CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207768Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	207768
Priority or Standard	Standard
Submit Date(s)	June 27, 2014
Received Date(s)	June 30, 2014
PDUFA Goal Date	April 30, 2015
Division / Office	DPARP/ODEII
Reviewer Name(s)	Suzette Peng, MD
Review Completion Date	Wednesday, March 25, 2015
Established Name	Codeine polistirex and chlorpheniramine polistirex ER (COD-CPM ER)
(Proposed) Trade Name	Tuzistra XR
Therapeutic Class	Antitussive/antihistamine/ (b) (4)
Applicant	Tris Pharma, Inc.

Formulation(s)	Oral suspension
Dosing Regimen	10 mL every 12 hours, with or without food, not to exceed 2 doses (20 mL) in 24 hours
Indication(s)	Relief of cough and (b) (4) upper respiratory allergies
Intended Population(s)	Adults 18 years of age and older

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

No table of figures entries found.

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The recommendation on regulatory actions is approval of New Drug Application (NDA) 207768 for codeine polistirex and chlorpheniramine polistirex extended-release (COD-CPM ER) oral suspension for the relief of cough and symptoms associated with upper respiratory allergies or a common cold in adults 18 years of age and older.

1.2 Risk Benefit Assessment

Overview of the Clinical Program

Tris Pharma, Inc. submitted NDA 207768 on June 27, 2014, to support the approval of Tuzistra XR (COD-CPM ER oral suspension) for the relief of cough and (b) (4) upper respiratory allergies in adults 18 years of age and older. (b) (4)

This applications is a 505(b)(2) application and relies on the following: (1) information from 21 CFR regarding the use of codeine and chlorpheniramine maleate as safe and efficacious antitussive and antihistamine products and (2) the basis of approval for reference product, Codeprex® Pennkinetic™. Of note, Codeprex Pennkinetic was withdrawn from the market for reasons unrelated to safety. The applicant has performed 2 pivotal bioavailability (BA) studies to support the development and registration of this COD-CPM ER oral suspension. Study 3007117 was a single dose study in 32 healthy subjects, comparing the test product to reference product under fasting and fed conditions. Study 3007116 was a multiple dose study in 32 healthy subjects. Both studies were sufficient to show that the pharmacokinetic (PK) parameters were bioequivalent between test and reference product.

No separate efficacy studies were performed. Efficacy information was based on what is available in the monograph and what is known regarding the reference product.

In regards to safety, data from the 2 pivotal BA studies were assessed. However, the exposure from these 2 BA studies was very low, and, thus, no definitive conclusions can be made from these studies alone. Rather, these studies served as an adjunct to what is known in regards to safety from the monograph and from the reference product.

Overall, the adverse events in both studies were low and were comparable between all treatment arms (test and reference product). The most common adverse events were constipation, headache, and dizziness. There were no deaths and no serious adverse events. No unexpected adverse events occurred. Therefore, the safety profile of this product appears to be acceptable. The labeling will reflect important safety considerations, including the risk of respiratory deprrsion and death with with the use of codeine in the post-operative setting in children. Although the applicant is not currently seeking an indication in children, there is the possibility of off-label use.

Risk-Benefit Assessment

The overall risk-to-benefit profile of this COD-CPM ER oral suspension for the relief of cough and symptoms associated with upper respiratory allergies or a common cold is favorable. The pivotal BA studies, the OTC monograph, and the reference product all support the efficacy and safety of the COD-CPM ER oral suspension.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no current recommendations for postmarket risk evaluation and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

No specific Phase 4 requirements or commitments are recommended at this time.

This application does not meet Pediatric Research Equity Act (PREA) requirements to perform a pediatric study. In comparison to the approved (although no longer marketed) reference drug Codeprex Pennkinetic ER suspension, this COD-CPM ER oral suspension does not contain a new active ingredient, is not being used for a new indication, is not a new dosage form, is not a new dosing regimen, and does not utilize a new route of administration. This COD-CPM ER oral suspension differs from the reference product by the dosage strength of codeine, and it has been determined that this difference does not trigger PREA.

2 Introduction and Regulatory Background

2.1 Product Information

This submission is a 505(b)(2) New Drug Application (NDA 207768) for use of a codeine polistirex and chlorpheniramine polistirex (COD-CPM) extended release (ER) oral suspension, equivalent to 20mg codeine phosphate and 4mg chlorpheniramine maleate per 5mL. The proposed indication is for "relief of cough an (b) (4) upper respiratory allergies in adults 18 years of age and older." As an extended-release formulation, the Applicant proposes a dosing regimen of 10mL (equivalent to 40mg codeine phosphate and 8mg chlorpheniramine maleate) every 12 hours, with or without food, not to exceed 2 doses (20mL) in 24 hours in adults 18 years of age and older.

As a basis for the 505(b)(2) submission, the applicant relies on the Agency's safety and efficacy findings from the following sources:

(1) Basis of approval for the reference product, Codeprex™ Pennkinetc® (NDA 021369)

(2) The over-the-counter (OTC) monographs
- 21 CFR 341.14(a)(2)(ii) Codeine phosphate as a safe and efficacious antitussive drug product
- 21 CFR 341.12(c) Chlorpheniramine maleate as a safe and efficacious antihistamine drug product
- 21 CFR 341.74(d)(ii): The recommended dosing for codeine phosphate as an antitussive product is 10 to 20mg every 4 to 6 hours, not to exceed 120mg in 24 hours.
- 21 CFR 341.72(d)(3): The recommended dosing for chlorpheniramine maleate as an antihistamine product is 4mg every 4 to 6 hours, not to exceed 24mg in 24 hours.
- 21 CFR 341.40(d) Permitted use of codeine phosphate and chlorpheniramine maleate in combination

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 prophylamine derivative antihistamine (H1-receptor antagonist) of the alkylamine class that also possesses anticholinergic and sedative activity.

Antihistamines diminish or abolish the major actions of histamine in the body by competitive, reversible blockade of H1 receptors in tissues and, thereby, prevent released histamine from dilating capillaries and causing edema of the respiratory mucosa. Chlorpheniramine maleate is used for the relief of allergic symptoms (rhinorrhea, sneezing, oronasopharyngeal irritation or itching, lacrimation, and red/irritated/itching eyes) caused by histamine release. It is used either alone or in fixed combination with other agents for relief of the symptom listed above as well as other symptoms (nasal/sinus congestion, cough) associated with inhaled irritants or allergic rhinitis (hay fever).

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). 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 suspension under review in this NDA contains 40mg of codeine phosphate (in polistirex) representing 29.4mg of free codeine base in each dose (10 mL). Similarly, the ER suspension contains 8mg of chlorpheniramine maleate (in polistirex) representing 5.6mg of free chlorpheniramine base in each dose (10 mL).

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 solely 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.

Table 1. 21 CFR Part 341 Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for OTC Human Use

341.12 Antihistamine	(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
341.14 Antitussive	(a) Oral antitussives (1) Chlophedianol hydrochloride (2) Codeine ingredients (i) Codeine (ii) Codeine phosphate (iii) Codeine sulfate (3) Dextramethorphan (4) Dextromehorphan hydrobromide (5) Diphenhydramine citrate (6) Diphenhydramine hydrochloride (b) Topical antitussives (1) Camphor (2) Menthol
341.16 Bronchodilator	(a) Ephedrine (b) Ephedrine hydrochloride (c) Ephedrine sulfate (d) Epinephrine (e) Epinephrine bitartrate (f) Racephedrine hydrochloride (g) Racepinephrine hydrochloride
341.18 Expectorant	Guaifenesin
341.20 Nasal decongestant	(a) Oral nasal decongestants (1) Phenylephrine hydrochloride (2) Pseudroephedrine hydrochloride (3) Pseudoephedrine sulfate (4) Phenylephrine bitartrate in an effervescent dosage form (b) Topical nasal decongestants (1) Levmetamfetamine (2) Ephedrine (3) Ephedrine hydrochloride (4) Ephedrine sulfate (5) [Reserved] (6) Naphazoline hydrochloride

	(7) Oxymetazoline hydrochloride (8) Phenylephrine hydrochloride (9) Propyhexadrine (10) Xylometazoline hydrochloride

Source: Title 21 of the Code of Federal Regulations.

2.3 Availability of Proposed Active Ingredient in the United States

Multiple products are currently available in the US containing codeine as an individual or combination product for cold/cough and for analgesia. Some examples of products with codeine include codeine sulfate, Tylenol #3 (acetaminophen/codeine phosphate), and Fioricet with Codeine (butalbital/acetaminophen/caffeine/codeine phosphate). Similarly, chlorpheniramine is an active ingredient in multiple products, as an individual ingredient or as part of a combination product. Examples of products with chlorpheniramine include Chlor-Trimeton (chlorpheniramine, NDA 07638), Vicks NyQuil Cold & Flu Relief (acetaminophen/chlorpheniramine/destromehorphan), and Advil Allergy/Sinus tablets (ibuprofen/pseudophedrine/chlorpheniramine, NDA 21441).

The focus of this review is the combination of codeine and chlorpheniramine for cold and cough. There are a number of immediate release (IR) liquid products containing codeine and chlorpheniramine available on the market. These contain the active ingredients at concentrations that enable them to be marketed in accordance with 21 CFR Part 341; therefore, none have been approved via an NDA. Most of these products contain codeine phosphate at 10mg per 5mL, and almost all contain chlorpheniramine at 2mg per 5mL.

In the past 3 decades, two extended-release drug products containing codeine and chlorpheniramine have been approved in the US.

