

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206323Orig1s000**

**PHARMACOLOGY REVIEW(S)**

**PHARMACOLOGY/TOXICOLOGY REVIEW**  
**Labeling**

**NDA number:** 206323

**Supporting document/s:** SDN1

**Applicant:** Spriaso, LLC.

**Review Division:** Division of Pulmonary, Allergy, and Rheumatology Products

**Reviewer:** Marcie L. Wood, PhD, Nonclinical Supervisor

**Product:** Codeine Phosphate and Chlorpheniramine Maleate Extended Release Tablets

**Pharmacologic class:** Opiate agonist antitussive/Histamine-1 (H1) receptor antagonist

**Indication:** Relief of cough and symptoms associated with upper respiratory allergies or a common cold.

**Subject:** Labeling comments

Codeine phosphate and chlorpheniramine maleate extended release tablets contain 54.3 mg codeine phosphate (equivalent to 40 mg of free codeine base) and 8 mg of chlorpheniramine maleate (equivalent to 5.6 mg of chlorpheniramine) per tablet. Adults and children 18 years of age and older are recommended to take 1 tablet every 12 hours, not to exceed 2 doses in 24 hours. The maximum daily doses of codeine phosphate and chlorpheniramine maleate are 108.6 mg and 16 mg, respectively (equivalent to 80 mg of codeine and 11.2 mg of chlorpheniramine, respectively).

The nonclinical sections of the labeling for this product (primarily 8.1 – Pregnancy; 12.1 – Mechanism of Action; 13.1 – Carcinogenesis, Mutagenesis, Impairment of Fertility) follow the format of a recently approved product, Tuzistra XR (NDA 207768), which also contains codeine and chlorpheniramine. As with Tuzistra product labeling, animal to human dose ratios in sections 8.1 and 13.1 of the NDA 206323 label were calculated using the maximum daily doses of codeine and chlorpheniramine bases, not their respective salts. This was done to maintain consistency between the two product labels. Differences in codeine dose ratios in sections 8.1 and 13.1 of the respective labels are noted, and exist due to differences in codeine base amounts for the respective products. Codeine dose ratios for the current NDA are slightly smaller, as the maximum daily amount of codeine base is larger. There are no differences in chlorpheniramine animal to human dose ratios between the two products, as the maximum daily amount of chlorpheniramine is the same in both products.

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/s/  
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MARCIE L WOOD  
06/18/2015

**PHARMACOLOGY/TOXICOLOGY REVIEW**  
**Chemistry Consult**

**NDA number:** 206323

**Supporting document/s:** SDN1

**Applicant:** Spriaso, LLC.

**Review Division:** Division of Pulmonary, Allergy, and Rheumatology Products

**Reviewer:** Marcie L. Wood, PhD, Nonclinical Supervisor

**Product:** Codeine Phosphate and Chlorpheniramine Maleate Extended Release Tablets

**Pharmacologic class:** Opiate agonist antitussive/Histamine-1 (H1) receptor antagonist

**Indication:** Relief of cough and symptoms associated with upper respiratory allergies or a common cold.

**Subject:** Response to Consult Requested by Yong Hu

In an email inquiry on January 13, 2015, Dr. Hu initiated a request for feedback on the drug product specifications of two impurities, (b) (4)

The applicant proposed a (b) (4) drug product specification of NMT (b) (4)% and a (b) (4) drug product specification of NMT (b) (4)%. This review evaluates the proposed specifications for these two drug product impurities.

(b) (4) (b) (4) The applicant proposed that the weight of evidence (which included a negative Ames test, a positive in vitro chromosomal aberration assay, and a negative in vivo micronucleus assay) indicated that (b) (4) is not genotoxic, and thus a (b) (4) drug product specification of NMT (b) (4)% was acceptable as per ICH Q3B. Since (b) (4) genotoxicity assays had not been reviewed under (b) (4) DMF # (b) (4) (the drug substance manufacturer of codeine for the current NDA), an information request was sent to the DMF holder on February 9, 2015, to request the study reports for these assays. The DMF holder submitted the requested study reports on February 13, 2015, and the study reports were subsequently reviewed by Dr. Grace Lee (see Dr. Lee's review under DMF # (b) (4) dated April 20, 2015). Dr. Lee's review concluded that additional information (i.e., a comet assay with (b) (4)) would be needed to clarify the (b) (4) genotoxicity results.

