analgesic after tonsillectomy and/or adenoidectomy. This safety concern arose from deaths that occurred in children who were post-operative from tonsillectomy and/or adenoidectomy and who were ultra-rapid metabolizers of codeine. As of February 2013, the Agency added a boxed warning for the use of codeine in this setting. In addition, codeine is an opioid that has the potential for abuse. Dependence and tolerance may develop upon repeated administration. The proposed drug codeine phosphate and chlorpheniramine maleate ER tablets is a controlled substance under Schedule II of the Controlled Substance Act. The labeling will reflect the risk of overdose and drug abuse potential.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

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.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Office of Scientific Investigation (OSI) inspection was requested for multiple dose steady state relative bioavailability study (Study LPCN 1084-13-001) by the clinical pharmacology review team. The clinical site and analytical sites were QPS Bio-Kinetic,

Springfield, MO and (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.

3.2 Compliance with Good Clinical Practices

The two pivotal clinical pharmacology studies in this application were conducted in accordance with Good Clinical Practices. The applicant certified that they did not use and would not use in any capacity the services of any person debarred under to Section 306(a) and 306(b) of the Federal Food, Drug, and Cosmetic Act in connection with their application. [Module 1, Volume 1.1, Section 1.3.3, page 1]

3.3 Financial Disclosures

The Applicant's compliance with the Final Rule on Financial Disclosure by Clinical Investigators is attested in Module 1.3.4 of this NDA application. The Applicant certifies that it did not enter into financial arrangements with any investigator whereby the value of compensation could be affected by the outcome of the study as defined in 21 CFR 54.2(a), that no investigator received significant payments as defined in 21 CFR 54.2(f), that none of the investigators disclosed a proprietary interest in the product (Category 3), or possessed a significant equity interest in the Applicant as defined in 21 CFR 54.2(b). [Module 1, Volume 1.1, Section 1.3.4, pages 1-2]

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Codeine and chlorpheniramine maleate extended-release tablet is a white to off-white (b) (4) uncoated, standard round extended release matrix tablet. Each extended release tablet of codeine and chlorpheniramine maleate contains codeine phosphate 54.3 mg (equivalent to 40 mg of free base) and chlorpheniramine maleate 8 mg. The active ingredients and all excipients of the proposed drug product are listed in Table 2 below.

Table 2: Composition of Proposed Codeine-Chlorpheniramine ER Tablets

Ingredient	Function	mg/tablet	% w/w
Codeine Phosphate, USP ¹	Active	54.30	(b) (4)
Chlorpheniramine Maleate, USP	Active	8.00	(b) (4)
Magnesium Stearate, NF (b) (4)			(b) (4)
Colloidal Silicon Dioxide, (b) (4)			(b) (4)
(b) (4) Lactose Monohydrate (b) (4)			(b) (4)
Hypromellose (b) (4)			(b) (4)

	(b) (4)		
Lactose Monohydrate, NF			
Microcrystalline Cellulose, (b) (4) NF			
Magnesium Stearate, NF (b) (4)			
Colloidal Silicon Dioxide, NF (b) (4)			
Total Weight		200.00	100.00

¹ 54.30 mg of Codeine Phosphate, USP is equivalent to 40.0 mg of Codeine

Source: Quality Overall Summary 2.2. Drug Product, Page 1.

Codeine phosphate USP used in the test formulation is manufactured by (b) (4)
 Chlorpheniramine Maleate
 USP used in the test formulation is manufactured by (b) (4)

A detailed review of the CMC portion of the application may be found in Dr. Yong Hu's ONDQA review.

4.2 Clinical Microbiology

It is not expected to have a microbiological attribute for the proposed drug as a solid tablet dosage form. The Applicant performed a USP <61> microbiological enumeration evaluation with samples from three submission batches. All three lots showed no detected CFUs for total aerobes or for yeast and mold. [Quality Overall Summary 2.3.p.5 Drug Product, Page 44.]

4.3 Preclinical Pharmacology/Toxicology

Chlorpheniramine is considered to be GRASE as an antihistamine drug (21 CFR 341.72) and codeine phosphate is considered to be GRASE as an orally active antitussive drug (21 CFR 341.74) in the daily dosage in this application. No new non-clinical toxicology studies were required or performed for this application.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Codeine is a semisynthetic narcotic antitussive and analgesic with multiple actions qualitatively similar to those of morphine. The precise mechanism of action of codeine and other opiates is not known; however, codeine is believed to act centrally on the cough center. In excessive doses, codeine will depress respiration. Codeine can produce miosis, euphoria, and physical and physiological dependence.

Chlorpheniramine is a propylamine derivative antihistamine drug (H₁ receptor antagonist) that also possesses anticholinergic and sedative activity. It prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa.

4.4.2 Pharmacodynamics

No PD studies were performed.

4.4.3 Pharmacokinetics

This is a clinical pharmacology program. The proposed drug is supported by comparison of the bioavailability and bioequivalence of the proposed drug to that of the reference drug, the OTC monograph doses of IR codeine and chlorpheniramine tablets. The PK data from the clinical pharmacology studies is summarized in Section 5.3 of this review, and additional detail may be found in Clinical Pharmacology review by Sheetal Agarwal, Ph. D., RAC.

5 Sources of Clinical Data

The pharmacokinetics results of the 2 clinical pharmacology studies in this application were briefly reviewed and summarized in Section **Error! Reference source not found.** This review includes an abbreviated Section **Error! Reference source not found.** because the drug development program is based on clinical pharmacology studies and no new clinical studies are required to support this application, and, thus, no efficacy data are reviewed.

Safety data supporting this application are reviewed and presented in Section **Error! Reference source not found.** The Applicant's Summary of Clinical Safety (SCS) included a summary of safety information from 2 clinical pharmacology studies. The safety information from these studies included adverse event data, laboratory test and vital signs data. In addition, the Applicant searched the FDA Adverse Event Reporting System (FAERS) postmarketing adverse events database and summarized the postmarketing spontaneous adverse event reports for codeine and chlorpheniramine.