- Pentuss® (Fisons, NDA 018928, approved on 08/14/1985) contained codeine, 10mg free base equivalents, and chlorpheniramine, 2.8mg free base equivalents, per 5mL. This was equivalent to 10mg codeine phosphate and 4mg chlorpheniramine maleate. It was withdrawn from the market in 1996 for reasons unrelated to safety or efficacy.

- Codeprex™ Pennkinetic® (UCB Inc., NDA 021369) contained codeine, 20mg free base equivalents, and chlorpheniramine, 2.8mg free base equivalents per 5mL. Codeprex was never marketed in the US, and UCB eventually withdrew the NDA for reasons unrelated to safety and efficacy (memo dated 03/20/2007). As mentioned, Codeprex is the reference drug product.

2.4 Important Safety Issues With Consideration to Related Drugs

Both codeine and chlorpheniramine (as individual and combination products) have been available for use for a long time, and there are numerous publicly available nonclinical and clinical study reports. Therefore, the safety of each of the active ingredients has been well established.

The primary risk of codeine use is respiratory depression and, to a lesser degree, circulatory depression. Respiratory depression is a particular concern when codeine is used as an analgesic after tonsillectomy and/or adenoidectomy. As of February 2013, the Agency added a boxed warning for the use of codeine in this setting. This safety concern arose from deaths that occurred in children with OSA who were post-operative from tonsillectomy and/or adenoidectomy and who were ultra-rapid metabolizers of codeine. It should be noted that the COD-CPM ER oral suspension is not currently seeking labelling for children.

In addition, the following are important safety issues associated with codeine. These are safety issues that should be represented in the product's PI (prescribing information).

- Codeine can produce drug dependence and has the potential for being abused.
- Because opioids like codeine can elevate cerebrospinal fluid pressure, respiratory depression can be exaggerated in the presence of head injury, intracranial lesions, or other conditions that are associated with an increase in intracranial pressure (pre-existing or new).
- Again, because codeine is an opioid, it may lead to GI hypomobility. Therefore, in patients with underlying intestinal motility disorders, chronic use of codeine may lead to obstructive bowel disease.
- Similarly, codeine may lead to paralytic ileus when used with anticholinergics.
- Codeine may also obscure the diagnosis or clinical course of patients with acute abdominal conditions.

The most frequently observed adverse reactions with codeine administration include drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, sweating, and constipation. Other adverse reactions include allergic reactions, euphoria, dysphoria, abdominal pain, and pruritus. In addition, patients with increased intracranial pressure, head trauma, or other intracranial lesions have the potential for increased elevation of cerebral spinal fluid pressure. Other CNS effects include anxiolysis and feelings of relaxation. Codeine may also cause miosis.

Common adverse effects of chlorpheniramine are sedation (drowsiness, dizziness, weakness) and CNS stimulation (restlessness, insominia, nervousness).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Pre-IND Meeting

A pre-IND meeting was held on October 26, 2012, between FDA and representatives from Tris Pharma, Inc. The meeting provided general advice on the Chemistry, Manufacturing, and Controls (CMC), nonclinical, and clinical development plan for the COD-CPM ER oral suspension. The Agency agreed that a 505(b)(2) NDA submission would be an acceptable approach for this product that was a new dosage strength. As a 505(b)(2) application, the referenced list drug would need to be a specific drug, not just the OTC monograph 21 CFR 341. The Agency generally agreed with the proposed single-dose and multi-dose PK studies to demonstrate bioequivalence between the test product and the reference product. (b) (4) Lastly, the Agency agreed that no further toxicology studies were required for safety assessments of the active ingredients.

IND Submission

Tris Pharma, Inc. submitted IND (b) (4) for COD-CPM ER oral suspension on July 29, 2013. A CMC information request was sent to Tris on August 13, 2013, asking for more details on drug product manufacturing. On August 15, 2013, Tris submitted an amendment to DMF 027314 with additional information and responses to the Agency's questions. Tris received verbal approval to proceed on August 27, 2013 and subsequent received the formal STUDY MAY PROCEED letter on September 18, 2013. The letter included additional recommendations from clinical pharmacology including a dietary restriction for grapefruit, grapefruit juice, grapefruit-containing products, orange juice, or orange-containing products to be instituted one week prior to dosing until study completion. Per Tris, the single-dose study (3007117) had already been initiation, so this recommendation was not instituted. However, it was instituted as an amendment for study 3007116 (multi-dose study).

Proprietary Name Review

On December 12, 2013, Tris submitted a Request for Proprietary Name Review for COD-CPM ER oral suspension for the name Tuzistra XR. The Agency found that the name was acceptable and conveyed this conditional acceptance on June 7, 2014.

Pediatric Study Plan

On December 3, 2013, Tris Pharma, Inc. submitted an initial Pediatric Study Plan (iPSP), which requested a full waiver of studies for all pediatric groups. The Agency responded to the iPSP on February 26, 2014. (b) (4)

[redacted]

(b) (4)

[redacted] Of note, the Agency has subsequently determined that the application does not trigger PREA during review of this NDA.

2.6 Other Relevant Background Information

Not applicable

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The electrical NDA submission was well-organized and complete, and there were no amendments.

3.2 Compliance with Good Clinical Practices

Tris states that the clinical development program for COD-CPM ER oral suspension was conducted in compliance with the protocol, International Conference on Harmonisation (ICH), Guideline for Good Clinical Practice (GCP): Consolidated Guidance (E6), and applicable regulatory requirement(s) including clinical research

guidelines established by the Basic Principles defined in the US 21CFR Parts 50, 56, 312 and the principles enunciated in the Declaration of Helsinki.

The protocol, Informed Consent documents, and all other study-related material were reviewed by the IntegReview Ethical Review Board. The Board is constituted and operates in accordance with the principles and requirements described in the US CFR Part 56. Written informed consent was obtained from each subject prior to performing any baseline study-specific evaluations.

The Office of Scientific Investigations (OSI) was requested to perform routine audits of the clinical sites because the pivotal study is a comparative bioavailability study and because the reference solution is prepared in-house. The Division of Bioequivalence and GLP Compliance (DBGLPC) in OSI recommends accepting the data without on-site inspections of the clinical site, Worldwide Clinical Trials Early Phase Services (WCT), San Antonio, TX, and the bioanalytical site, (b) (4) DBGLPC elucidates the reasoning in a memo dated November 4, 2014. In summary, OSI inspected the clinical site four times during the last 2 years and the bioanalytical site seven times during the last 2 years. Audits included a thorough review of study records, study protocol compliance, informed consent documents, case report forms, examination of facilities and test article accountability, as well as interview and discussions with the firm's management and staff. The audits of the analytical site resulted in all NAIs (no action indicated). The audits of the clinical site did results in 2 VAIs (voluntary action indicated) and 1 OAI (official action indicated). Per DBGLPC, it is unlikely that the same irregularities and errors that resulted in the VAIs. Additionally, the pivotal BA studies in this NDA were performed from December 2013 to January 2014, after corrective actions to the OAI were verified. The most recent inspection of the clinical site (April 2014) resulted in NAI and provides assurance that the pivotal BA studies were performed without significant irregularities. Given DBGLPC's conclusions, an OSI audit was not performed for this NDA.

3.3 Financial Disclosures

Tris Pharma, Inc. submitted FDA Form 3454 certifying that Tris did not enter any financial arrangement with the clinical investigator (b) (6) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). Tris also certified that the clinical investigator was required disclose to the Applicant whether the investigator had a proprietary interest in this product or a significant equity in the Applicant as defined in 21 CFR 54.2(b), and no such disclosures were made. Lastly, Tris certified that this investigator was not the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

A clinical review of the financial disclosure is located in Section 9.5 Financial Disclosure Review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

For this NDA, Tris Pharma, Inc. filed Drug Master File (DMF) 027314 to describe the formulation development, manufacture, and testing of the drug product, codeine polistirex and chlorpheniramine polistirex ER oral suspension, and the reference product, codeine phosphate and chlorpheniramine maleate IR oral solution.

For the ER oral suspension, codeine phosphate and chlorpheniramine maleate are used as drug substances in the manufacturing process. The phosphate and maleate (b) (4). Therefore, the strength of the active ingredients should reflect what is actually in the drug product, i.e., the free base codeine and chlorpheniramine. This was communicated to the Applicant at the time of IND review.

The COD-CPM ER oral suspension contains 14.7mg codeine base and 2.8mg chlorpheniramine base in 5 mL. This is equivalent to 20mg of codeine phosphate and 4mg of chlorpheniramine maleate per 5 mL. The inactive ingredients are purified water, sodium polystyrene sulfonate, ethyl maltol, pvoidone, triacetin, polyvinyl acetate, polysorbate 80, citric acid, sodium citrate, sucrose, starch, D&C Red No.30, glycerin, methylparaben, propylparaben, propyl gallate, xantham gum, and cherry flavor.

Table 2 compares the composition (strengths) of the COD-CPM ER oral suspension under review along with the reference listed drug (RLD) Codeprex Pennkinetic as well as Pentuss, the other ER product. The major difference between the products is the dosage strength of the codeine base.

Table 2. Composition of Proposed and Currently Approved COD-CPM ER Products

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

Source: NDA 207768, Section 3.2.P.1.2, Description and Composition of Drug Product.
Agency CMC review by Drs. Ciby Abraham and Craig Bertha

The IR solution product was manufactured by Tris as a reference product for conducting the pivotal BA studies since there are no prescription ER and/or IR products currently on the market containing codeine phosphate and chlorpheniramine maleate combination. The solution formulation contains 20mg codeine phosphate and 4mg chlorpheniramine maleate per 5mL. The solution contains the following excipients: glycerin, methylparaben, propylparaben, propyl gallate, purified water, ethyl maltol, citric acid anhydrous, sodium citrate, sucrose, and cherry flavor.

