CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206323Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	June 22, 2015
From	Lydia I Gilbert-McClain, MD, FCCP
Subject	Division Director Summary Review
NDA# **Supplement#**	206-323
Applicant	Nexgen on behalf of Spriaso LLC
Date of Submission	August 20, 2014
PDUFA Goal Date	June 22, 2015
Proprietary Name / Established (USAN) names	No approved proprietary name/ Codeine phosphate and chlorpheniramine maleate extended release tablets, 40mg, 80 mg
Dosage forms / Strength	Oral tablet (extended release 40 mg of codeine (as codeine phosphate) and 8 mg of chlorpheniramine maleate/tablet
Proposed Indication(s)	Relief of cough and symptoms associate with upper respiratory allergies or a common cold in adults 18 years of age and older.
Recommended Action:	Approval
Materials reviewed	Action package

1. Introduction

This 505(b) (2) new drug application (NDA 206-323) submission by Nexgen on behalf of Spriaso LLC (the Applicant) received August 22, 2014 (submitted August 20), is for an extended release oral tablet combination product of codeine phosphate and chlorpheniramine maleate for the proposed indication of *"relief of cough* (b) (4) *common cold,* (b) (4) *upper respiratory allergies in adults 18 years of age and older."* The Applicant lists Codeprex™ Pennkinetic® (UCB Inc. NDA 021-369) as the reference product for this application. There are no outstanding discipline issues for this application and all disciplines recommend approval. This summary review provides an overview of the salient aspects of the application and the reasons to support the regulatory action.

2. Background

On April 30, 2015, the Agency approved an extended release oral suspension of codeine polistirex and chlorpheniramine polistirex (Tuzistra XR) under NDA 207-768 (Tris Pharma, Inc.) for cough and cold symptoms in adults 18 years of age and older. Prior to this approval, there had not been any marketed codeine/chlorpheniramine extended release products in the market since 1996 although there had been two products approved in the past. The first product to be ever approved was PENTUSS (under NDA 18,928) on August 14, 1985, and contained 10 mg of codeine and 4 mg of Chlorpheniramine /5 mL. That product was withdrawn from the market in 1996 for reasons unrelated to safety or efficacy. The other product (under NDA 21,369) developed by Celltech Pharmaceuticals was approved on June 1, 2004 and contained codeine polistirex and chlorpheniramine polistirex equivalent to 20 mg codeine and 4 mg chlorpheniramine maleate respectively in each 5 mL of product but the product was never marketed. The NDA holder withdrew the NDA on February 21, 2007 but not for reasons related to safety or efficacy. The Applicant's proposed product is for an extended release tablet (different formulation) and thus was submitted as a 505(b) (2).

3. CMC/Device

The chemistry team recommendation is for approval the facilities assessment from the Office of Process and Facilities is complete and there are no approvability issues.

The drug substances are codeine phosphate and chlorpheniramine maleate, both of which conform to their respective USP monographs. The codeine phosphate is manufactured by (b) (4) under DMF (b) (4) and the chlorpheniramine maleate by (b) (4) under DMF (b) (4) 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). (b) (4) hypromellose (b) (4) 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 (b) (4) 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 required or performed for this application.

5. Clinical Pharmacology/Biopharmaceutics

The Applicant submitted two (2) pivotal clinical pharmacology studies to support the application (**LPCN 1084-12-002** and **1084-13-001)**.

Study LPCN 1084-12-002 was a single-dose, crossover study evaluating the relative bioavailability of the extended release (ER) tablet compared to the reference immediate release (IR) tablet and the food effect on the ER tablet. Each ER tablet contained 40 mg codeine phosphate and 8 mg chlorpheniramine maleate and each IR tablet contained 20 mg codeine phosphate and 4 mg chlorpheniramine maleate.

Table 1: Bioavailability Parameters at Steady State in Fasted Conditions

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)	52	14.5	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

The table shows that the bioavailability parameters for the ER and IR products fell within the bioequivalence goal posts of 80 – 125% bioequivalence limits. In addition the effect of food was evaluated and showed that the bioavailability of codeine from the ER tablet in fed conditions is similar to that of the IR tablet in fasted conditions (Cmax and AUC_{inf} values). As such, the effect of food on the ER tablet is not considered to be clinically relevant.

Study 1084-**13-001 was a multiple-dose**, 2-way crossover study that evaluated the relative bioavailability of the ER tablet compared to the reference product. The study showed that at steady state the 90% CIs for the test/reference for both codeine and chlorpheniramine were within the 80-125% confidence limits for bioequivalence.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical - Efficacy

The application relies on a comparison of the bioavailability of the proposed drug product to that of immediate release reference products. No clinical efficacy studies were conducted, because bioequivalence was demonstrated.

8. Safety

The safety of the product is based on establishing bioequivalence of the product compared to the reference products. In addition, for the original NDA submission, the Applicant provided a Summary of Clinical Safety including reference to the monograph and 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 was not held for this NDA. The 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 for approval of combination products with these individual ingredients (codeine and chlorpheniramine) for cough/cold indications.

10. Pediatrics

As a new dosage form this product triggers PREA. The applicant has an agreed upon pediatric plan and it was discussed at the Pediatric Review Committee (PeRC) meeting on May 27. PeRC has agreed with the plan which is a deferral for PK and safety studies in children 6 to 17 years of age and a waiver for patients under 6years of age. The EMA recently announced recommendations regarding use of codeine-containing cough/cold products in the pediatric population because of safety concerns and limited (or lack of) demonstration of efficacy. These recommendations call for a "contraindication" in children below 12 years of age and a "do not recommend" recommendation for children 12 to 18 years of age. In light of this recommendation, FDA is re-evaluating the use of codeine –containing cough/cold products in children and the PREA requirements for this application may change in the future depending on the outcome of this reevaluation.

11. Other Relevant Regulatory Issues

Inspections

The Office of Scientific Investigation (OSI) was requested to conduct an inspection for the multiple dose steady state relative bioavailability study (Study LPCN 1084-13-001). The clinical site inspected was the QPS Bio-Kinetic at 1816 W. Mount Vernon St., Springfield, MO 65802. Following review the Office concluded that the data from the study could be relied upon for Agency review.

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

The Applicant submitted multiple trade names none of which were deemed acceptable. (b) (4)

Physician Labeling

The Applicant submitted a label in Physician's Labeling Rule (PLR) format but the label had to undergo extensive revisions to ensure that it 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 was 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

A detailed review of the carton and immediate container labels was conducted by the individual disciplines of the Division in consultation with the other labeling review groups in the Agency. The Division and Applicant have agreed on final carton and container labeling.

Patient Labeling and Medication Guide

There is no separate medication guide for this product and the Applicant was asked to provide a patient package insert (similar to what was developed for Tuzistra) and the Applicant and the Division have come to agreement on the patient labeling.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The submitted pharmacology data support the bioequalence of the ER product to the immediate release reference product and can therefore be approved. The Applicant proposes the product for use in adults 18 years of age and older and this is reasonable. The label will reflect that safety and efficacy in children under 18 years of age has not been established.

- 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 and literature and AERS database searches, 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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