CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207768Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	April 30, 2015
From	Lydia I Gilbert-McClain, MD, FCCP
Subject	Division Director Summary Review
NDA# **Supplement#**	207,768
Applicant	Tris Pharma, Inc.
Date of Submission	June 27, 2014
PDUFA Goal Date	April 30, 2015
Proprietary Name / Established (USAN) names	Tuzistra XR/ Codeine polistirex and chlorpheniramine polistirex Extended Release Oral Suspension
Dosage forms / Strength	Oral suspension (extended release) codeine polistirex which contains 14.7 mg of codeine (equivalent to 20 mg codeine phosphate) and chlorpheniramine polistirex, which contains 2.8 mg of chlorpheniramine (equivalent to 4 mg chlorpheniramine maleate) per 5 mL
Proposed Indication(s)	Relief of cough and (b) (4) upper respiratory allergies in adults 18 years of age and older.
Recommended Action:	Approval with revised indication statement
Materials reviewed	

1. Introduction

This 505(b) (2) new drug application (NDA 207,768) submission by Tris Pharma, Inc. (the Applicant) received June 30, 2014, is for an extended release oral suspension combination product of codeine polistirex and chlorpheniramine polistirex for the proposed indication of *"relief of cough and* (b) (4) *upper respiratory allergies in adults 18 years of age and older."* The Applicant lists Codeprex™ Pennkinetic® (UCB Inc. NDA021-369) 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

There are currently no extended release codeine cough/cold products on the market. There have been two products approved in the past. The first product (under NDA 18,928) was approved on August 14, 1985, as PENTUSS and contained 10 mg of codeine and 4 mg of Chlorpheniramine /5 mL. This product was withdrawn from the market in 1996 for reasons unrelated to safety or efficacy.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. That product was never marketed and 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 the same formulation as the Celltech Pharma codeine/chlorpheniramine extended release suspension product, however, the Applicant's product could not be submitted under the 505(j) pathway because the strength of the individual ingredients are different as noted below:

Table 1: Comparison of Applicant's codeine/chlorpheniramine ER product to Reference product

	Codeine/CPM ER oral suspension	Codeprex Pennkinetic
Active ingredient Strength (per 5 mL)		
Codeine Base	14.7 mg (anhydrous)	20 mg
Chlorpheniramine Maleate	4 mg	4 mg
Chlorpheniramine Base	2.8 mg	n/a
Active Ingredient in Single Adult Dose (10 mL)		
Codeine Base	29.4 mg (anhydrous)	40 mg
Chlorpheniramine Maleate	8 mg	8 mg
Chlorpheniramine Base	5.6 mg	n/a

3. CMC/Device

The proposed product is a reddish pink colored viscous suspension of codeine polistirex and chlorpheniramine polistirex. Each 5 mL of the proposed product contains 14.7 mg codeine base (equivalent to 20 mg of codeine phosphate) and 2.8 mg of chlorpheniramine base (equivalent to 4 mg of chlorpheniramine maleate) per 5 mL. The inactive ingredients are purified water, sodium polystyrene sulfonate, ethyl maloti, povidone, triacetin, polyvinyl acetate, polysorbate 80, citric acid, sodium citrate, sucrose, starch, D&C Red No.30, glycerin, methylparaben, propylparaben, propyl gallate, xanthan gum, and cherry flavor. There are no outstanding product quality, microbiology, DMF, or facilities inspection issues. The product will be supplied in 16 oz. Amber (b) (4) containers (b) (4) The stability data support a 24 month expiry at 20 C to 25°C with excursions permitted to 15° C to 30°C.

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 four (4) clinical pharmacology studies in this application two of which were the pivotal bioavailability studies (**3007116** and **3007117**). These studies evaluated the relative bioavailability of the codeine /chlorpheniramine extended release oral suspension (Test Product) against single ingredient immediate release products (Reference Product). The reference product for this NDA Codeprex™ Pennkinetic® is currently discontinued, therefore, for comparative bioavailability studies the Applicant utilized an in-house manufactured codeine phosphate and chlorpheniramine maleate (COD-CPM) IR oral solution, containing 20 mg codeine phosphate and 4 mg chlorpheniramine maleate per 5 mL. This methodology is acceptable as both codeine and chlorpheniramine are monograph ingredients.