There are no chemistry, manufacturing, or control issues that would prevent approval of the COD-CPM ER oral suspension.

4.2 Clinical Microbiology

This COD-CPM ER oral suspension is not an anti-microbial product. A microbiology review of DMF (b) (4) confirmed that this is a non-sterile, (b) (4), oral suspension and, thus, there are no clinical microbiology issues that would prevent approval.

4.3 Preclinical Pharmacology/Toxicology

No preclinical pharmacology or toxicology studies were conducted with the COD-CPM ER oral suspension.

As a 505(b)(2) application, Tris Pharma, Inc. relies on the Agency's previous findings for codeine and chlorpheniramine both individually and in combination to support the application. Specifically, for nonclinical data, the applicant refers to the published literature on nonclinical pharmacology, PK, and metabolism of the active ingredients. In addition, the applicant reviewed the literature for selective references to established nonclinical information and for new, publically-available (since 2004 when Codeprex Pennkinetic was approved) nonclinical information related to codeine and chlorpheniramine that might inform safety and efficacy. The literature was searched in PubMed, ToxNet, FDA.gov, and RepDose for the following key topics: absorption, adverse events and toxicology, carcinogenicity, CNS effects, distribution, effects on endocrine system, embryonic and fetal development, embryotoxiciy, excretion, fertility, fetal development, fetotoxicity, genotoxicity, hypersensitivity, immune system, metabolism, mutagen, mutagenicity, pharmacodynamics, pharmacokinetics, pharmacology, preclinical toxicity, reproductive toxicity, respiratory depression, and toxicity. Per Tris Pharma, Inc., this literature search uncovered some reports that confirm prior nonclinical findings or elucidated a mechanism of action; however, literature review uncovered no significant new nonclinical data on the safety and efficacy of either codeine or chlorpheniramine, administered alone or in combination.

4.4 Clinical Pharmacology

The clinical development program in this application was comprised of 2 pivotal and 2 pilot clinical pharmacokinetic studies. Table 6 summarizes the studies that make up the clinical program. The 2 pilot studies (3006726 and 3007132) were conducted to support early formulation development. The 2 pivotal studies (3007116 and 3007117) evaluated the relative bioavailability between COD-CPM ER oral suspension and a reference product following single and multiple dose administration. These pivotal studies were conducted to support the development and registration of the new ER product, and, thus, these are the studies that are important to review from a clinical and clinical pharmacology perspective. The design of studies 3007116 and 3007117 is described in detail below in Sections 5 Sources of Clinical Data.

4.4.1 Mechanism of Action

The precise mechanism of action of codeine is not known, but it is believed to act in the medulla with depression of the cough center and to a lesser degree the respiratory center. Chlorpheniramine is an antihistamine and also possesses anticholinergic and sedative activity.

4.4.2 Pharmacodynamics

As detailed above, the clinical development program was comprised of 4 bioavailability studies. No PD studies were performed.

4.4.3 Pharmacokinetics

The PK results from the two pivotal comparative bioavailability studies have been thoroughly reviewed by the Agency's clinical pharmacology team, Ritesh Jain, PhD, and Satjit Brar, PharmD, PhD. Please see the primary clinical pharmacology review for details. Below is a summary taken from Dr. Jain and Brar's review.

Study 3007117 is the single dose study, and the PK results are discussed here first. The following pharmacokinetic variables were calculated for each treatment: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, and $t_{1/2}$. The results of Study 3007117 are shown in the Table 3 below.

Table 3. 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 Suspension) and Reference Product (COD-CPM IR Solution) under Fasted Conditions. (Study 3007117)

Parameter	Codeine			90% Confidence Interval
	Geometric Mean [a]		%Ratio [b]	
	Test	Ref		
AUC_{last} (ng·h/mL)	324.9	384.1	84.6	81.0 - 88.3
AUC_{inf} (ng·h/mL)	336.5	393.2	85.6	82.1 - 89.2
C_{max} (ng/mL)	49.5	53.9	91.7	85.3 - 98.5
Parameter	**Chlorpheniramine**			**90% Confidence Interval**
	Geometric Mean [a]		**%Ratio [b]**	
	Test	**Ref**		
AUC_{last} (ng·h/mL)	267.1	307.1	86.9	83.4 - 90.7
AUC_{inf} (ng·h/mL)	287.9	324.1	88.8	85.3 - 92.6
C_{max} (ng/mL)	7.7	11.47	67.3	64.7 - 69.9

[a] Geometric Mean for Test Formulation-Fasted (COD-CPM ER Suspension) and Reference Product-Fasted (COD-CPM IR Solution) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
Source: NDA 207768 study 3007117 and FDA Clinical Pharmacology Review (Drs. Ritesh Jain and Satjit Brar)

For codeine, the 90% CIs for the test/reference ratios of the geometric means for both C_{max} and AUC_{inf} were within the BE limits of 80 – 125%. For chlorpheniramine, the 90% CI for the ratio of the geometric means for AUC_{inf} was within the BE limits of 80 – 125%,

while the 90% CIs for C_{max} fell outside the BE limits (90% CI = 64.7 – 69.9, point estimate = 67.3). Typically, the ER product is expected to have lower C_{max} since the ER product is designed to reduce the peaks and provide slower drug release as compared to the IR product.

In addition, the effect of food on the pharmacokinetics of COD-CPM ER suspension was evaluated in study 3007117 where COD-CPM ER Oral Suspension was administered under fed (high fat meal) and fasted conditions. Results of the food effect assessment are presented in Table 4 below.

Table 4. 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 (Study 3007117)

Parameter	Codeine			90% Confidence Interval
	Geometric Mean [a]		%Ratio [b]	
	Fed	Fasted		
AUC_{inf} (ng·h/mL)	423.1	337.2	125.5	118.8 – 132.5
C_{max} (ng/mL)	55.9	49.7	112.7	103.5 – 122.6
Parameter	**Chlorpheniramine**			**90% Confidence Interval**
	Geometric Mean [a]		**%Ratio [b]**	
	Fed	**Fasted**		
AUC_{inf} (ng·h/mL)	284.2	288.8	98.4	93.8-103.2
C_{max} (ng/mL)	6.4	7.7	83.6	78.5-89.0

[a] Geometric Mean based on Least Squares Mean of log transformed parameter values
[b] Ratio(%) = Geometric Mean (Fed)/Geometric Mean (Fasted)
Source: NDA 207768 Study 3007117 and FDA Clinical Pharmacology Review (Drs. Ritesh Jain and Satjit Brar)

Food has no impact on the C_{max} of codeine. However, in the presence of food, an increase in exposure ~25% (AUC_{inf}) for codeine was observed. However, in the same study, head-to-head comparison of AUC_{inf} of the COD-CPM ER oral suspension under fed state to the COD-CPM IR oral solution under fasting condition showed similar exposure with ratios of geometric means for AUC_{inf} within the BE limits of 80%-125%. Therefore, increased exposure of codeine from COD-CPM ER suspension with high fat meal is comparable to COD-CPM IR solution in the fasted state. Based on monograph limits for codeine and chlorpheniramine, COD-CPM IR solution is used as the reference formulation in this application. Similar exposure data with COD-CPM ER formulation in the presence of food to that with COD-CPM IR solution in fasted state suggest that the increased exposures in the presence of food are within the allowed monograph range.

For chlorpheniramine, the 90% CI for fed/fasted ratios of the geometric means for AUC_{inf} was within the BE limits of 80%-125%, while the 90% CIs for C_{max} fell outside the BE limits (90% CI = 78.5-89.0, point estimate = 83.6). This slight decrease in chlorpheniramine C_{max} is considered not to be clinically significant.

The multidose BA study was study 3007116. The following pharmacokinetic variables were calculated for each treatment: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, and $t_{1/2}$. The results of study 3007116 are shown in the table below.

Table 5. 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 Suspension) and Reference Product (COD-CPM IR Solution) in Fasted Conditions. (Study 3007116)

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

[a] Geometric Mean for Test Formulation-Fasted (COD-CPM ER Suspension) and Reference Product-Fasted (COD-CPM IR Solution) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref);
Source: NDA 207768 Study 3007116 and FDA Clinical Pharmacology Review (Drs. Ritesh Jain and Satjit Brar)

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

It was noted that, for codeine, the C_{min} value from the reference ER product was about 36% lower compared to that from the IR product at steady state. Visual inspection of the mean pharmacokinetic profile indicated a lower systemic exposure from the ER product compared to the IR product between 9 and 12 hours, i.e., the last 3 hours of the dosing interval. The lowest dose for codeine that is allowed by the monograph for cold and cough indication is 10 mg every 6 hours (total daily dose of 40 mg). In this application, the dose of codeine with the ER product is equivalent to codeine phosphate 40 mg every 12 hours (total daily dose of 80 mg). Since much lower doses of codeine in allowed by the monograph as compared to the proposed dose in this application, lower C_{min} values between hours of 9-12, is of limited clinical relevance. In addition, Tuzistra XR is a combination product containing two active ingredients: codeine phosphate, an antitussive for relief of cough, and chlorpheniramine maleate, an antihistamine for relief (b) (4) As a combination product, both the codeine and chlorpheniramine components will contribute to the relief of symptoms associated with the common cold (the desired indication) and, thus, Tuzistra XR does not rely solely on codeine for its indicated benefit. Therefore the lower C_{min} values for codeine between hours of 9-12 are of limited relevance. These aspects were discussed internally between the Office of Clinical Pharmacology and the Division of Pulmonary, Allergy and Rheumatology Products, and it was concluded that the lower C_{min} was not an issue for approval.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Tris Pharma, Inc. performed 4 pharmacokinetic (PK) studies as part of the clinical development program. Two pilot PK studies (Study 3006726 and Study 3007132) were conducted to support early formulation development. Both of these studies are briefly described in Table 6.