5.1 Tables of Studies/Clinical Trials

Table 3: Summary of Clinical Pharmacology Studies

Study # (Time)	Study Type	Treatment Groups	Design	Subject No.	Subject age
LPCN 1084-12-002 (Nov 04 – Nov 29, 2012)	Single Dose BA/BE & Food Effect Study	A. 1 ER Cod and CPM* Tab, fast B. 1 ER Cod and CPM Tab, fed C. 2 IR Cod and CPM Tab (1 Tab q6h), fast	Randomized, open label, 3- period, crossover	24/23#	Healthy men and women, 18-64 years old
LPCN 1084-13-001 (March 16 – April 5, 2013)	Multiple Dose BA/BE Study	A.1 ER Cod and CPM Tab, q12h for 6.5 days B. 1 IR Cod and CPM Tab, q6h for 6.5 days	Randomized, open label, 2- period, crossover	38/37#	Healthy men and women, 18-64 years old

* Codeine Phosphate and Chlorpheniramine Maleate

#Enrolled/finished

Source: Summary of Clinical Safety, pages 9-10.

5.2 Review Strategy

The pharmacokinetics results of the 2 clinical pharmacology studies in this application are briefly reviewed and summarized in Section **Error! Reference source not found..** No efficacy studies are required or performed, and, thus, no efficacy data are reviewed.

Safety data supporting this application are reviewed and presented in Section **Error! Reference source not found..** The Applicant's Summary of Clinical Safety (SCS) included a summary of safety information from 2 clinical pharmacology studies. The safety information from these studies included adverse event data, laboratory test and vital signs data. In addition, the Applicant searched the FDA Adverse Event Reporting System (FAERS) postmarketing adverse events database and summarized the postmarketing spontaneous adverse event reports for codeine and chlorpheniramine.

5.3 Discussion of Individual Studies/Clinical Trials

There are 2 pivotal clinical pharmacology studies in this submission.

Study **LPCN 1084-12-002** was a single-dose, crossover study evaluating relative BA of the ER tablet compared to the reference IR tablet and food effect on ER tablet. Twenty-four (24) healthy adult volunteers were assigned to receive the one dose ER tablet (40 mg codeine and 8 mg chlorpheniramine maleate) under fed and fasting conditions and two doses of the reference IR tablets (20 mg codeine IR tablet and 4 mg chlorpheniramine maleate) every 6 hours in a randomized sequence.

As shown in Table 4, the PK data indicated that the systemic exposures of both codeine and chlorpheniramine from the ER product to be comparable to the reference IR product. The 90% confidence intervals for the geometric mean ratio for AUC for both the components and C_{max} for chlorpheniramine with the ER product were within the 80 - 125% bioequivalence limits when compared to the IR product. The ER product yielded a slightly lower C_{max} for codeine as compared to the reference IR product. The presence of a standard high-fat, high-calorie meal had no significant effect on PK (except for C_{max}) of the codeine and chlorpheniramine ER tablet. As shown in Table 5, AUC of codeine, AUC and C_{max} of chlorpheniramine within BE limits of 80-125%. The presence of the meal led to a higher C_{max} for codeine (a fed/fasting ratio of 128% with the 95% CI of 116.45 – 140.80).

Table 4: Summary of PK Data for BA/BE, Study LPCN 1084-12-002

PK Parameter	Codeine			90% Confidence Interval
	Geometric Mean		% Ratio (B/C)	
	B(ER Fasting)	C (IR Fasting)		
AUC _{last} (ng.h/mL)	361	384	93.8	88.60 – 99.38
AUC _{inf} (ng.h/mL)	371	395	94.0	88.66 – 99.72
C _{max} (ng/mL)	44.2	52.0	85.0	77.30 – 93.49
PK Parameter	Chlorpheniramine			90% Confidence Interval
	Geometric Mean		% Ratio (B/C)	
	B(ER Fasting)	C (IR Fasting)		
AUC _{last} (ng.h/mL)	284	284	100	96.33 – 104.13
AUC _{inf} (ng.h/mL)	298	297	100	96.49 – 104.34
C _{max} (ng/mL)	8.71	9.18	94.8	88.35 – 101.80

Source: Study Report for LPCN 1084-12-002, page 66.

Table 5: Summary of PK Data for Food Effect, Study LPCN 1084-12-002

PK Parameter	Codeine			90% Confidence Interval
	Geometric Mean		% Ratio (A/B)	
	A (Fed)	B (Fasting)		
AUC _{last} (ng.h/mL)	415	361	115	108.60 – 121.82
AUC _{inf} (ng.h/mL)	421	371	113	107.08 – 120.20
C _{max} (ng/mL)	56.6	44.2	128	116.45 – 140.80
PK Parameter	Chlorpheniramine			90% Confidence Interval
	Geometric Mean		% Ratio (A/B)	
	A (Fed)	B (Fasting)		
AUC _{last} (ng.h/mL)	274	284	96.4	92.72 – 100.17
AUC _{inf} (ng.h/mL)	287	298	96.3	92.67 – 100.15
C _{max} (ng/mL)	9.52	8.71	109	101.93 – 117.34

Source: Study Report for LPCN 1084-12-002, page 66.

Study LPCN 1084-13-001 was an open-label, randomized, multiple-dose, 2-way crossover comparative bioavailability study during which 38 healthy adult 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. Mean and statistical analysis of the PK parameters for codeine and chlorpheniramine are shown in Table 6 below.

In this study, systemic exposures 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 for both the components and C_{max} for chlorpheniramine with the ER product were within the 80 - 125% bioequivalence limits when compared to the IR product. As that in the single dose PK study, the ER product yielded a slightly lower C_{max} value for codeine as compared to the reference IR product.

Table 6: Summary of Steady State PK Data, Study LPCN 1084-13-001

PK Parameter	Geometric Mean		% Ratio (A/B)	90% Confidence Interval
	Treatment A	Treatment B		
Codeine				
C _{max} (ng/mL)	71.5	84.2	85.0	78.91 – 91.46
AUC ₁₂ (ng.h/mL)	487	523	93.1	89.42 – 97.03
Chlorpheniramine				
C _{max} (ng/mL)	36.9	35.2	105	100.39 - 109.33
AUC ₁₂ (ng.h/mL)	382	376	102	97.46 – 105.78

Treatment A: one (1) codeine 40 mg (as codeine phosphate)/chlorpheniramine maleate 8 mg extended-release tablet 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 four times a day, 6 hours apart, for 6.5 days.

