CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206323Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 29, 2015
From	Anthony G. Durmowicz, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	206323
Applicant	Nexgen on behalf of Spriaso LLC
Date of Submission	August 22, 2014
PDUFA Goal Date	June 22, 2015
Proprietary Name / Established (USAN) names	None Designated / Codeine Phosphate and Chlorpheniramine Maleate Extended Release Tablets, 40 mg / 8 mg
Dosage forms / Strength	Oral tablet (extended release) 40 mg of codeine (as codeine phosphate) and 8 mg of chlorpheniramine maleate/tablet
Indication(s)	Relief of cough and symptoms associated with upper respiratory allergies or a common cold in adults and 18 years of age or older.
Recommended Action:	Approval pending CMC facility inspection

1. Introduction

This submission by the Applicant dated 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, 40 mg/ 8 mg. The indication will be for relief of cough and symptoms associated with upper respiratory allergies or a common cold in adults and 18 years of age or older. The Applicant has submitted this application through 505(b)(2) pathway and is relying on the FDA's safety and efficacy findings from the following sources: 1) basis of approval for reference product, Codeprex™ Pennkinetic® (NDA 021369); and 2) OTC monographs for codeine phosphate 21 CFR 341.14(a)(2)(ii) and chlorpheniramine maleate in 21 CFR 341.12(c).

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

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

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

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

The bioavailability study submitted by the Applicant has established the bioequivalence of each component of their cough/cold combination oral suspension test drug product, codeine and chlorpheniramine, to each of the respective reference drugs. As such, pending results of the inspection of the manufacturing facility, the recommended action for this NDA is approval. This review will summarize the Division's assessments of the application, most notably the demonstration of bioequivalence between the Applicant's proposed combination product oral solution and each of the individual reference drug products, codeine and chlorpheniramine. Summaries will also be provided for applicable discipline-specific sections.

2. Background

This 505(b)(2) application is to market a combination product containing codeine phosphate and chlorpheniramine maleate, as an extended release oral tablet containing 54.3 mg codeine phosphate representing 40 mg of free codeine base and 8 mg of chlorpheniramine maleate in each tablet. This formulation is being developed to provide patients and clinical practitioners with an alternative dose strength and formulation for an extended release cough and cold preparation with a twice daily dosing regimen. The Applicant proposed a dosing regimen of 40 mg codeine (54.3 mg codeine phosphate) and 8 mg chlorpheniramine maleate contained in 1 ER tablet every 12 hours, with or without food, not to exceed 2 doses (tablets) in 24 hours in adults 18 years of age and older.

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

Codeine is a semi-synthetic opioid analgesic for the relief of mild to moderately severe pain, the treatment of diarrhea, and for the symptomatic relief of nonproductive cough, alone or in combination with other antitussives or expectorants. Codeine and other related opioids act by depressing the cough reflex by a direct central action on the cough center in the medulla. Chlorpheniramine is a propylamine derivative antihistamine of the alkylamine class that possesses anticholinergic and sedative activity.

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

Three similar products have been approved in the past:

- Fisons Corporation previously marketed Pentuss (NDA 18-928, approved on 08/14/1985) containing 10 mg/5 mL of codeine and 4 mg/5 mL of chlorpheniramine. It was, however, withdrawn from the market in 1996 for reasons unrelated to safety or efficacy (no memo in DARRTS).

- Celltech Pharmaceuticals received approval for Codeprex Pennkinetic ER Suspension (NDA 21-369 approved on 06/21/2004), containing codeine polistirex and chlorpheniramine polistirex equivalent to 20 mg codeine and 4 mg chlorpheniramine maleate respectively in each 5 mL of product. Codeprex, although approved, was never marketed in the US and the sponsor eventually withdrew the NDA for reasons unrelated to safety and efficacy (memo in DARRTS dated 03/20/2007).

- Vernalis and Tris Pharma received approval for a liquid suspension codeine/chlorpheniramine extended release preparation (Tradename Tuzistra XR) was recently approved for use in adults for "relief of cough and symptoms associated with upper respiratory allergies or a common cold" on April 30, 2015.

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

Sponsors can use either of the three entities, i.e, free base codeine (MW 300) or codeine phosphate (MW 406) or codeine sulfate (MW 750) to calculate a dose within the recommendations included in the OTC monograph. Therefore, the free base amount of codeine may be different in different formulations approved under the same OTC monograph. The ER (b) (4) under review in this NDA contains 40 mg codeine phosphate (b) (4) and 8 mg of chlorpheniramine maleate in each tablet.