For the current NDA, a (b) (4) specification of NMT (b) (4)% would result in a daily intake of (b) (4) mcg of (b) (4) (based on a total daily dose of 80 mg of codeine). This exceeds acceptable daily levels of a potentially genotoxic impurity for a product intended for chronic daily use (i.e., 1.5 mcg). However, given the intended short-term use of the proposed drug product, exposure to higher levels of (b) (4) are considered acceptable. Previously, drug product levels of (b) (4) were limited to NMT (b) (4)% in Codaprex (NDA 21369). Therefore, the current applicant was also requested to lower the drug product specification of (b) (4)

to NMT (b) (4)%. The applicant agreed to lower the specification as requested. Therefore, there are no outstanding nonclinical concerns for the (b) (4) specification in the drug product.

(b) (4)

The applicant's proposed drug product specification of NMT (b) (4)% for (b) (4) exceeded the ICH Q3B qualification threshold of NMT 0.5%. In an information request dated March 26, 2015, the applicant was requested to revise the specification to NMT (b) (4)% or provide safety information to justify a higher limit. The applicant responded to the request on April 10, 2015, and argued that (b) (4), and thus, the higher specification was justified. The applicant did not, however, provide adequate data to support their claim. A follow-up information request was sent to the sponsor on April 20, 2015, requesting that the applicant provide additional information to support the higher specification, or alternatively, to revise the drug product (b) (4) specification to NMT (b) (4)%. The applicant responded on May 4, 2015, and agreed to lower the specification to NMT (b) (4)%. Therefore, there are no outstanding concerns for the (b) (4) specification in the drug product.

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MARCIE L WOOD  
05/23/2015

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: 206323  
Supporting document/s: SDN1  
Applicant's letter date: August 20, 2014  
CDER stamp date: August 22, 2014  
Product: Codeine Phosphate and Chlorpheniramine  
Maleate Extended Release Tablets  
Indication: Relief of cough and symptoms associated with  
upper respiratory allergies or a common cold  
Applicant: Spriaso, LLC  
Review Division: Division of Pulmonary, Allergy, and  
Rheumatology Products  
Reviewer: Marcie L. Wood, PhD, Nonclinical Supervisor  
Division Director: Badrul Chowdhury, MD, PhD  
Project Manager: Laura Musse, RN, MS, CRNP

*Template Version: September 1, 2010*

**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 206323 are owned by Spriaso, LLC or are data for which Spriaso, LLC has obtained a written right of reference. Any information or data necessary for approval of NDA 206323 that Spriaso, LLC does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 206323.

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## **Executive Summary**

### **1.1 Introduction**

Spriso, LLC submitted a 505(b)(2) NDA on August 22, 2014, for codeine phosphate and chlorpheniramine maleate extended release tablets. Each tablet contains 54.30 mg of codeine phosphate (40 mg codeine free base) and 8 mg chlorpheniramine maleate. The proposed indication is relief of cough and symptoms associated with upper respiratory allergies or a common cold.

### **1.2 Brief Discussion of Nonclinical Findings**

No nonclinical studies were required or submitted in support of this NDA. There is extensive clinical experience with both codeine, an opioid antitussive, and chlorpheniramine, an antihistamine.

The applicant references, in part, the established safety and efficacy of the active ingredients based on their monograph status. Both are recognized monograph drugs under 21 CFR 341.74 and 21 CFR 341.72, respectively, and the combination of these two drugs is permitted under 21 CFR 341.40: Combination Cough, Cold, and Bronchodilator Drug Products.