Source: Study Report for LPCN 1084-13-001, page 76.

Reviewer's comments:

Detailed PK data analysis can be found in Clinical Pharmacology review by Sheetal Agarwal, Ph.D., RAC. It is noted that C_{max} for codeine with the ER product was slightly lower as compared to the reference IR product in both single dose and multiple dose BE studies. As commented in Dr. Sheetal Agarwal' review, it is expected for ER formulations to have lower C_{max} than that of IR formulations because ER formulation is typically designed to reduce the sharp peak observed with IR formulations.

In the food effect study, the presence of the meal led to a higher C_{max} for codeine (a fed/fasting ratio of 128% with the 95% CI of 116.45 – 140.80). The significant food effect on codeine exposure could potentially be a safety concern. The OTC monograph specifies that as an antitussive, the oral dosage for codeine in adults and children 12 years of age and over is 10 to 20 mg every 4-6 hours, NTE 120 mg in 24 hours. The dose regimen for the proposed drug is 1 tablet, containing 40 mg of codeine and 8 mg of chlorpheniramine maleate, NTE 2 tablets (80 mg of codeine and 16 mg of chlorpheniramine maleate) in 24 hours. Thus, even at the high margin of 40% higher

exposure of codeine with food, the patients would still be under the safe level of codeine exposure as specified in the OTC monograph. Therefore, the food effect on the codeine exposure for the proposed drug is not clinically important given the proposed dose regimen. In addition, Dr. Sheetal Agarwal's review has shown that the codeine PK from the ER tablet in fed conditions is similar to that of the IR tablet in fasting conditions. As such, the clinical pharmacology reviewer concluded that the effect of food on the ER tablet is not considered relevant from the clinical pharmacology perspective.

6 Review of Efficacy

Efficacy Summary

This application is supported by comparison of the bioavailability and bioequivalence of the proposed drug product to that of the reference drug, the OTC monograph doses of IR codeine and chlorpheniramine tablets. No clinical efficacy studies were required to support this application.

A summary of the clinical pharmacology data supporting this application is found in Section 5.3 of this review, and additional detail may be found in Clinical Pharmacology review by Sheetal Agarwal, Ph. D., RAC.

6.1 Indication

The indication for the proposed drug product is "Relief of cough and symptoms associated with upper respiratory allergies or a common cold". The proposed dose regimen is one tablet every 12 hours, not to exceed 2 tablets in 24 hours.

6.1.1 Methods

Not Applicable

6.1.2 Demographics

Not Applicable

6.1.3 Subject Disposition

Not Applicable

6.1.4 Analysis of Primary Endpoint(s)

Not Applicable

6.1.5 Analysis of Secondary Endpoints(s)

Not Applicable

6.1.6 Other Endpoints

Not Applicable

6.1.7 Subpopulations

Not Applicable

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not Applicable

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not Applicable

6.1.10 Additional Efficacy Issues/Analyses

Not Applicable

7 Review of Safety

Safety Summary

The Applicant's Summary of Clinical Safety (SCS) consisted of a summary of safety information from 2 clinical pharmacology studies, postmarketing spontaneous adverse events report, and a literature survey. The safety information from these studies included adverse event data, laboratory test and vital signs data.

The Applicant searched the FDA Adverse Event Reporting System (FAERS) postmarketing adverse events database for codeine and chlorpheniramine. The database includes unsolicited information on adverse experiences from patients and health care professionals. The reports covered all codeine and chlorpheniramine drugs' postmarketing adverse events reported to the FDA Adverse Event Reporting System (FAERS) for codeine and chlorpheniramine from July 1, 2009 to June 30, 2014. In general, the reported adverse event cases were complicated by the use of multiple drugs. The reports did not differentiate the drug was taken as analgesics or antitussive.

The Applicant performed a search of the medical literature for information relevant to safety of codeine and chlorpheniramine, and compiled 20 literature references for

information relevant to safety of codeine and chlorpheniramine in general. The literature survey revealed no new safety signals for codeine and chlorpheniramine.

The safety data from the clinical pharmacology studies in adult subjects did not identify a safety signal. The adverse event data from the clinical pharmacology studies in adult subjects did not suggest an association of adverse events and gender or race/ethnicity. Postmarketing adverse events were consistent with those previously reported for codeine and chlorpheniramine. Given the extensive exposure to codeine and chlorpheniramine, postmarketing adverse events did not raise new concerns regarding a safety signal. The applicant's search of the medical literature for safety information related to codeine and chlorpheniramine identified no new safety signal for adverse events. The safety update revealed no new safety signals.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

As already noted in Section 5.2, the 2 pivotal bioavailability studies are used for the safety evaluation,.

7.1.2 Categorization of Adverse Events

All adverse events (AEs) were recorded by subjects in the patient record. Subjects were continuously monitored for general well-being and adverse events in the clinical pharmacology studies. Subjects were instructed to inform the study physician and/or research personnel of any AEs that occurred at any time during the study. The adverse events and information concerning the onset, duration, severity, action taken, and the relationship to treatment medication were collected and recorded on the Case Report Form (CRF). The adverse events were collected and recorded in primary system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 12.0.

With the medical judgment of a physician, a serious adverse event (SAE) is any adverse event occurring that results in any of the following outcomes:

- Death
- Life-threatening AE (i.e., one that places the subject, in the view of the initial reporter, at immediate risk of death from the AE as it occurs)
- Persistent or significant disability/incapacity
- Requires in-patient hospitalization (i.e., admission), or prolongs hospitalization
- Congenital anomaly or birth defect

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

As the two pivotal BA studies have different study designs, safety data were not pooled.