As no IR or ER codeine and chlorpheniramine combination products were marketed in the US at the time of this NDA submission, the relative BA assessments were conducted using a codeine and chlorpheniramine combination IR tablet manufactured by the Applicant as the reference product. This issue was discussed during pre-submission meetings and was considered acceptable.

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

3. CMC/Device

The chemistry team recommendation is for approval pending the facilities assessment from the Office of Process and Facilities.

The drug substances are codeine phosphate and chlorpheniramine maleate, both of which conform to their respective USP monographs. The codeine phosphate is manufactured by [redacted] under DMF [redacted] and the chlorpheniramine maleate by [redacted] under DMF [redacted] Both drug substances are highly water soluble. The DMF referenced for drug substance information is judged adequate.

The drug product is codeine phosphate and chlorpheniramine maleate extended-release tablet. Each tablet contains 54.3 mg codeine phosphate (equivalent to 40 mg codeine) and 8 mg chlorpheniramine maleate (equivalent to 5.6 mg chlorpheniramine). [redacted] hypromellose [redacted] The other excipients include lactose monohydrate, polysorbate 80, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate. Alcohol dose-dumping assessment did not suggest increased release of drug substances in the presence of alcohol.

The tablets are packaged in a 100-count within a HDPE heavy wall round bottle, with a child resistant cap fitted with an aluminum heat-sensitive foil liner [redacted] and a desiccant pack. The stability data support a 24 month shelf life. The product is manufactured by Nexgen Pharma, Inc.

The recommendation is also approval from a quality microbiology perspective.

4. Nonclinical Pharmacology/Toxicology

No new non-clinical pharmacology/toxicology studies were performed or required for this application.

5. Clinical Pharmacology/Biopharmaceutics

The Applicant has submitted 2 clinical pharmacology study reports. Two pivotal clinical studies (Study 1084-12-002 and Study LPCN 1084-13-001) were then conducted to support the development and registration of the COD-CPM ER tablet (Test Product):

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

Treatment A: 1 ER tablet, 30 minutes following a high-fat breakfast

Treatment B: 1 ER tablet, following a 10-hour overnight fast

Treatment C: Reference Product (Fasted), 1 IR tablet, following a 10-hour overnight fast, and 1 IR tablet at 6 hours after the first dose

Each ER tablet contained 40 mg codeine phosphate and 8 mg chlorpheniramine maleate. Each IR table contained 20 mg codeine phosphate and 4 mg chlorpheniramine maleate.

The treatment phases were separated by washout periods of at least 7 days. The following pharmacokinetic variables were calculated for each treatment: AUC0-t, AUC0-inf, Cmax, Tmax, and t1/2. The results of Study 3007117 are shown in the Table 1 below.

Table 1: Geometric Mean, Ratios of Geometric Means and the 90% Confidence Intervals for the Pharmacokinetic Parameter of Codeine and Chlorpheniramine Following Single Dose Administration of Test (COD-CPM ER Tablet) and Reference Product (COD-CPM IR Tablet) under Fasted Conditions. (Study LPCN 1084-12-002)

Parameter	Codeine			90% Confidence Interval
	Geometric Mean [a]		%Ratio [b]	
	Test	Ref		
AUC_{last} (ng·h/mL)	361	385	94	88.60 – 99.38
AUC_{inf} (ng·h/mL)	371	395	94	88.66 – 99.72
C_{max} (ng/mL)	44	52	85	77.30 – 93.49
Parameter	**Chlorpheniramine**			**90% Confidence Interval**
	Geometric Mean [a]		%Ratio [b]	
	Test	Ref		
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)	8.7	9.2	94.8	88.35 – 101.80

[a] *Geometric Mean for Test Formulation-Fasted (COD-CPM ER Tablet) and Reference Product-Fasted (COD-CPM IR Tablet) based on Least Squares Mean of log-transformed parameter values*
[b] *Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref); Source: Study LPCN 1084-12-002*

The systemic exposures of both codeine and chlorpheniramine from the ER product were found to be comparable to the reference IR product. The 90% confidence intervals for the geometric mean ratio for AUC_{last} and AUC_{inf} for both the components with the ER product were within the 80-125% bioequivalence limits when compared to the IR product. The ER product yielded lower C_{max} values for codeine and chlorpheniramine as compared to the reference IR product. The 90% confidence intervals for the geometric mean ratio for C_{max} for codeine with the ER product fell outside of the 80-125% bioequivalence limits at the lower end as indicated in Table 1. This is expected from an ER product, as typically, it is designed to reduce peaks observed with the IR product, and provides slower drug release as compared to the IR product. Therefore, the lower codeine C_{max} with the ER product is not of a concern.