Table 6 also summarizes the 2 pivotal bioavailability studies that were conducted to support development and registration of the new ER product, studies 3007117 and 3007116. For the purposes of the clinical review for NDA approval, only these 2 pivotal studies will be reviewed.

Table 6. Listing of Clinical Studies

Study	Objective	Study Design	Test Product	Number of Subjects	Duration of Treatment
3006726 Pilot BA	Compare rate of absorption and oral BA of test ER oral suspension to equivalent IR oral solution	Single-dose, open-label, randomized, 2-period crossover	Test: ER oral suspension 10mL at 0 hr (20mg/4mg per 5mL) Reference: IR oral solution 5mL at 0 hr and 6 hr (20mg/4mg per 5mL)	Healthy 14 enrolled 14 completed	18 days
3007132 Pilot BA	Compare rate of absorption and oral BA of test ER oral suspension to equivalent IR oral solution	Single-dose, open-label, randomized, 2-period crossover	Test: ER oral suspension 10mL at 0 hr (20mg/4mg per 5mL) Reference: IR oral solution 5mL at 0 hr and 6 hr (20mg/4mg per 5mL)	Healthy 14 enrolled 14 completed	18 days
3007116 BA	Compare rate of absorption and oral BA of test to equivalent oral dose of reference	**Multiple-dose**, 2-period, 2-treatment, 2-way crossover	Test: ER oral suspension (20mg/4mg per mL) Reference: Oral solution (20mg/4mg per mL)	Healthy 32 enrolled 32 completed	27 days
3007117 BA	Compare BA of test under fasted and fed conditions Evaluate relative BA of test to reference	**Single-dose**, 3-period, open-label, 3-way crossover	Test: ER oral suspension(20mg/4mg per 5mL) Reference: Oral solution (20mg/4mg per 5mL)	Healthy 36 enrolled 32 completed	32 days

Source: NDA 207768, Section 5.2, Tabular Listing of All Studies.

5.2 Review Strategy

Tris Pharma, Inc., submitted this application under Section 505(b)(2) of the Food, Drug, & Cosmetic Act, which permits approvals to be based on the Agency's previous findings of efficacy and safety of approved or OTC monograph reference products. Thus, this NDA relies on the safety and efficacy findings that provided the basis of approval for the reference product, Codeprex™ Pennkinetic®. In addition, it relies on supportive evidence from the following monograph products:

- Codeine phosphate in 21 CFR 341.14(a)(2)(ii) as a safe and efficacious antitussive
- Chlorpheniramine maleate in 21 CFR 341.12(c) as a safe and efficacious antihistamine
- Dosing for codeine phosphate in 21 CFR 341.74(d)(ii)
- Dosing for chlorpheniramine maleate in 21 CFR (d)(3)

- Use of codeine phosphate and chlorpheniramine maleate in combination in 21 CFR 341.40(d)

No efficacy studies were required or performed, and, thus, no efficacy data will be reviewed. A limited safety assessment will be based on a review of the safety data from the pivotal bioavailability studies 3007116 and 3007117.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study 3007116

Overview of Study Design

Study 3007116 was a multi-dose, open-label, randomized, 2-period, 2-treatment crossover study in which 32 healthy adult subjects received the following:

- Two single-dose administrations of the test product, codeine polistirex and chlorpheniramine polistirex ER oral suspension (equivalent to codeine phosphate 20mg and chlorpheniramine maleate 4mg in each 5mL) at 0 and 12 hours on Days 1 through 6 (inclusive) and one single-dose administration of the test product at 0 hour on Day 7. A single-dose administration was 10mL of the test product. (Treatment A)
- Four single-dose administrations of the reference product, codeine phosphate and chlorpheniramine maleate IR oral solution (20mg/4mg per 5 mL) at 0, 6, 12, and 18 hours on Days 1 through 6 (inclusive) and two single-dose administrations (0 and 6 hours) on Day 7. A single-dose administration was 5mL of the reference product. (Treatment B)

With this study design, each subject served as his/her own control, precluding the need for a separate control group. Each treatment period was separated by at least a 14-day washout, following Day 7, 0-hour dose in Period 1. Per the applicant, this study design is typical for comparative bioavailability and bioequivalence studies.

Subjects were admitted to the research center at least 10.5 hours prior to study drug administration to ensure a minimum 10-hour fast. Subjects remained in the research center until 24 hours after the last dose in each study period. The first drug administration on each study day occurred after a minimum 10-hour overnight fast. All doses were administered with approximately 240 mL (8 oz) of room temperature water. After the first morning dose on Day 7, no food was allowed until 4 hours postdose in order to maintain fasting conditions. Except for the 240 mL of room temperature water provided with each dose, no water was consumed for 1 hour prior through 1 after dose.

During each study period, 6 mL blood samples were obtained daily prior to each morning dose and Day 7 at selected times through 12 hours following the first morning dose. A total of 54 PK blood samples were collected from each patient.

Inclusion Criteria

- Subjects must have been a male or non-pregnant, non-breastfeeding female
- Subjects must have been between 18 and 55 years-of-age (inclusive)
- Subjects' body mass index (BMI) must have been between 18 and 30 kg/m2 (inclusive), and the subject must have weighed a minimum of 50 kg (110 lbs)
- Female subjects must have agreed to use one of the following forms of birth control from screening until 14 days after completion of study.
    - Vasectomized partner (at least 6 months prior to dosing)
    - Post-menopausal (at least 2 years prior to dosing)
    - Surgically sterile (bilateral tubal ligation, hysterectomy, bilateral oophorectomy) at least 6 months prior to dosing
    - Double barrier (diaphragm with spermicide; condoms with spermicide)
    - Intrauterine device (IUD)
    - Abstinence (with agreement to use double barrier method if subject became sexually active during the study)
    - Implanted or intrauterine hormonal contraceptives in use for at least 6 consecutive months prior to study dosing and throughout the study duration
    - Oral, patch, or injected contraceptives or vaginal hormonal device (i.e., NuvaRing) in use for at least 3 consecutive months prior to study dosing and throughout the study duration
- Subject must have voluntarily consented to participate in the study and provided his/her written informed consent prior to the start of any study-specific procedures
- Subject must have been willing and able to remain in the study unit for the entire duration of each confinement period
- Subject's vital signs (measured sitting after 3 minutes rest) must have been within the following ranges. An out-of-range vital sign may have been repeated once. Predose vital signs were assessed by the Principal Investigator or designee prior to study drug administration.
    - Heart rate: 40-100 bpm
    - Systolic blood pressure: 90-140 mmHg
    - Diastolic blood pressure: 50-90 mmHg

Exclusion Criteria

- History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic,

oncologic, or psychiatric disease or any other condition that, in the opinion of the Investigator, would have jeopardized the safety of the subject or the validity of the study results
- Specific history or presence of respiratory depression, acute or severe bronchial asthma or hypercarbia, emphysema or chronic bronchitis, glaucoma, paralytic ileus, or trouble urinating due to an enlarged prostate gland
- Clinically significant abnormal finding on physical exam, medical history, electrocardiogram (ECG), or clinical laboratory results at screening
- History or presence of allergic or adverse response to codeine, chlorpheniramine, any excipients in either the test or the reference products, or related drugs
- Subject had been on a significantly abnormal diet during the 4 weeks preceding the first dose of study medication
- Blood or plasma donation within 60 days prior to the first dose of study medication
- Participation in another clinical trial (randomized subjects only) within 30 days prior to the first dose of study medication
- Use of any over-the-counter (OTC) medication, including nutritional supplements but excluding acetaminophen, within 7 days prior to the first dose of study medication
- Use of any prescription medication, except hormonal contraceptive or hormonal replacement therapy, within 14 days prior to the first dose of study medication
- Subjects who had discontinued the use of implanted, intrauterine, or injected hormonal contraceptives must not have used any for 6 months prior to the first dose of study medication
- Subjects who had discontinued the use of oral, patch, or vaginal hormonal contraceptives must not have used any for 1 month prior to the first dose of study medication
- Treatment with any known drugs that are moderate or strong inhibitors/inducers of CYP enzymes such as barbiturates, phenothizines, cimetidine, carbamazepine, etc. within 30 days prior to the first dose of study medication
- Use of tobacco products within 60 days prior to the first dose of study medication
- History of substance abuse or treatment (including alcohol) within the past 2 years
- Female with a positive pregnancy test result
- Positive urine screen for drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, opiates) or cotinine
- Positive test for Hepatitis B surface antigen, Hepatitis C antibody, or Human Immunodeficiency Virus (HIV) at screening *or* previous treatment for HBV, HCV, or HIV infection
- Subjects were required to adhere to the following **restrictions** during the length of the study:
    - In addition to the exclusion criterion regarding OTC medication at screening, subjects must not have taken OTC medications until the end-of-study visit without evaluation and approval by the Investigator
    - In addition to the exclusion criterion regarding prescription medication, subjects must not have taken any prescription medications, with the exception

of female hormonal contraceptives or hormonal replacement therapy, until the end-of-study visit without evaluation and approval by the Investigator

- Subjects must not have consumed beverages and foods containing alcohol or caffeine/xanthine from 48 hours prior to the first dose of study medication until the end-of-study visit. Subjects were instructed to not consume any of the above products; however, allowance for an isolated single incidental consumption may have been evaluated and approved by the Investigator based on the potential for interaction with the study drug.
- Subjects must not have consumed grapefruit, grapefruit juice, grapefruit-containing products, oranges, orange juice, or orange-containing products for 1 week prior to the first dose of study medication until study completion.
- In addition to the exclusion criterion regarding blood or plasma donations, subjects must not have donated blood or plasma until the end-of-study visit. It was recommended that blood/plasma donations not be made for at least 60 days after the end-of-study visit.
- In addition to the exclusion criterion regarding tobacco products, subjects must not have used tobacco products until the end-of-study visit.
- Subjects must not have engaged in strenuous exercise from 48 hours prior to the first dose of study medication until the end-of-study visit.
- Female subjects must have utilized one of the allowed forms of birth control listed in the Inclusion Criteria from screening until 14 days after completion of the study.