7.2 Adequacy of Safety Assessments

The number of subject exposure is limited in the pharmacology studies, and there were no new safety signals for codeine and chlorpheniramine. The efficacy and safety of the proposed drug product are supported by the OTC monograph for codeine and chlorpheniramine maleate. Given the extensive experience with use of codeine as an antitussive and chlorpheniramine as an antihistamine, this reviewer concludes that the overall patient exposure and safety assessment of the proposed drug is adequate.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 62 subjects were exposed to investigational drug, Codeine Phosphate and Chlorpheniramine Maleate ER Tablet (40 mg of free codeine base and 8 mg of chlorpheniramine maleate per tablet), in 2 clinical pharmacology studies in adult subjects. The study subjects were exposed from a single dose to multiple doses for 6.5 days. Twenty-four subjects exposed to a single dose in Study LPCN 1084-12-002 and 38 subjects exposed to multiple doses for 6.5 days in Study LPCN 1084-13-001.

Table 7 summarizes the demographics of the subjects in the 2 clinical pharmacology studies. The majority of the subjects are white and young. Study LPCN 1084-13-001 has more male subjects (71.1%) than Study LPCN 1084-12-002 (41.7% male subjects).

Table 7: Demographics of subjects in 2 Clinical Pharmacology Studies

Demographic characteristic	LPCN 1084-12-002 (N=24)		LPCN 1084-13-001 (N=38)	
	n	(%)	n	(%)
Gender				
Female	14	(58.3)	11	(28.9)
Male	10	(41.7)	27	(71.1)
Race				
White	19	(79.2)	32	(84.2)
Non-White or unknown	5	(20.8)	6	(15.8)
Age, years				
Mean ± SD	27.7 ± 7.1		29.6 ± 8.1	
Range	18 - 64		18 - 64	

Source: Summary of Clinical Safety, page 13.

7.2.2 Explorations for Dose Response

There was no exploration for dose response. This is reasonable as the dose is based on the monograph.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing was performed in this NDA program.

7.2.4 Routine Clinical Testing

Routine clinical tests (hematology, clinical chemistry and urinalysis) were only conducted at screening in the clinical pharmacology studies. These tests were not safety endpoints of the Applicant's clinical pharmacology studies and findings were not relevant to the safety profile of the proposed drug.

Routine vital sign assessments were conducted before and during the administration of treatment drugs in clinical pharmacology studies. No clinically significant changes from baseline data were noted.

7.2.5 Metabolic, Clearance, and Interaction Workup

No specific metabolic, clearance, or interaction studies were performed in this NDA program.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not conducted.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in the 2 clinical pharmacology studies.

The Applicant provided an analysis of adverse events from postmarketing adverse events reported to the FDA Adverse Event Reporting System (FAERS) for codeine and chlorpheniramine from July 1, 2009 to June 30, 2014.

In searching FAERS database for codeine from July 1, 2009 to June 30, 2014, there were 4,838 adverse event reports with 1,427 deaths (29.5%). In general, the reported adverse event cases were complicated by the use of multiple drugs. The reports did not differentiate the drug was taken as analgesics or antitussive. Also the death reports

reflected a large fraction of suicide (323 completed cases, 7% of all reported adverse events). Because codeine may be used in symptomatic treatment for many end stage diseases, without the knowledge of dosage forms, diseases, co-administered medications, a simple search of FAERS, a spontaneous post-marketing adverse event reporting database, does not provide meaningful safety information for codeine as an antitussive drug. Also in searching FAERS database for chlorpheniramine from July 1, 2009 to June 30, 2014, there were 1,927 adverse event reports with 60 deaths (3.1%). Again, without the knowledge of dosage forms, diseases, co-administered medications, a simple search of FAERS, a spontaneous post-marketing adverse event reporting database, did not provide meaningful safety information for chlorpheniramine.

7.3.2 Nonfatal Serious Adverse Events

There were no serious adverse events (SAEs) reported in the 2 clinical pharmacology studies.

In searching FAERS database for codeine from July 1, 2009 to June 30, 2014, there were 4,838 adverse event reports with 927 hospitalizations (19.2%). In general, the reported adverse event cases were complicated by the use of multiple drugs. The reports did not differentiate the drug was taken as analgesics or antitussive. Because codeine may be used in symptomatic treatment for many end stage diseases, without the knowledge of dosage forms, diseases, co-administered medications, a simple search of FAERS, a spontaneous post-marketing adverse event reporting database, does not provide meaningful safety information for codeine as an antitussive drug. Also in searching FAERS database for chlorpheniramine from July 1, 2009 to June 30, 2014, there were 1,927 adverse event reports with 122 hospitalizations (6.3%). Again, without the knowledge of dosage forms, diseases, co-administered medications, a simple search of FAERS, a spontaneous post-marketing adverse event reporting database, does not provide meaningful safety information for chlorpheniramine.

7.3.3 Dropouts and/or Discontinuations

There were two dropouts from the clinical pharmacology studies. In Study LPCN 1084-12-002, one subject dropped early from the study during the first period due to refusing to follow the study protocol to finish the meal for the food effect study. In Study LPCN 1084-13-001 one subject was dropped early from the study due to increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) during the Treatment B (taking the reference IR codeine phosphate)/chlorpheniramine maleate tablets).

Reviewer's comment:

These data did not present a safety signal.

7.3.4 Significant Adverse Events

There were no significant adverse events reported in the clinical pharmacology studies.

7.3.5 Submission Specific Primary Safety Concerns

There are no submission specific primary safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse events reported in the clinical pharmacology studies are summarized in Table 8. Dizziness, headache, and somnolence were the most frequent adverse events in the multiple dose study. There were no significant differences in adverse events profile between the proposed ER tablets and the reference IR tablets. The adverse events did not suggest new safety signals.