In addition, the effect of food on the pharmacokinetics of COD-CPM ER suspension was evaluated in Study LPCN 1084-12-002 where COD-CPM ER Oral Tablet was administered under fed (high fat meal) and fasted conditions. Results of the food effect assessment are presented in Table 2 below.

Table 2: Food effect assessment; Geometric Mean, Ratios of Geometric Means and the 90% Confidence Intervals for the Pharmacokinetic Parameter of Codeine and Chlorpheniramine Following Single Dose Administration Under Fed and Fasted Conditions

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

[a] *Geometric Mean based on Least Squares Mean of log transformed parameter values*
[b] *Ratio(%) = Geometric Mean (Fed)/Geometric Mean (Fasted)*
Source: Study 3007117

Table 3: Mean (±SD) PK Data of ER Tablet Administered under Fed and the IR Tablet under Fasting Conditions (Study LPCN 1084-12-002)

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

For chlorpheniramine, the 90% CI for fed/fasted ratios of the geometric means for AUC_{inf} and Cmax was within the BE limits of 80%-125%.

The presence of food led to a 28% increase in C_{max} and a 13% increase in the AUC for codeine and had no effect on chlorpheniramine PK (Table 2). A BE analysis comparing codeine PK in ER fed vs. IR fasted conditions (Table 3) indicated that codeine PK from the ER tablet in fed conditions is similar to that of the IR tablet in fasted conditions, i.e., C_{max} and AUC_{inf} values of codeine from ER tablet are within BE limits of 80-125% of the reference. As such, the effect of food on the ER tablet is not considered relevant.

Based on monograph limits for codeine and chlorpheniramine, a COD-CPM IR tablet is used a reference formulation in this application. Similar exposure data with COD-CPM ER formulation in the presence of food to that with COD-CPM IR tablet in fasted state suggests that the increased exposures in the presence of food are within the allowed monograph range.

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

Treatment A: 1 codeine phosphate 40 mg/chlorpheniramine maleate 8 mg ER tablet 2 times a day, 12 hours apart, for 6.5 days

Treatment B: Reference Product (Fasted), 1 codeine phosphate 20 mg/chlorpheniramine maleate 4 mg IR tablet 4 times a day, 6 hours apart, for 6.5 days

Each subject received each of three treatments once. The following pharmacokinetic variables were calculated for each treatment: C_{max} and $AUC_{0\text{-}12hr}$. The results of Study 1084-13-001 are shown in the table below.

Table 3: **Steady State Assessment: Geometric Mean, Ratios of Geometric Means and the 90% Confidence Intervals for the Pharmacokinetic Parameter of Codeine and Chlorpheniramine Following Multiple Dose Administration of Test (COD-CPM ER Tablet) and Reference Product (COD-CPM IR Tablet) in Fasted Conditions.**

Parameter	Codeine			90% Confidence Interval
	Geometric Mean [a]		%Ratio [b]	
	Test	Ref		
$AUC_{0\text{-}12}$ (ng·h/mL)	487	523	93.1	89.42 – 97.03
C_{max} (ng/mL)	71.5	84.2	85.0	78.91 – 91.46
Parameter	**Chlorpheniramine**			**90% Confidence Interval**
	Geometric Mean [a]		%Ratio [b]	
	Test	Ref		
$AUC_{0\text{-}12}$ (ng·h/mL)	382	376	102	97.46 – 105.78
C_{max} (ng/mL)	36.9	35.2	105	100.39 – 109.33

[a] *Geometric Mean for Test Formulation-Fasted (COD-CPM ER Tablet) and Reference Product-Fasted (COD-CPM IR Tablet) based on Least Squares Mean of log-transformed parameter values*
[b] *Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref);*
Source: Study 1084-13-001

At steady state, both for codeine and chlorpheniramine, the 90% CIs for the test/reference ratios of the geometric means for both C_{max} and $AUC_{0\text{-}12hr}$ were within the BE limits of 80 – 125%. Therefore, at steady state the pharmacokinetic parameters were bioequivalent between the test and the reference product.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The application relies on a bioavailability comparison and the OTC monograph. No clinical studies were conducted or required as bioequivalence was demonstrate.

8. Safety

The safety of the product is based on establishing bioequivalence of the proposed product to the approved reference products. In addition, the Applicant provided a Summary of Clinical Safety which referenced the monograph and included a literature survey and a summary of the safety data from the clinical pharmacology studies. The submitted data did not reveal any new safety signals.

9. Advisory Committee Meeting

An advisory committee meeting is not necessary for this application. The two active ingredients present in this product are well known as individual drug substances, and as previously discussed, based on the current monograph and the Agency's prior precedent, the combination of products of these classes are accepted for the proposed indications.