Schedule of Assessments

See Table 12 in Section 9.4 Schedule of Assessments for frequency and timing of PK and safety measurements for study 3007116.

Endpoints

The objective of this study was to compare the rate of absorption and oral bioavailability of a test formulation of codeine polistirex and chlorpheniramine polistirix ER oral suspension to an equivalent dose of the reference product, codeine phosphate and chlorpheniramine maleate IR oral solution when administered under fasted steady-state conditions.

Therefore, no efficacy variables were determined. Instead, plasma PK characteristics of the test and reference compounds were assessed from blood samples drawn at 0 hour (predose) on Days 1 through 6 and at 0 hour (predose) and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 11.0, and 12.0 hours after the first morning dose on Day7. The following PK parameters were calculated:

C_{max}	The maximum drug concentration in plasma determined directly from individual concentration-time data
C_{min}	The minimum drug concentration in plasma determined directly from individual concentration-time data
T_{max}	Time to reach maximum concentration
T_{min}	Time to reach minimum concentration
Flux	The degree of fluctuation in drug concentration during the dosing interval, calculated as $(C_{max}- C_{min})/ C_{avg}$
Swing	The degree of maximum and minimum concentrations over the dosing interval, calculated as $(C_{max}- C_{min})/ C_{min}$
C_{avg}	Average plasma concentration, calculated as AUC_{0-12}/tau Tau is the dosing interval, defined as 12 hours
AUC_{0-12}	The area under the plasma concentration-time curve from time-zero to 12 hours post dose. This is calculated using the linear trapezoidal rule.

In addition to PK parameter, subjects were closely monitored during each confinement period in the research facility. Investigators assessed safety using the following parameters: physical examinations, vital sign assessments, clinical laboratory evaluations, electrocardiograms (ECGs), and reported or observed adverse events (AEs). These safety measures are further discussed in Section 7 Review of Safety.

Sample Size Determination

Sample size was estimated using PK data acquired in a pilot study, study 3007132, which used a prototype product of codeine polistirex and chlorpheniramine polistirex ER oral suspension. In this pilot study, the geometric mean ratios (Test/Reference) for the exposure parameters C_{max} and AUCs ranged from 77.27 to 94.72% and the ANOVA CV% (a measure of intra-subject variability) ranged from 8.77% to 12.28%. The sample size was calculated using a power of 80% and an alpha error of 5%. The power was defined as the probability of having a 90% confidence interval to a Test/Reference ratio within the acceptance criteria of 80-125%. Based on a difference of up to 10% for PK parameters across treatments and an intra-subject CV of up to 20%, it was determined that 32 subjects should complete the study. Since variability was expected to be lower during a steady state dosing regimen, additional or back-up subjects were considered not to be needed. Therefore, a total of 32 subjects were enrolled.

Statistical Methods

All statistical analyses were performed in SAS (Version 9.1 or later).

For continuous variables, the number of non-missing observations, the mean, median, standard deviation, minimum and maximum were presented. For all tabulations of changes from baseline data, the lower and upper 95% confidence limits for the mean for the population and for the individual treatments were given. Categorical data, on the other hand, were presented in contingency tables with cell frequencies and percentages for the patient population and for the individual treatments.

For the handling of PK data, the concentration-time data for codeine and chlorpheniramine that are below the limit of qualification (BLQ) were treated as zero in the tabulation of these data. Concentration-time data for codeine and chlorpheniramine were summarized separately by treatment using descriptive statistics (e.g., n, arithmetic mean, median, standard deviation, minimum, maximum, and coefficient of variation) at each scheduled collection time. Individual and mean plasma concentration-time profiles and spaghetti plots for codeine and chlorpheniramine were provided for each treatment, and plots were created using both linear and semi-logarithmic scales.

Concentration-time data for codeine and chlorpheniramine were transferred from the Watson Laboratory Information Management System directly to Phoenix WinNonlin (Version 6.3) using the Custom Query Builder option for analysis. Data were analyzed by noncompartmental methods in WinNonlin. As already noted, concentration-time data that are BLQ were treated as zero in the data summarization and descriptive statistics. In the PK analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed. Embedded and/or terminal BLQ concentrations were treated as "missing." Full precision concentration data and actual sample times were used for all PK and statistical analyses.

On Days 1-6 inclusive, a C_{trough} (the plasma concentration immediately prior to the first morning dose) was obtained. On Day 7, C_{avg}, C_{max}, C_{min}, Flux, Swing, T_{max}, T_{min}, and AUC_{0-12} were obtained; all of these PK parameters are described above. PK parameters of codeine and chlorpheniramine were summarized separately by treatment using descriptive statistics.

The natural logarithmic-transformed PK parameters were analyzed for differences between treatments using an ANOVA model with factors for sequence, subject within sequence, period, and treatment. The log-transformed PK exposure parameters $\ln(C_{max})$ and $\ln(AUC_{0-12})$ were used in the statistical analyses, as this is what is recommended in the Agency guidance for statistical approaches to establishing bioequivalence and the Agency guidance for bioavailability and bioequivalence studies

of orally administered drug products. The 90% confidence interval for the ratio of the geometric means of the test product and the reference listed drug under fasted conditions (Treatment A/TreatmentB) were calculated for each parameter to evaluate the rate of absorption and oral bioavailability. Similar drug exposure between test and reference on Day 7 were established if the 90% confidence intervals for $\ln(C_{max})$ and $\ln(AUC_{0-12})$ were within the 80% to 125% interval. The log-transformed PK exposure parameters $\ln(C_{min})$ and $\ln(C_{avg})$ and associated 90% confidence interval and ratio of geometric means were calculated.

Protocol Conduct and Violations

For this study, Trish Pharma, Inc. listed 9 protocol deviations in 7 subjects. Five of them involved not performing a vital signs measurement at the specified time or in the specified manner (i.e., after a 3 minute sit); 2 involved the inability to verify a 1 hour fast prior to dosing; 2 involved an alteration in the pre-dose sample outside the assessment window. The applicant concluded that none of these deviations had an effect on the conduct of the study, the safety of study subjects, or the validity of the study data.

There were no changes in the conduct of the study or in the planned analyses.

5.3.2 Study 3007117

Overview of Study Design

Study 3007117 was a single-dose, open-label, randomized, 3-period, 3-treatment crossover study in which 36 healthy adult subjects were enrolled. Subjects received each of the following treatments per treatment period:

- One single dose (0 hour) of the test formulation following an overnight fast of at least 10 hours (Treatment A)
- One single dose (0 hour) of the test formulation following an overnight fast of at least 10 hours, then consumption of an FDA-defined standard high-fat, high-calorie breakfast meal (Treatment B)
- Two single dose administrations (0 hour and 6 hour) of the reference product following an overnight fast of at least 10 hours (Treatment C)

The test product was codeine polistirex and chlorpheniramine polistirex ER oral suspension (equivalent to codeine phosphate 20mg and chlorpheniramine maleate 4mg per 5 mL). One dose was 10 mL. The test product was used for Treatments A and B. The reference product was codeine phosphate and chlorpheniramine maleate IR oral solution (equivalent to codeine phosphate 20mg/chlorpheniramine maleate 4mg per 5

mL). One dose was 5 mL. These are the same investigational products used in study 3007116.

The subjects fasted for 4 hours following each dose. Water was allowed ad lib during the study except for 1 hour prior through1 hour post dose. Each 0-hour drug administration was separated by a washout period of at least 14 days. As with study 3007116, this study design allowed each subject to serve as his/her own control, thereby precluding the need for a separate control group.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria, as well as the study restrictions, were the same as those in study 3007116.

Schedule of Assessments

Table 13 in Section 9.4 Schedule of Assessments details the frequency and timing of PK and safety measurements in study 3007117.

Endpoints

The primary objectives of this study were PK and safety, so no efficacy endpoints were evaluated. Blood (plasma) PK characteristics were assessed after each dose of study medication. Blood samples were drawn within 60 minutes prior to dose administration and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0, and 96.0 hours after dose administration. The following PK parameters were calculated:

C_{max}	The maximum drug concentration in plasma determine directly from individual concentration-time data
T_{max}	Time to reach maximum concentration
C_{last}	The last quantifiable drug concentration determined directly from individual concentration-time data
T_{last}	Time of the last measurable concentration
λ_z	The observed elimination rate constant, estimated by linear regression through at least 3 data points in the terminal phase of the log concentration-time profile

$T_{1/2}$	The observed terminal elimination half-life calculated as $T_{1/2} = \ln(2)/ \lambda_z$
AUC_{last}	Area under the plasma concentration-time curve from time-zero to the time of the last quantifiable concentration, calculated using the linear trapezoidal rule
AUC_{inf}	Area under the concentration-time curve from time-zero extrapolated to infinity, calculated as $AUC_{inf} = AUC_{last} + C_{last}/ \lambda_z$
$AUC_{Extra}(\%)$	Percentage of AUC_{inf} based on extrapolation

As with study 3007116, subjects were also monitored closely for safety during the confinement period. Safety was assessed by physical examinations, vital sign assessments, clinical laboratory evaluations, ECGs, and reported or observed AEs.