Table 6: Adverse Events Reported in 2 Clinical Pharmacology Studies

Adverse event	Study LPCN 1048-12-001 (N=24)			Study LPCN 1084-13-001 (N=38)	
	Treatment A n (%)	Treatment B n (%)	Treatment C n (%)	Treatment A n (%)	Treatment B n (%)
Subjects with any AE	6 (25)	6 (25)	5 (21)	16 (42)	19 (50)
Dizziness	0	1 (4.2)	0	1 (2.6)	7 (18.9)
Headache	0	2 (8.3)	4 (17.4)	5 (13.2)	6 (16.2)
paraesthesia	0	0	0	2 (5.3)	1 (2.7)
Somnolence	3 (13.0)	1 (4.2)	0	3 (7.9)	6 (16.2)
Abnormal dreams	0	0	0	2 (5.3)	1 (2.7)
Cough	1 (4.3)	0	0	0	1 (2.7)
Dry throat	0	0	0	0	1 (2.7)
Hiccups	0	0	0	0	1 (2.7)
Nasal congestion	2 (8.7)	0	0	0	0
Oropharyngeal pain	0	0	1 (4.3)	0	2 (5.4)
Rhinorrhea	0	0	0	0	1 (2.7)
Sinus congestion	0	0	0	1 (2.6)	0
Abdominal pain	0	0	0	0	2 (5.4)
Constipation	0	0	0	1 (2.6)	5 (13.5)
Dry mouth	0	0	0	1 (2.6)	0
Gingival pain	0	0	0	1 (2.6)	0
Mouth ulceration	0	0	0	0	1 (2.7)
Nausea	0	3 (12.5)	1 (4.3)	1 (2.6)	3 (8.1)
Toothache	0	0	0	1 (2.6)	0
Arthralgia	0	0	0	1 (2.6)	2 (5.4)
Back pain	0	0	0	1 (2.6)	0
Joint stiffness	0	0	0	0	1 (2.7)
Muscle spasm	0	0	0	0	2 (5.4)
Muscle weakness	0	0	0	0	1 (2.7)
Musculoskeletal pain	0	0	0	1 (2.6)	0
Erythema	0	0	1 (4.3)	0	0
Cold sweat	0	0	0	0	1 (2.7)
Hyperhidrosis	0	0	0	0	2 (5.4)

Rash	1 (4.3)	0	0	0	0
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Study LPCN 1084-12-002: Treatment A - 1 codeine 40 mg (as codeine phosphate)/ chlorpheniramine maleate 8 mg ER tablet, fed; Treatment B - 1 codeine 40 mg (as codeine phosphate)/ chlorpheniramine maleate 8 mg ER tablet, fasting; Treatment C - 2 codeine 20 mg (as codeine phosphate)/ chlorpheniramine maleate 4 mg IR tablet, 1 tablet q6h.

Study LPCN 1084-13-001: Treatment A - 1 codeine 40 mg (as codeine phosphate)/ chlorpheniramine maleate 8 mg ER tablet two times a day, 12 hours apart, for 6.5 days; Treatment B - 1 codeine 20 mg (as codeine phosphate)/chlorpheniramine maleate 4 mg IR tablet four times a day, q6h for 6.5 days.

Source: Summary of Clinical Safety, pages 15-17.

7.4.2 Laboratory Findings

Laboratory examinations (hematology, clinical chemistry and urinalysis) were only conducted at screening in the clinical pharmacology studies. Laboratory tests were not safety endpoints of the Applicant's clinical pharmacology studies and findings were not relevant to the safety profile of the product.

7.4.3 Vital Signs

Vital sign assessments were conducted before and during the administration of treatment drugs in clinical pharmacology studies. No clinically significant changes from baseline data were noted.

7.4.4 Electrocardiograms (ECGs)

ECG testing was not conducted in the 2 clinical pharmacology studies.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies or trials were performed in this NDA.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable.

7.5.2 Time Dependency for Adverse Events

Not applicable.

7.5.3 Drug-Demographic Interactions

Not applicable.

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

No specific drug-drug interaction studies were conducted for the proposed drug. The information about drug interactions is based on the reference product, the monograph, and what is known regarding the active ingredients. Use of MAO inhibitors or tricyclic antidepressants with codeine may increase the effect of either the antidepressant or codeine. Concurrent use of opioids, antihistamines, anti-psychotics, anti-anxiety agents or other CNS depressants including alcohol concomitantly with codeine may result in additive CNS depression. The Applicant's proposed labeling appropriately addressed the potential these drug-drug interactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity studies were performed with this application. The carcinogenicity data presented in the product labeling are based on nonclinical data from published literature. In 2-year animal studies, codeine showed no evidence of tumorigenicity at oral doses up to 70 and 400 mg/kg/day for rats and mice, respectively; and chlorpheniramine showed no evidence of tumorigenicity at oral doses up to 30 and 50 mg/kg/day for rats and mice, respectively.

7.6.2 Human Reproduction and Pregnancy Data

No human reproduction and pregnancy data collected in the 2 clinical pharmacological studies. The Applicant has not observed or reported adverse events associated with drug exposure during pregnancy in the postmarketing surveillance of codeine and chlorpheniramine. The Applicant's proposed labeling indicates that the product is a pregnancy category C drug for the lack of adequate and well-controlled studies in pregnant women. As with other opioids, use of codeine during labor can produce respiratory depression in the neonate.

Reviewer's comment:

On August 17, 2007, FDA published a Public Health Advisory and a Healthcare Professional Information sheet addressing the risk of morphine overdose in nursing

infants whose mothers are taking codeine and who are ultra-rapid metabolizers of codeine [<http://www.fda.gov/cder/drug/advisory/codeine.htm>, <http://www.fda.gov/cder/drug/InfoSheets/HCP/codeineHCP.htm>]. An infant death was reported recently that was due to morphine overdose due to this risk. FDA has asked manufacturers of prescription codeine-containing products to add a boxed warning regarding the death related to ultra-rapid metabolism of codeine, and to include information about the potential risks of codeine use in nursing women who are ultra-rapid metabolizers of codeine in the "Warnings and Precautions" section of the products' full prescribing information.

7.6.3 Pediatrics and Assessment of Effects on Growth

The 2 clinical pharmacology studies in this submission included no pediatric subjects. Although the OTC monograph specifies that IR codeine can be used as an antitussive in pediatric patients 6 years of age and older [21 CFR 341.74], there is no information regarding the exposure and safety of codeine in an ER formulation in pediatric patients. The Applicant submitted an initial pediatric study plan (iPSP) for this NDA on 5/11/2014,

(b) (4)

It is appropriate to partially waive the pediatric studies in patients <6 years of age because of safety concerns for the use of codeine in patients <6 years of age. For pediatric population 6 to <18 years of age, PK and safety studies are needed to assess the adequate dosage and safety of the proposed ER tablets.