Further, other extended release drug products containing codeine and chlorpheniramine have been approved in the US (NDAs 18928, 21369, and 207768).

### **1.3 Recommendations**

#### **1.3.1 Approvability**

The drug product, codeine phosphate and chlorpheniramine maleate extended release tablets, is recommended for approval from the nonclinical perspective.

#### **1.3.2 Additional Non Clinical Recommendations**

None

#### **1.3.3 Labeling**

Labeling will be addressed in a separate review.

## **2 Drug Information**

### **2.1 Drug**

Generic Name: Codeine phosphate and chlorpheniramine maleate extended release tablets

## Chemical Name:

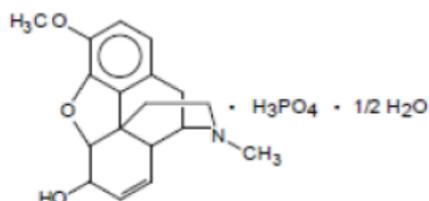
Codeine phosphate: Morphinan-6-ol, 7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-, (5 $\alpha$ ,6 $\alpha$ )-, phosphate (1:1)(salt), hemihydrate  
 Chlorpheniramine maleate: 2-Pyridinepropanamine,  $\gamma$ -(4-chlorophenyl)-N,N-dimethyl,(Z)-2-butenedioate (1:1)

## Molecular Formula/Molecular Weight:

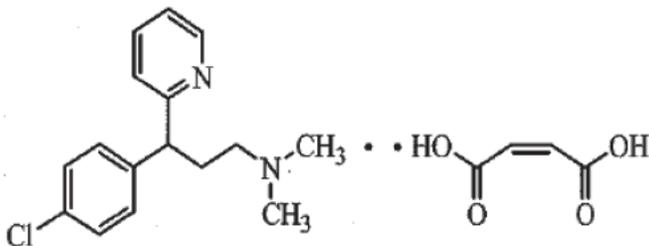
Codeine phosphate: C<sub>18</sub>H<sub>21</sub>NO<sub>3</sub>•H<sub>3</sub>PO<sub>4</sub>•1/2H<sub>2</sub>O / 406.37 g/mol  
 Chlorpheniramine maleate: C<sub>16</sub>H<sub>19</sub>ClN<sub>2</sub>•C<sub>4</sub>H<sub>4</sub>O<sub>4</sub> / 390<sup>(b) (4)</sup>g/mol

## Structure or Biochemical Description:

## Codeine phosphate:



## Chlorpheniramine maleate:



## Pharmacologic Class:

Codeine phosphate: Opiate agonist antitussive

Chlorpheniramine maleate: Histamine-1 (H1) receptor antagonist

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 106992 (Codeine phosphate and chlorpheniramine maleate extended release tablets; Spriaso, LLC)

DMF (b) (4)

DMF (b) (4)

## 2.3 Drug Formulation

Codeine phosphate and chlorpheniramine maleate extended release tablets contain 54.3 mg codeine phosphate equivalent to 40 mg of free codeine base and 8 mg of chlorpheniramine maleate per tablet. The composition of codeine phosphate and

chlorpheniramine maleate extended release tablets is provided in the table below. Maximum daily levels of excipients are within levels found in approved oral products.

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)
Total Weight		200.00	100.00

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

(b) (4)

## 2.4 Comments on Novel Excipients

There are no novel excipients in the drug product formulation.

## 2.5 Comments on Impurities/Degradants of Concern

Impurities will be addressed in a separate review.

## 2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population is adults

(b) (4)

The proposed dosing regimen is 1 tablet (codeine 40 mg/chlorpheniramine maleate 8 mg) every 12 hours, not to exceed 2 tablets in 24 hours.

Due to safety concerns regarding use of a long-acting narcotic in children, the clinical review is recommending approval of the proposed drug product in adults only (i.e., 18 years of age and older).