Sample Size Determination

The same method to determine sample size for study 3007116 was used for study 3007117. Based on PK data from a pilot study 3007132, the applicant determined 32 subjects should complete the study. To account for the possibility of drop-outs, 36 subjects were enrolled.

Statistical Methods

Statistical analysis was performed in SAS (Version 9.3), using the PROC GLM procedure and Phoenix WinNonlin (Version 6.3) using the Linear Mixed Effect Module. The concentration-time data were transferred from Watson Laboratory Information Management System (LIMS, Version 7.2.0.03) directly to Phoenix WinNonlin using the Custom Query Builder option for analysis. Data were analyzed using noncompartmental methods in WinNonlin. In the PK analysis, BLQ concentrations were treated as zero from time zero up to the time at which the first quantifiable concentration was observed.

The natural logarithmic-transformed PK parameters were analyzed for differences between treatments using an ANOVA model with factors for sequence, subject within sequence, period, and treatment. As already noted with study 3007116, based on the Agency's guidances, the log-transformed PK exposure parameters, $\ln(C_{max})$, $\ln(AUC_{last})$, and $\ln(AUC_{inf})$, were used in the statistical analysis to determine bioavailability and bioequivalence. The 90% confidence interval for the ratio of the geometric means of the

test product and the reference listed drug was calculated for each parameter to evaluate bioavailability. Similar bioavailability between test and reference (Treatment A/Treatment C) was established if the 90% confidence intervals for $\ln(AUC_{last})$ and $\ln(AUC_{inf})$ were within the 80% to 125% interval. Additionally, the 90% confidence interval for the ratio of the geometric means of the test formulation under fed conditions (Treatment B) vs. the test formulation under fasted conditions (Treatment A) was calculated for each parameter to evaluate the impact of the presence of food on the maximum and total exposure of codeine and chlorpheniramine. No significant food effect was concluded if the 90% confidence intervals for $\ln(C_{max})$, $\ln(AUC_{last})$, and $\ln(AUC_{inf})$ were within the 80% to 125% interval.

Protocol Conduct and Violations

Tris Pharma, Inc. reported 15 protocol deviations in 13 subjects. Four resulted in early termination from the study and are further described in Section 7.3.3 Dropouts and/or Discontinuations. Overall, the applicant concluded that none of the deviations had a material effect on the conduct of the study, the safety of the study subjects, or the validity of the study data.

In study 3007117, there were no changes in the protocol conduct or the planned analyses.

6 Review of Efficacy

Efficacy Summary

Codeine and chlorpheniramine are included both separately and in combination in the Cough/Cold Monograph. The daily doses of codeine and chlorpheniramine in this COD-CPM ER oral suspension correspond with what is recommended in the Cough/Cold Monograph. Therefore, no efficacy studies were performed as part of the development program for this product.

6.1 Indication

The proposed indication is for the relief of cough and (b) (4) upper respiratory allergies in adults 18 years of age and older.

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

This 505(b)(2) application relies on the OTC monograph, reference drug, and available literature to determine the safety of its COD-CPM ER oral suspension. The safety data from the pivotal BA studies serve as an adjunct to what is already accepted and understood from clinical use.

The overall patient exposure from the pivotal BA studies is low and the overall number of adverse events is low. Thirty-two subjects completed study 3007117 (single-dose study), and 32 subjects completed study 3007116 (multi-dose study). In study 3007117, a total of 9 subjects reported 16 treatment-emergent AEs. In Study 3007116, a total of 56 AEs were reported by 22 subjects, which comprised of 20 AEs in 13 (40.6%) subjects following Treatment A and 36 AEs in 19 (59.4%) subjects following Treatment B. There were no severe or serious AEs, and there were no deaths. The common AEs in these 2 pivotal studies are known side effects of codeine and/or chlorpheniramine, including constipation, headache, dizziness, and somnolence. Thus, the safety assessment from the 2 pivotal studies did not reveal any unexpected adverse events or new safety signals.

In summary, the safety profiles of codeine and chlorpheniramine have been well-established from long-time use in clinical practice and from publicly available literature. The safety data from the pivotal BA studies, though small, substantiated what is already known.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

As already noted in Section 5.2, for purposes of safety evaluation, the 2 pivotal bioavailability studies will be used. These are studies 3007117 and 3007116. Frequently in this review, Study 3007117 will be discussed first, as this was the single-dose study.

7.1.2 Categorization of Adverse Events

The investigational staff recorded all adverse events (AEs), queried or spontaneously volunteered by the subjects. Subjects were instructed to inform the study physician and/or research personnel of any AEs that occurred at any time during the study. Subjects were monitored for AEs from the beginning of confinement through the end-of-study visit. Reported or observed AE, as well as the treatment administered, were documented in the source documents and on the case report form (CRF). All AEs were followed to resolution.

Tris Pharma, Inc. utilized standard definitions for adverse events:

- Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related
- Any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without judgment of causality
- An AE can arise from any use of the drug (e.g., off-label or use in combination with another drug) and from any route of administration, formulation, or dose (including overdose).

In addition, Tris Pharma, Inc. provided the following definitions for the following safety terminology:

- Adverse reaction is an event that is considered to be related to the study drug.
- A serious adverse event (SAE) is an AE that fulfills at least one of the following criteria:
    - Fatal
    - Life-threatening (i.e., the patient was at the risk of death at the time of the event. On the other hand, this is not an event that would have hypothetically caused death if it were more severe.)
    - Requiring inpatient hospitalization or prolongation of existing hospitalization
    - Resulting in persistent or significant disability/incapacity
    - Congenital anomaly/birth defect
    - An important medical event that may not be immediately life-threatening or result in death or in hospitalization but may jeopardize the patient or require an intervention to prevent one of the outcomes listed above
- An unexpected AE is an AE this is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed.

All adverse events were assessed for a relationship to the study drug. The Principal Investigator or Sub-Investigator determined the relationship between the AE and the investigational product based on clinical judgment. AEs were then categorized as related or not related. An AE was considered “related” if (1) it followed a reasonable temporal sequence from the study product administration and cannot be reasonably

explained by the subject's clinical state or other factor or (2) it followed a reasonable temporal sequence from the study product administration and represented a known reaction to the drug under study or other drugs in its class or predicted by the known pharmacological properties of the drug or (3) it resolves with discontinuation of the investigational product and/or recurs with rechallenge. On the other hand, an AE that is "not related" is one that starts before study drug administration and/or which can be reasonably explained by the subject's clinical state or other factors.

Each sign or symptom was graded for severity, and the date and time of onset, cessation, and resolution were recorded. Severity was defined on a 3-point scale (mild vs. moderate vs. severe).

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

As the 2 pivotal BA studies have different study designs, safety data are not pooled. In the review the safety data, conclusions are made for the more significant findings, i.e., number of deaths or serious adverse events, based on findings from both studies.

7.2 Adequacy of Safety Assessments

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

Table 7. Drug Exposure for Pivotal Studies

Treatment	# of doses	Single codeine/ chlorpheniramine dose	Total codeine/ chlorpheniramine dose
Study 3007117			
A: COD-CPM ER oral suspension (fasted)	1	40 mg/8 mg	40 mg/8 mg
B: COD-CPM ER oral suspension (fed)	1	40 mg/8 mg	40 mg/8 mg
C: Codeine phosphate and chlorpheniramine maleate reference IR product (fasted)	2	20 mg/4 mg	40 mg/8 mg
Study 3007116			
A: COD-CPM ER oral suspension (fasted)	13[a]	40 mg/8 mg	520 mg/104 mg
B: Codeine phosphate and chlorpheniramine maleate reference IR product (fasted)	26[b]	20 mg/4 mg	520 mg/104 mg

a Over 7 days with 2 doses/day on Days 1-6 and 1 dose on Day 7
b Over 7 days with 4 doses/day on Days 1-6 and 2 doses on Day 7
Source: NDA 207768, Summary of Clinical Safety, Section 2.7.4.1.2, Table 3.

Table 7 summarizes the study drug exposure for each of the pivotal BA studies.

- In Study 3007117, subjects received either a single dose of study drug or 2 doses of the reference product, per study period. Therefore, subjects received a total dose equivalent to 120 mg codeine phosphate and 24 mg chlorpheniramine maleate over 3 study periods. Of the 36 subjects enrolled, 32 subjects received all scheduled doses.
- Study 3007116 was a multi-dose study. By the time of completion, subjects received a total 1040 mg codeine phosphate and 208 mg chlorpheniramine over 14 days. All enrolled subjects (32) completed the study, and, thus, all subjects in this study had the above exposure.

Table 8 summarizes the demographics of the study subjects. The study demographics are similar between the 2 studies. The majority of the subjects are young, white (mostly Hispanic or Latino) males and females without a smoking history. In addition, based on the inclusion and exclusion criteria (described in Section 5.3.1 and 5.3.2), these subjects are all relatively healthy.

Table 8. Summary of Demographics for Subjects in Pivotal BA Studies

Parameters	Study 3007117	Study 3007116
	All Subjects (N=36)	All Subjects (N=32)
Age [n(%)]		
18-39 years	29 (80.6)	23 (71.9)
40-55 years	7 (19.4)	9 (28.1)
Gender [n(%)]		
Female	17 (47.2)	14 (43.8)
Male	19 (52.8)	18 (56.3)
Weight (kg)		
Mean	69.7	74.0
Range	50.80 to 89.30 kg	51.00 to 92.60 kg
Height (cm)		
Mean	166.1	168.8
Range	152.00 to 181.00	149.50 to 187.00
BMI Range (kg/m^2)	20.20 to 30.00	20.20 to 30.00
Ethnicity [n(%)]		
Hispanic or Latino	23 (63.9)	17 (53.1)
Not Hispanic or Latino	13 (36.1)	15 (46.9)
Race [n(%)]		
American Indian or Alaska Native	1 (2.8)	--
Black or African American	6 (16.7)	8 (25.0)
Asian	1 (2.8)	2 (6.3)
White	28 (77.8)	22 (68.8)
Smoking history [n(%)]		
Yes	10 (27.8)	3 (9.4)
No	26 (72.2)	29 (90.6)

Source: NDA 207768, Summary of Clinical Safety, Section 2.7.4.1.3, Table 4.
Study 300716 Study Report, Table 14.1.2, page 65.
Study 300717 Study Report, Table 14.1.2, page 60.