An information request (IR) was sent to the Applicant on 7/4/2014, stating that the Division agreed to the request for a partial waiver for pediatric studies in patients <6 years of age. However, PK (b) (4) studies should be conducted for the proposed ER formulation in pediatric population 6 to <18 years of age. In the subsequently revised pediatric study plan the Applicant requests a partial waiver for pediatric studies in patients <6 years of age, and plans to conduct a PK study and a safety study as listed below.

- Conduct a study to assess the pharmacokinetics of each active component in proposed drug product in approximately 25 - 35 children ages 6-17 years with symptoms of the common cold. The results of this study will be used to determine the appropriate dose of the proposed drug product to evaluate in a safety study in children ages 6 -17 years.
- Conduct a study to assess the safety of the proposed drug product in approximately 400 - 450 children 6 -17 years of age with symptoms of the common cold. The dose used in this study will be based upon the results of the pharmacokinetic study in children ages 6 -17 years.

Because adult studies are completed and the proposed drug is ready for approval in adults, the intent would be for the Applicant to conduct pediatric PK and safety studies as post-market required studies (PMRs) to support pediatric use.

The proposed dose for chlorpheniramine maleate is the same as the dose in the OTC monograph. Since the proposed dose is within the doses that were declared by the Agency to be safe and effective for the OTC use, no additional PK and safety data are necessary to support the chlorpheniramine dose in pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There was no overdose experience reported in the 2 clinical pharmacological studies. The Applicant searched the FAERS postmarketing adverse events reporting database and showed that 229 cases of reported overdose (4.7% of all adverse events) associated with codeine. The data did not differentiate whether codeine was taken as antitussives or at higher dosages as analgesics. The Applicant identified no new pattern of overdose for the ingredients of the proposed drug.

Codeine is a controlled substance that is known to have certain level of abuse potential. The data collected by the Drug Abuse Warning Network (DAWN) showed that that codeine/combinations accounted for 5,836 (1.2%) of the 495,732 total drug-related ED visits in 2004. Note that the data did not differentiate the drug abuse cases from codeine as antitussive or higher doses of analgesics.

7.7 Additional Submissions / Safety Issues

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), the Applicant submitted a safety update under the NDA 206-323 on March 4, 2015. There are no new safety data included in the safety update.

8 Postmarket Experience

The proposed drug product codeine phosphate and chlorpheniramine maleate ER Tablets has not been marketed.

The Applicant provided an analysis of adverse events from postmarketing adverse events reported to the FDA Adverse Event Reporting System (FAERS) for codeine and chlorpheniramine from July 1, 2009 to June 30, 2014.

There were 4,838 cases reporting adverse events in association with the use of codeine. Of the total reports, there were 2,838 female cases (59%), 1,595 male cases (33%), and the rest were the gender not specified or unknown. The most common reports were drug hypersensitivity (1,120 cases, 23%), toxicity to various agents (510

cases, 11%), drug abuse (344 cases, 7%), completed suicide (323 cases, 7%), vomiting (269 cases, 6%), nausea (262 cases, 5%), and overdose (229 cases, 4.7%). In general, the reported adverse event cases were complicated by the use of multiple drugs. The reports did not differentiate the drug was taken as analgesics or antitussive. For chlorpheniramine there were 1,927 adverse events reported during this period. Of the total reports, there were 1,168 female cases (61%), 644 male cases (33%), and the rest were the gender not specified or unknown. The most common reports were drug ineffective (387 cases, 20%), somnolence (196 cases, 10%), drug effect decreased (180 cases, 9%), and overdose (81 cases, 4%).

The postmarketing experience did not reveal new safety signals for codeine and chlorpheniramine.

9 Appendices

9.1 Literature Review/References

The Applicant compiled 20 literature references for information relevant to safety of codeine and chlorpheniramine in general. The literature survey revealed no new safety signals for codeine and chlorpheniramine.

9.2 Labeling Recommendations

Proposed labeling was submitted in Physician's Labeling Rule (PLR) format. The labeling referenced to the labeling of Codeprex Pennkinetic ER oral suspension (NDA 21-369 approved on 06/21/2004). The negotiations of the final labeling are ongoing at the time of this review, and will be harmonized with the labeling of TUZISTRA XR (codeine polistirex and chlorpheniramine polistirex) ER oral suspension (NDA 207-768), which was recently approved on 4/30/2015.

9.3 Advisory Committee Meeting

An Advisory Committee Meeting was deemed unnecessary for this 505(b)(2) application. The two active ingredients present in this product are well known as OTC monograph drug substances, and, based on the current monograph and the Agency's prior precedent, the combination of products of these classes are acceptable for the proposed indications.

9.4 Financial Disclosure Review

Clinical Investigator Financial Disclosure Review Template

Application Number: **206323**

Submission Date(s): **August 22, 2014**

Applicant: Nexgen Pharma on behalf of Spriaso, LLC

Product: Codeine phosphate and chlorpheniramine maleate

Reviewer: Xu Wang, M.D., Ph.D.

Date of Review: January 5, 2015

Covered Clinical Study (Name and/or Number): Clinical pharmacology studies
LPCN1084-12-002 and LPCN1084-13-001

Was a list of clinical investigators provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 12		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3454): None		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study:</p> <p>Significant payments of other sorts:</p> <p>Proprietary interest in the product tested held by investigator:</p> <p>Significant equity interest held by investigator in sponsor of covered study:</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.¹ Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

¹ See [web address].