Study 3007116 was a multiple-dose, open-label, randomized, two-period, and two-treatment crossover study conducted in 32 healthy adult subjects to establish the pharmacokinetic profile of the Test Product, in comparison with the COD-CPM IR solution (Reference Product), at steady state. The study showed that both the AUC_{0-12} and C_{max} for codeine and chlorpheniramine in the Test Product were bioequivalent to the Reference Product. Of note, the C_{min} for codeine was outside of the 90% confidence limits (see table below taken from Dr. Janet Maynard's CDTL memo) but this observation is not expected to impact the overall efficacy of the product.

Table 2: Bioavailability Parameters at Steady State in Fasted Conditions

Parameter	Codeine			90% Confidence Interval
	Geometric Mean [a]		%Ratio [b]	
	Test	Ref		
AUC_{0-12} (ng·h/mL)	367.9	412.9	89.1	85.1 – 93.3
C_{max} (ng/mL)	61.5	65.5	93.9	87.7-100.5
C_{min} (ng/mL)	9.4	14.5	**64.4**	**60.8-68.3**
C_{avg} (ng/mL)	30.6	34.4	89.1	85.1-93.2
Parameter	**Chlorpheniramine**			**90% Confidence Interval**
	Geometric Mean [a]		**%Ratio [b]**	
	Test	**Ref**		
AUC_{0-12} (ng·h/mL)	365.3	376.3	97.1	91.8-102.6
C_{max} (ng/mL)	35.8	36.2	98.8	92.8 – 105.1
C_{min} (ng/mL)	24.4	25.6	95.1	89.1-101.7
C_{avg} (ng/mL)	30.4	31.3	97.0	91.8-102.6

Study **3007117** evaluated the effect of food on the Test Product following administration with a high-fat, high-calorie meal and the results support a statement in labeling that the product could be taken with or without food because the bioavailability of the Test Product under fed conditions is similar to that of the Reference Product under fasted conditions.

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

During the drug development period the Applicant was advised that their proposed product would trigger PREA and they submitted a Pediatric study plan (b) (4) However, upon further discussion at the Pediatric Review Committee (PeRC) meeting on March 4, 2015, it was determined that the application does not trigger PREA since the product does not contain a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. (b) (4)

11. Other Relevant Regulatory Issues

Inspections
The Office of Scientific Investigation (DSI) was requested to conduct an inspection for the multiple dose steady state relative bioavailability study (Study 3007116). Since the clinical site had been inspected four times during the last two years, the Division of Bioequivalence and GLP compliance (DBGLPC) recommended that we accept the data without on-site inspection in view of the recent multiple inspections that had been conducted. I concur with this recommendation.

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 proposed trade name, Tuzistra XR , was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and deemed acceptable.

Physician Labeling

The Applicant submitted a label in Physician's Labeling Rule (PLR) format. The label was revised to be consistent with other similar cough and cold combination products, such as Zutripro, Vituz, and Codeprex. Changes were made to the Indication section to reflect the population, for which it would be used, those with respiratory tract symptoms due to the common cold and respiratory allergies. Further, a boxed warning was added 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 metabolizers of Codeine due to CYP2D6 polymorphism. Additionally, the Warnings and Precautions were updated to reflect the risk of dose-related respiratory depression and drug dependence.

The Applicant initially proposed to label the product as (b) (4) respectively. However, the salts of the drug substances are exchange (b) (4) The CMC labeling committee for OPQ, and the medical team came to an agreement that the Applicant should use

the USAN name and use the strength of the base for both drug substances which would be consistent with USP <1121> Monograph "Naming Policy for Salt Drug Substances in Drug Products." Therefore, the label notes that the proposed drug is codeine polistirex and chlorpheniramine polistirex extended release oral suspension with strengths expressed as 14.7 mg codeine and 2.8 mg chlorpheniramine. A statement of equivalence to the respective codeine phosphate and chlorpheniramine maleate salts is included in the package insert. Labeling discussions have been completed and the Applicant and the Division have come to agreement on the labeling.

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. The Applicant has proposed a patient package insert 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
  None

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/s/

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04/30/2015