Overall, the exposure to the study drug from these 2 bioavailability studies is small in terms of assessment of safety. Additionally, the demographics of the study subjects, although similar in both studies, represent a narrow population. Given these limitations, the data from these studies serve as an adjunct to what is already available in the monograph to determine the safety of this COD-CPM ER oral suspension.

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 with this COD-CPM ER oral suspension.

7.2.4 Routine Clinical Testing

Section 9.4 Schedule of Assessments elaborates on the laboratory testing performed during the pivotal bioavailability studies. Essentially, routine chemistry, hematology, and urinalysis were checked at screening and at the end of study. Other laboratory testing included serology, urine drug/alcohol screening, and pregnancy test.

7.2.5 Metabolic, Clearance, and Interaction Workup

No specific metabolic, clearance, or interaction studies were performed with the COD-CPM ER oral suspension.

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

Not applicable.

7.3 Major Safety Results

In Study 3007117, a total of 9 subjects reported 16 treatment-emergent AEs. Table 9 lists these treatment-emergent AEs. Five AEs followed administration of Treatment A; 3 AEs followed administration of Treatment B; 8 AEs followed administration of Treatment C (reference product). Of the 16 AEs, 12 were categorized as mild in severity, and 4

were moderate. Thus, there were no severe AEs. Tris Pharma, Inc. determined that 12 out of the 16 AEs were treatment related. In Table 4, the AEs shaded in grey are those determined to be *not* treatment-related. All AEs resolved without any treatment administered.

One AE in Study 3007117 was deemed to be of clinical significance. This is the subject with a rash in Table 9, which was noted after receiving reference product in Period 2 and during check-in for Period 3. The AE was determined to be moderate in severity, but it led to the subject's withdrawal from the study. This AE will be further discussed in Section 7.3.4 Significant Adverse Events.

Table 9. Treatment Emergent AEs in Study 3007117

Adverse Event (AE) MedDRA SOC/Preferred Term	Dosing Condition		
	Treatment A (Test Product/ Fasted) N=34	**Treatment B** (Test Product/ Fed) N=34	**Treatment C** (Reference Product/Fasted) N=34
Total Number of Subjects with AEs	**4 (11.8%)**	**3 (8.8%)**	**5 (14.7%)**
GASTROINTESTINAL DISORDERS	2 (5.9%)	--	1 (2.9%)
Abdominal pain	1 (2.9%)	--	--
Abdominal pain upper	--	--	1 (2.9%)
Gastrointestinal hypomobility	1 (2.9%)	--	--
INFECTIONS AND INFESTATIONS		1 (2.9%)	
Viral upper respiratory tract infection		1 (2.9%)	
NERVOUS SYSTEM DISORDERS	3 (8.8%)	--	3 (8.8%)
Dizziness	--	--	3 (8.8%)
Headache	2 (5.9%)	--	1 (2.9%)
Presyncope	1 (2.9%)	--	--
RESPIRATORY, THORACIC, and MEDIASTINAL DISORDERS	--	2 (5.9%)	--
Epistaxis	--	1 (2.9%)	--
Hiccups	--	1 (2.9%)	--
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	--	--	1 (2.9%)
Rash	--	--	1 (2.9%)
VASCULAR DISORDERS	--	--	1 (2.9%)
Orthostatic hypotension	--	--	1 (2.9%)

Source: NDA 207768, Study 3007117 Report Body, Tables 14.3.2 and 14.3.3, pages 113-114.

In Study 3007116, a total of 56 AEs were reported by 22 subjects, which comprised of 20 AEs in 13 (40.6%) subjects following Treatment A and 36 AEs in 19 (59.4%) subjects following Treatment B. Table 10 details all the AEs that were reported in study 3007116. Forty-two of the AEs were deemed mild, and 14 were moderate. Thus, like study 3007117, there were no AEs classified as severe. Tris Pharma, Inc. attempted to determine relatedness and argues that 44 AEs reported by 20 (62.5%) subjects were related to study treatment. In Table 10, the 12 AEs that were considered not related are shaded in grey. Of note, although the entire row for each unrelated AE is shaded grey,

1 case of back pain after Treatment A and 1 case of dizziness after Treatment C were considered related.

Table 10. Treatment Emergent AEs in Study 3007116

Adverse Event (AE) MedDRA SOC/Preferred Term	Dosing Condition	
	Treatment A (Test Product/Fasted) N=32	Treatment B (Reference Product/Fasted) N=32
Total Number of Subjects with AEs	**13 (40.6%)**	**19 (56.2%)**
EAR AND LABYRINTH DISORDERS	--	1 (3.1%)
Vertigo	--	1 (3.1%)
GASTROINTESTINAL DISORDERS	9 (28.1%)	15 (46.9%)
Abdominal pain	1 (3.1%)	--
Constipation	9 (28.1%)	13 (40.6%)
Gastroesophageal reflux disease	--	1 (3.1%)
Nausea	1 (3.1%)	1 (3.1%)
Oral discomfort	--	1 (3.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	--	1 (3.1%)
Thirst	--	1 (3.1%)
INFECTIONS AND INFESTATIONS	2 (6.3%)	2 (6.3%)
Viral upper respiratory tract infection	2 (6.3%)	2 (6.3%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3 (9.4%)	2 (6.3%)
Back pain	2 (6.3%)	1 (3.1%)
Muscle spasms	1 (3.1%)	1 (3.1%)
NERVOUS SYSTEM DISORDERS	3 (9.4%)	9 (28.1%)
Dizziness	--	2 (6.3%)
Headache	2 (6.3%)	3 (9.4%)
Presyncope	1 (3.1%)	1 (3.1%)
Somnolence	--	4 (12.5%)
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	--	1 (3.1%)
Nasal congestion	--	1 (3.1%)

Source: NDA 207768, Study 3007116 Report Body, Tables 14.3.2 and 14.3.3, pages 126-128.

Given the small number of subjects and the low number of total AEs, limited conclusions are possible from either BA study. In both studies, the more common SOCs for both the study drug and the reference product were gastrointestinal disorders and nervous system disorders. What can be noted, however, is that there were no severe or serious AEs reported in either study. Additionally, no AEs were unexpected from what is known regarding the safety profile of codeine and chlorpheniramine. The safety for the COD-CPM ER oral suspension at the proposed doses is also supported by the monograph and in the published literature.

7.3.1 Deaths

No deaths occurred during the conduct of either pivotal PK study.

7.3.2 Nonfatal Serious Adverse Events

No nonfatal serious adverse events occurred during the conduct of the pivotal PK studies.

7.3.3 Dropouts and/or Discontinuations

All subjects who participated in Study 3007116 completed the study. There were no withdrawals.

In contrast, in Study 3007117, four subjects discontinued the study early. Therefore, 32 of 36 subjects (88.9%) completed all 3 study periods. Of the 4 discontinuations, 3 subjects left for personal reasons. One subject withdrew from the study due to an adverse event, described further below in Section 7.3.4 Significant Adverse Events.

The 3 subjects who discontinued the study drug for personal reasons all left at different time periods of study. One subject left against medical advice prior to the 12-hour blood collection in Period 2. Another subject withdrew consent due to personal reasons at the Period 2 check-in. The third subject withdrew consent due to personal reasons prior to the 96-hour outpatient check-in in Period 1.

7.3.4 Significant Adverse Events

One AE in study 3007117 was considered to be clinically significant, and the subject was withdrawn from the study. Subject 307 was a 36 year-old Latina female, who developed a rash described as urticarial patches on her “low back, under arms, calves, behind knees, wrists, and itchy hands.” The rash was reported during the Period 3 check-in, following receipt of Treatment C (reference product) in Period 2. The rash was considered to be moderate. The applicant concluded that the AE was not felt to be related to the study medication. It is noted, however, that rash and pruritus have been previously described as adverse reactions to codeine use.

No other adverse event was deemed clinically significant.

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

For both studies, the most common AE fell under the SOC of gastrointestinal disorders. In study 3007116, the most common GI adverse event was constipation occurring in 9 subjects after Treatment A (test product) and 13 subjects after receiving Treatment B (reference product). In study 3007117, there was no AE of constipation, but 1subject reported an AE of gastrointestinal hypomobility with Treatment A (Test Product/Fasted). As constipation and gastric hypomobility are known AE with codeine, these occurrences are not unexpected.

Other than constipation, the other most frequent AEs fell under the SOC Nervous System Disorders and Musculoskeletal and Connective Tissue Disorders. In study 3007116, headaches (2 subjects after Treatment A [test product] and 3 subjects after Treatment B [reference product) and somnolence (4 subjects after reference product) were reported by more than 1 subject. Dizziness and pre-syncope are reported as separate events, but, for the purpose of this assessment, I will combine the events. One subject after Treatment A (test product) and 3 subjects after Treatment B (reference product) reported dizziness or pre-syncope; however, it should be noted that most of these AEs were deemed by Tris Pharma, Inc. to be unrelated to the treatment. In study 3007117, headaches (2 subjects after Treatment A [test product/fasted] and 1 subject after Treatment C [reference product]) and dizziness/pre-syncope (3 subjects after reference product and 1 subject after Treatment A [test product/fasted], respectively) were reported more than once. Headaches, somnolence, and dizziness have all been described in the side effect profiles of both codeine and chlorpheniramine and, in these BA studies, occurred after both the test product and the reference product.