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The Applicant has submitted the financial disclosure information with the NDA. The Applicant contracted with 3 research institutes to conduct the four clinical pharmacology studies in this NDA. A list of 28 investigators from 3 institutes certified having no financial interests or arrangement with the Applicant, and the investigators were not the recipient of significant payments of other sorts as defined in 21 CER 54.2(f). [Form FDA 3454]

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

/s/

XU WANG
05/18/2015

ANTHONY G DURMOWICZ
05/18/2015

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Products (HFD-570)

APPLICATION: NDA 206-323	TRADE NAME None
APPLICANT/SPONSOR: Spriaso LLC	USAN NAME Codeine Phosphate and Chlorpheniramine Maleate ER Tablets, 40/8 mg
MEDICAL OFFICER: Xu Wang, M.D., Ph.D.	
TEAM LEADER: Anthony G. Durmowicz, M.D.	CATEGORY: Antitussive/antihistamine
REVIEW DATE: 10/26/2014	ROUTE: Oral

SUBMISSIONS REVIEWED IN THIS DOCUMENT

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
08/22/2014	08/22/2014	NDA 206-323	NDA

RELATED APPLICATIONS

<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>
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REVIEW SUMMARY:

This is a 505(b)(2) application for an extended release oral tablet containing codeine phosphate and chlorpheniramine maleate 40/8 mg. The proposed indication is "Temporary relief of cough (b)(4) common cold (b)(4) upper respiratory allergies, (b)(4)." As a basis for the 505(b)(2) application, the Applicant cites OTC Monograph to support the safety and efficacy of codeine (21 CFR 341.14) and chlorpheniramine (21 CFR 341.12). The Applicant also cites Codeprex (Codeine and Chlorpheniramine ER Suspension, NDA 21-369) as a model NDA program for the proposed drug. The drug development program is a clinical pharmacology program to determine the bioequivalence of the proposed drug to the reference drugs.

The submission includes 2 clinical pharmacology studies to evaluate the bioequivalence (BE) to the reference drugs, and the food effect on the proposed drug. A total of 62 healthy volunteers were enrolled in the 2 studies. The following pharmacokinetic variables were calculated for each treatment: AUC, C_{max}, T_{max}, Kel, and T_{1/2}. Dizziness, headache, and somnolence were the most common adverse events reported in the studies. There were no significant differences in adverse events between the proposed drug product and reference drugs. There were no deaths or non-fatal serious adverse events reported during the studies. The proposed product labeling is based on the approved product labeling for RLDs.

The Applicant submitted an initial pediatric study plan (iPSP) for this NDA on 5/11/2014 (b)(4). The Division sent out an information request (IR) on 7/4/2014 stating that the iPSP should include a request of partial waiver for pediatric studies in patients <6 years of age, and a plan to conduct a PK study (b)(4) study in patients 6 to 17 years of age. The Applicant submitted a revised iPSP on 8/15/2014 to request a partial waiver for pediatric studies in patients <6 years of age, and a plan to conduct a PK study in patients 6 to 17 years of age. In an IR to the Applicant on 9/2/2014, the Division reiterated that a safety study in patients 6 to 17 years of age is needed to evaluate the safety of the proposed drug in pediatric patient population. The Applicant has not submitted a revised iPSP at this time.

This application contains items required for filing and data that are organized adequately to allow reviewing. The NDA is filable.

OUTSTANDING ISSUES: A post-marketing AEs search for active ingredients of the proposed drug is needed.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	FILABLE <input checked="" type="checkbox"/>	NOT FILABLE _____
	APPROVAL _____	APPROVABLE _____ NOT APPROVABLE _____
OTHER ACTION:	COMMENTS FOR SPONSOR <input checked="" type="checkbox"/>	

1. GENERAL INFORMATION

This is a 505(b)(2) application for an extended release (ER) oral tablet containing codeine phosphate and chlorpheniramine maleate 40/8 mg. The proposed indication is “temporary relief of cough (b)(4) common cold (b)(4)

(b)(4) upper respiratory allergies (b)(4) The application is submitted electronically by Nexigen Pharma on behalf of Spriaso LLC.

As a basis for the 505(b)(2) submission route, the applicant is relying on the Agency's finding of safety and effectiveness as codeine phosphate and chlorpheniramine maleate are identified as having established safety and efficacy under the OTC Monograph (21 CFR 341.12 and 341.14), including in combination with one another (21 CFR 341.40). Additionally, the proposed drug product meets conditions of the applicable OTC Monograph deviating only by modifying the release rate from Immediate-Release (IR) to Extended-Release (ER) which qualifies it as a NDA deviation from applicable monograph as cited at 21 CFR 330.11.

1. CLINICAL DEVELOPMENT PROGRAM

The clinical pharmacology program for this combination product includes 2 bioavailability (BA)/bioequivalent (BE) studies to address the BE and food effect for the proposed product (Table 1).

Table 1 Clinical pharmacology studies in the NDA application

Type of study	Study ID	n	Objectives of the study	Reference drug
BA/BE and Food effect	LPCN1084-12-002	24	Single-dose BA/BE and Food effect of proposed drug	IR codeine and chlorpheniramine tablets
BA/BE	LPCN1084-13-001	38	Multiple-dose BA/BE of proposed drug product	IR codeine and chlorpheniramine tablets

2. FOREIGN MARKETING AND REGULATORY HISTORY

An IND for the proposed drug was filed with the Division on 10/14/2009. The drug development program is a clinical pharmacology program to determine the bioequivalence of the proposed drug to the reference drugs. There were no significant regulatory issues with regard to the development program of the proposed drug.

The proposed drug product has not been marketed in any foreign markets.

3. ITEMS REQUIRED FOR FILING (21 CFR 314.50)

The following items pertinent to a clinical review are included in the submission:

- Application form (FDA 356h) [m1\1.1-forms\1.1.2-fda-form-356h]
- Index [index.xml]
- Summary [m2\2.7-clinical summary]
- Clinical technical section
 - Clinical study reports
 - Study 1084-12-002 [m5\5.3-clin-stud-rep\5.3.1-rep-biopharm-stud\5.3.1.2-compar-BA-BE-stud-rep]
 - Study 1084-13-001 [m5\5.3-clin-stud-rep\5.3.1-rep-biopharm-stud\5.3.1.2-multiple-dose-compar-BA-BE stud-rep]
 - Other pertinent data
 - none
 - Good clinical practice certification [m5\5.3-clin-stud-rep\5.3.1-rep-biopharm-stud\5.3.1.2-compar-BA-BE-stud-rep, 5.3.1.2-multiple-dose-compar-BA-BE stud-rep Section 5 Ethics]
 - Risk/benefit analysis:
 - not provided
 - Debarment certification [m1\1.3-administrative-information\1.3.3-debarment-certification]
 - Pediatric use [m1\1.9-pediatric-administrative-information\1.9.1-request-waiver-pediatric-studies]
- Labeling [m1\us\1.14-labeling\1.14.1-draft-labeling]
- Case report forms [m5\5.3.1-rep-biopharm-stud\5.3.1.2-compar-BA-BE-stud-rep\crfs, 5.3.1.2-multiple-dose-compar-BA-BE stud-rep\crfs]
- Financial disclosure [m1\1.3-administrative-information\1.3.4-financial-certification-disclosure]