## 2.7 Regulatory Background

A drug product IND (IND 106922) was submitted by Lipocine on October 14, 2009. An EOP2 meeting between Lipocine and the FDA occurred on October 4, 2010. Sponsorship of the IND was transferred to Spriaso, LLC on July 31, 2013. A preNDA

meeting between Spriaso, LLC and the FDA occurred on October 10, 2013. The NDA was received on August 22, 2014.

### **3 Studies Submitted**

#### **3.1 Studies Reviewed**

No nonclinical studies were required or submitted.

### **4 Pharmacology**

No nonclinical pharmacology studies were required or submitted.

### **5 Pharmacokinetics/ADME/Toxicokinetics**

No nonclinical pharmacokinetics/ADME/toxicokinetics studies were required or submitted

### **6 General Toxicology**

No general toxicology studies were required or submitted.

### **7 Genetic Toxicology**

No genetic toxicology studies were required or submitted.

### **8 Carcinogenicity**

No carcinogenicity studies were required or submitted.

### **9 Reproductive and Developmental Toxicology**

No reproductive and developmental toxicology studies were required or submitted.

### **10 Special Toxicology Studies**

No special toxicology studies were required or submitted.

### **11 Integrated Summary and Safety Evaluation**

Spriaso, LLC submitted a 505(b)(2) NDA on August 22, 2014, for codeine phosphate and chlorpheniramine maleate extended release tablets. Each tablet contains 54.30 mg of codeine phosphate (40 mg codeine free base) and 8 mg chlorpheniramine maleate. The proposed indication is relief of cough and symptoms associated with upper respiratory allergies or a common cold. The proposed dosing regimen is 1 tablet every 12 hours, not to exceed 2 tablets in 24 hours.

No nonclinical studies were required or submitted in support of this NDA. There is extensive clinical experience with both codeine, an opioid antitussive, and chlorpheniramine, an antihistamine.

The applicant references, in part, the established safety and efficacy of the active ingredients based on their monograph status. Codeine and chlorpheniramine are recognized monograph drugs under 21 CFR 341.74 (codeine doses not to exceed 120 mg for patients  $\geq$  12 years of age) and 21 CFR 341.72 (chlorpheniramine doses not to exceed 24 mg for patients  $\geq$  12 years of age), respectively, and the combination of these two drugs is permitted under 21 CFR 341.40: Combination Cough, Cold, and Bronchodilator Drug Products.

Further, other extended release drug products containing codeine and chlorpheniramine have been approved in the US (NDAs 18928, 21369, and 207768).

There are no outstanding pharmacology or toxicology issues for this NDA application, and approval is recommended from a nonclinical perspective.

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/s/  
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MARCIE L WOOD  
05/18/2015

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA Number: 206323**

**Applicant: Spriaso LLC**

**Stamp Date: August 22, 2014**

**Drug Name: Codeine**

**NDA Type: New**

**Phosphate and**

**Chlorpheniramine Maleate**

**Extended Release Tablet**

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		Note that this is a 505(b)(2) application and the Sponsor relies on information from the literature and monographs.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			Not applicable Note that this is a 505(b)(2) application and the Sponsor relies on information from the literature and monographs.
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			Not applicable Note that this is a 505(b)(2) application and the Sponsor relies on information from the literature and monographs.

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement  
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		Revision of labeling may be needed.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		Impurity issues will be addressed in consult with the reviewing chemist.
11	Has the applicant addressed any abuse potential issues in the submission?			Defer to the Medical Reviewer
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? \_\_\_\_\_ Yes\_\_\_\_\_**

If the NDA/BLA is not fileable from the pharmacology/toxicology 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.

Grace S. Lee, Ph.D, D.A.B.T. October 3, 2014  
 \_\_\_\_\_  
 Reviewing Pharmacologist Date

Marcie Wood, Ph.D. October 3, 2014  
 \_\_\_\_\_  
 Supervisor, Pharmacologist Date

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement  
010908

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GRACE S LEE  
10/03/2014

MARCIE L WOOD  
10/03/2014