10. Pediatrics

During the drug development period under IND 106992, the Applicant was advised that their proposed product would trigger PREA and they submitted an initial Pediatric study plan on May 11, 2014 which was inadequate. After subsequent communication with the Applicant, an agreed pediatric study plan included the conduct of PK and safety studies similar to what the Agency required for the currently marketed hydrocodone-containing cough cold products. A waiver was given for studies in pediatric patients under 6 years of age and a deferral for the PK and safety studies in patients 6 to 17 years of age. The agreed pediatric study plan and timelines were discussed at the Pediatric Review Committee (PeRC) meeting on May 27, 2015, at which time PeRC members agreed with the plan. It should be noted that the pediatric study plan is being implemented at a time when there is ongoing discussion regarding changes to codeine labels regarding respiratory depression and death that have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine. In light of these discussions, the requirements for conducting studies of codeine to relieve cough in pediatric patients as well as the use of codeine in pediatric patients in general may change in the future.

11. Other Relevant Regulatory Issues

Inspections

The Office of Scientific Investigation (DSI) and Division of Bioequivalence conducted inspections of the clinical study site and analytical laboratory testing site and found no abnormalities that would call into question the clinical or analytical data.

Compliance with Good Clinical Practices

The clinical pharmacology study in this application was conducted in accordance with Good Clinical Practices, and in particular with the requirements of 21 CFR Part 314.50(3)(i). The Applicant certified that the clinical contractor conducted the study in compliance with Institutional Review Board regulations and with Informed Consent Regulations.

Financial Disclosures

The Applicant certified that there was no financial arrangement with the clinical investigator whereby the value of the compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The clinical investigator certified that he was not a recipient of significant payments defined in 21 CFR 54.2(f).

12. Labeling

Proprietary Name

At the time of this review, a proposed trade name has not been agreed upon by the Office of Prescription Drug Promotion (OPDP).

Physician Labeling

The Applicant submitted a label in Physician's Labeling Rule (PLR) format which contained the require boxed warning to describe the risk of respiratory depression and death that have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid codeine metabolizers. The label is currently being finalized with an emphasis on ensuring consistency with the labeling of the recently approved Codeine and Chlorpheniramine ER Suspension, Tuzistra and other opioid-containing cough and cold products.

Carton and Immediate Container Labels

The carton was reviewed by the various disciplines including DMEPA and changes made for clarity and to improve readability.

Patient Labeling and Medication Guide

There was no separate medication guide or patient information sheet submitted by the Applicant for this product. Discussion is continuing whether a medication guide will be required if no separate patient information sheet is voluntarily submitted.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The Applicant submitted reports of their clinical pharmacology program which has established the bioequivalence of their proposed product to the individual reference products. In establishing bioequivalence, the program is able to rely on previous Agency determinations of the safety and efficacy of codeine phosphate and chlorpheniramine in the proposed combination product for symptomatic relief of cough and respiratory tract congestion associated with common cold when administered to adults 18 years of age and older at a dose of 40 mg/chlorpheniramine maleate 8 mg ER tablet every 12 hours by mouth. Therefore, the recommendation is for Approval for the adult population.

- Risk Benefit Assessment

The overall risk and benefit assessment of the proposed codeine and chlorpheniramine combination product, based on establishing bioequivalence to the individual reference products does not suggest an unfavorable risk benefit for these individual ingredients for the adult (18 years and older) population.

- Recommendation for Postmarketing Risk Management Activities
  None

- Recommendation for other Postmarketing Study Commitments

PREA-Required Studies

- Conduct a single-dose pharmacokinetic study whose primary objective is to identify the dose(s) of Codeine Phosphate and Chlorpheniramine Maleate ER tablet that results in exposures of codeine and chlorpheniramine in children (6 to 11 years) and adolescents (12 to 17 years) that are similar to the exposures seen in adults at the recommended dose. The population eligible for enrollment should be otherwise healthy children and adolescents with cough/cold symptoms for whom a combination product that includes an opioid antitussive would be an appropriate symptomatic treatment.

  Final Protocol Submission: July 2015
  Study Completion: January 2017
  Final Report Submission: October 2017

- Conduct an open-label, multi-dose safety and tolerability study in children (aged 6 to 11) and adolescents (aged 12 to 17 years). The population eligible for the study would be children and adolescents with cough/cold symptoms for whom a combination product that includes an opioid antitussive would be an appropriate symptomatic treatment. The study will enroll a total of approximately 400 children aged 6 to 17 inclusive in two cohorts (6-11years, 12 to 17 years). The dose used in this study will be based upon the results of the pharmacokinetic study in children ages 6 to 17 years.

  Final Protocol Submission: June 2018
  Study Completion: December 2020
  Final Report Submission: July 2021

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/s/

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