The Applicant submitted an initial pediatric study plan (iPSP) for this NDA on 5/11/2014 ^(b)₍₄₎. The Division sent out an information request (IR) on 7/4/2014 to advise that the iPSP should include a request of partial waiver for pediatric studies in patients <6 years of age, and a plan to conduct a PK study ^(b)₍₄₎ study in patients 6 to 17 years of age. The Applicant submitted a revised iPSP on 8/15/2014 to request a partial waiver for pediatric studies in patients <6 years of age, and a plan to conduct a PK study in patients 6 to 17 years of age. In an IR to the Applicant on 9/2/2014, the Division stated that a safety study in patients 6 to 17 years of age is needed to evaluate the safety of the proposed drug in pediatric patient population. The Applicant has not submitted a revised iPSP at this time.

There are no post-marketing adverse events reports for the active ingredients of the proposed drug, i.e., codeine and chlorpheniramine. The sponsor will be requested to conduct a search for post-marketing adverse events reported for the active ingredients of the proposed drug for a

period of last 5 years, including published literatures, FDA AERS database, and the company's database.

4. CLINICAL STUDIES

There are 2 clinical pharmacology studies in the application to address the BE and food effect for the proposed product (Table 1). A total of 62 healthy volunteers were enrolled in the 2 studies. The following pharmacokinetic variables were calculated for each treatment: AUC, C_{max} , T_{max} , Kel, and $T_{1/2}$.

Dizziness, headache, and somnolence were the most common adverse events reported in the studies. There was no significant difference in adverse events between the proposed drug product and RLDs. There were no deaths or non-fatal serious adverse events reported during the studies.

5. BRIEF REVIEW OF PROPOSED LABELING

The proposed product labeling is based on the approved product labeling for Codeprex, NDA 21-369. No major labeling issues are identified.

6. DSI REVIEW AND AUDIT

The clinical pharmacology review team has requested DSI audit for this NDA application. The study center at QPS Bio-Kinetic, Springfield, MO and the analytical site at (b) (4) for Study LPCN 1084-13-01 are requested for DSI audit.

7. SUMMARY

This is a 505(b)(2) application for an extended release oral tablet containing codeine phosphate and chlorpheniramine maleate 40/8 mg. The proposed indication is "Temporary relief of cough (b) (4) common cold (b) (4) (b) (4) pper respiratory allergies (b) (4) As a basis for the 505(b)(2) application, the Applicant cites OTC Monograph to support the safety and efficacy of codeine (21 CFR 341.14) and chlorpheniramine (21 CFR 341.12). The Applicant also cites Codeprex (Codeine and Chlorpheniramine ER Suspension, NDA 21-369) as a model NDA program for the proposed drug. The drug development program is a clinical pharmacology program to determine the bioequivalence of the proposed drug to the reference drugs.

The submission includes 2 clinical pharmacology studies to evaluate the bioequivalence (BE) to the reference drugs, and the food effect on the proposed drug. A total of 62 healthy volunteers were enrolled in the 2 studies. The following pharmacokinetic variables were calculated for each treatment: AUC, C_{max} , T_{max} , Kel, and $T_{1/2}$. Dizziness, headache, and somnolence were the most

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This application contains items required for filing and data that are organized adequately to allow reviewing. The NDA is filable.

8. REVIEW TIMELINE

The PDUFA action date is June 22, 2015. The schedule for review is provided in Table 1. Write-up will be concomitant with the review process. The review will culminate with the proposed label, which will include comparison to the referenced listed products and monographs. The final draft review will be completed by April 10, 2015.

Table 1: Review timeline for NDA 206-323

Milestone	Target date for completion
Filing and planning meeting	October 6, 2014
MCR Meeting	January 15, 2015
Label Meeting	TBD
Wrap-up meeting	TBD
Final draft review complete	April 10, 2015
PDUFA Action date (10 months)	June 22, 2015

9. COMMENTS FOR THE SPONSOR

Two clinical comments will be included in 74-day letter:

1. *Submit a 120-day safety update as required per 21 CFR 314.50(d)(5)(vi)(b).*
2. *Conduct a search for post-marketing adverse events reported for the active ingredients of your proposed drug for a period of last 5 years, including published literatures, FDA AERS database, and the company's database, if any. Submit the search result as tabular and descriptive summaries.*

Reviewed by:

Xu Wang, M.D., Ph.D.

Medical Officer, Division of Pulmonary, Allergy, and Rheumatology Products

Anthony G. Durmowicz, M.D.

Medical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products

cc: NDA 206-323
HFD-570/Division File
HFD-570/ Durmowicz /Medical Team Leader
HFD-570/Gilbert-McClain/Deputy Division Director
HFD-570/Wang/Medical Reviewer
HFD-715/Petullo/Biometrics Reviewer
HFD-570/Lee/Pharmacology-Toxicology Reviewer
ONDQA/Bertha/CMC Reviewer
OCP/Agarwal/Clinical Pharmacology Reviewer
HFD-570/Musse/CSO

Clinical Filing Checklist

NDA/BLA Number: 206-323 **Applicant: Spriaso LLC** **Stamp Date: August 22, 2014**
Drug Name: Codeine Phosphate and Chlorpheniramine **NDA/BLA Type: 505(b)(2)**
Maleate ER Tablets

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?			X	Active components of this combo product are GRASE
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			OTC Monograph codeine and chlorpheniramine
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?			X	

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 Indication:				
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			MedDRA Version 15.1
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	No deaths or discontinuations due to AEs
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission		X		

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
	discussions?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The revised iPSP is yet to be submitted.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	No foreign data
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ YES ___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

 Reviewing Medical Officer

 Date

 Clinical Team Leader

 Date

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

/s/

XU WANG
03/03/2015

ANTHONY G DURMOWICZ
03/03/2015