The only other AEs that were reported more than once was back pain in study 3007116. Two subjects following Treatment A (test product) and 1 subject following Treatment B (reference product) reported back pain. Back pain is not a known side effect of either codeine or chlorpheniramine, but all 3 of these cases were deemed unrelated to treatment by the applicant.

The following AEs were common to both studies: constipation/gastric hypomobility, headaches, dizziness/pre-syncope, and abdominal pain. Constipation, headaches, and dizziness have already been discussed. Abdominal pain was reported by 1 subject after Treatment A (test product) in study 3007116 and by 1 subject after Treatment A

(test product, fasted) in study 3007117. Like constipation, headaches, and dizziness, abdominal pain has been described in association with the use of both codeine and chlorpheniramine.

In conclusion, for both pivotal BA studies, the common AEs are not unexpected and are in line with what is known about the active agents in COD-CPM ER Oral Suspension. These AEs also occurred as frequently in subjects who received the test product as subjects who received reference product.

7.4.2 Laboratory Findings

The following laboratory tests listed in Table 11 were conducted in studies 3007117 and 3007116. These were checked at screening and at the end-of study for both studies. In study 3007117, an additional test for hemoglobin and hematocrit was performed at check-in to Period 3.

Table 11. Laboratory Tests in Studies 3007116 and 3007117

Hematology	Serum Chemistry	Urinalysis
• Hemoglobin • Hematocrit • Leukocyte count (Total, Diff) • Red blood cell count (RBC) • Platelet count	• Albumin • Blood urea nitrogen (BUN) • Creatinine • Total bilirubin • Alkaline phosphatase (ALP) • Aspartate transaminase (AST) • Alanine transaminase (ALT) • Sodium (Na+) • Potassium (K+) • Chloride (Cl-) • Lactate dehydrogenase (LDH) • Calcium (Ca) • Uric acid • Glucose	• pH • Specific gravity • Protein • Glucose • Ketones • Bilirubin • Blood • Nitrite • Leukocyte esterase • Urobilinogen

Source: NDA 207768, Summary of Clinical Safety, Tables 1, page 2.

Clinical investigators for both pivotal studies were responsible to determine the clinical significance of any values outside the reference ranges or marked changes from the screening values. Any value or change that was considered to be clinically significant needed to be recorded as an AE and followed until resolution.

In study 3007116, no investigator felt that any out-of-range values were clinically significant. It is worthwhile, however, to note a few findings.

- When analyzed as a change from baseline, the applicant did note that there was a consistent reduction in sodium during the study. Twelve subjects (37.5%) shifted from normal to low. No reason was provided for this shift, but it was felt not to be related to the study medication.

- One subject (subject 712) had normal screening liver associated enzymes (ALT 10 U/L and AST 21U/L) on 2 December 2013. At the end-of-study evaluation (11 January 2014), this subject's liver associated enzymes had increased to ALT 130 U/L and AST 229 U/L. Labs were then repeated on 24 January 2104, and the transaminases had returned to normal range with an ALT 10 U/L and AST 19 U/L. Therefore, the elevation in ALT and AST was not felt to be clinically significant.

Similarly, in study 300717, no out-of-range laboratory tests were judged to be clinically significant. Additionally, Tris-Pharma, Inc. did not find any clinically meaningful change from baseline.

In summary, no significant findings were noted from the laboratory tests in regards to safety.

7.4.3 Vital Signs

In study 3007117, blood pressure, pulse rate, respiration rate, and arterial oxygen saturation were measured prior to the dose administered at Hour 0; at post-dose Hours 2 (±0.5), 4 (±0.5), 8 (±0.5), 12 (±0.5), 24 (±0.5), 36 (±0.5), and 96 (±0.5); and at study exit or early termination. Temperature was measured prior to the dose administered at Hour 0, at post-dose Hours 36 (±0.5) and 96 (±0.5), and at study exit or early termination.

In study 3007116 (multi-dose study), blood pressure, pulse rate, respiration rate, arterial oxygen saturation, and temperature were measured at screening, at 0-hour on Days 1-7, and at 24 hours after 0-hour on Day 7. Also, blood pressure, pulse rate, respiration rate, and arterial oxygen saturation were measured post-dose Hours 1 (±0.5), 3 (±0.5), and 8 (±0.5) on Day 1 through 7 in each period.

As with the laboratory tests, clinical investigators for both studies were responsible for judging whether any post-dose findings that were outside of the acceptable range were clinically significant. Any clinically significant out-of-range finding was documented as an AE.

For study 3007117, there were no clinically relevant changes in group mean vital sign assessments for either treatment or reference product. There were, however, 2 AEs (both mild in severity) related to vital signs. One subject was diagnosed with orthostatic hypotension in Period 2 after receipt of Treatment C (reference product). It appears the diagnosis may have been based on change in systolic blood pressure from 94 to 76; the subject's position was not documented in the provided listing. Per the investigator, this AE was felt to be related to study medication. Another subject was assessed to have presyncope after venipuncture in Period 1 following receipt of Treatment C (reference

product). In the listing in the study report, this subject's blood pressure started at 119/62, dropped to 93/43, but returned to 113/59. This AE was not felt to be related to study medication. No other vital sign abnormalities were noted by the clinical investigators.

Clinical investigators for study 3007116 did not find that any out-of-range vital sign to be clinically significant. Similarly, there were no clinically relevant changes in group mean vital sign assessments for either treatment or reference product.

Thus, in regards to vital signs, for both studies, there were very few clinically significant out-of-range findings, and there were no unexpected changes in vital signs. Orthostatic hypotension and pre-syncope have been described in the side effect profile for both active ingredients. Of note, both of these AEs occurred after the reference product, but there are too few to make any conclusion or comparison with these studies.

7.4.4 Electrocardiograms (ECGs)

ECGs were recorded at screening at screening and at the end of study visit for both pivotal BA studies. Clinical investigators assessed if any abnormalities or marked changes from baseline were clinically significant, and those that were clinically significant were recorded as AEs. For both studies 3007117 and 3007116, there were no clinically significant ECG findings.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies or trials were performed.

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 with the COD-CPM ER oral suspension. The information about drug interactions is based on the reference product, the monograph, and what is known regarding the active ingredients. Notable drug interactions with the COD-CPM ER oral suspension include opioids, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants; monoamine oxidase inhibitors and tricyclic antidepressants; anticholinergics; inhibitors of CYP2D6 and inducers of CYP3A4; and phenytoin. The labeling will reflect drug-drug interactions that are clinically notable.

While there were not specific drug-drug interaction studies, study 3007117 evaluated the effect of food on bioavailability and safety. The relative bioavailability of COD-CPM ER oral suspension was modestly altered after a high-fat, high-calorie breakfast as compared to fasting conditions. However, there was no significant difference in safety. Given the low overall number of adverse events, it is difficult to really compare the safety profile with and without food. Based on the lack of clinically significant safety differences and the clinical pharmacology results, Tris Pharma, Inc. concluded that COD-CPM ER oral suspension may be administered with or without food.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity studies were performed with this application. Rather, carcinogenicity data will be based on nonclinical data from published literature on both codeine and chlorpheniramine.

7.6.2 Human Reproduction and Pregnancy Data

No human reproduction and pregnancy data were collected in the clinical pharmacological studies. Further, no adequate and well-controlled studies with this COD-CPM ER oral suspension were performed in pregnant women. Additionally, no reproductive studies were conducted. Pregnancy and reproductive information for the COD-CPM ER oral suspension will be based on the reference product, monograph, and what is known regarding the active ingredients. Therefore, the applicant seeks labeling for this COD-CPM ER oral suspension as a pregnancy category C.
For codeine, babies born to mothers who have taken opioids regularly prior to delivery will be physically dependent. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose.

For chlorpheniramine, retrospective human studies have found small but statistically significant associations between maternal use and inguinal hernia and eye/ear anomalies in children. Other retrospective studies have found that the frequency of general congenital anomalies was not increased among offspring of women who took chlorpheniramine during pregnancy.

Similarly, in nursing mothers, caution should be used in administering the COD-CPM ER oral suspension, as codeine, its metabolite morphine, and chlorpheniramine can be excreted in human milk. The clinical significance, however, is unknown.

The labeling will reflect these issues related to human pregnancy and reproductive data.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of specific doses of codeine and chlorpheniramine have been established in the monograph in children ages 6 to 18 years old. However, there are safety concerns related to use of this product in children as it is a long-acting product that contains two sedating medications. Further, there are concerns related to the use of cough and cold products in children and the use of codeine in children. Thus, Tris Pharma, Inc. will need to evaluate the PK and safety of the product in children if they decide to seek approval for children 6-18 years of age. Of note, the Division has

waived studies in children less than 6 years of age due to specific safety concerns related to respiratory depression in that age group. At this time, the product will only be approved for adults.

Prior to submission of the NDA, (b) (4) However, after further internal discussion, it was determined that this application does not trigger PREA because it does not include a new indication, new active ingredient, new dosing regimen, new dosage form, or new route of administration. COD-CPM ER oral suspension only differs from the approved reference product (Codeprex™ Pennkinetic®) by dose strength of codeine. During review of the NDA, PeRC determined that this does not trigger PREA.

(b) (4)

- (b) (4)

- (b) (4)

It will be at the applicant's discretion to pursue these studies if the applicant desires a claim for children.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no safety issues related to overdose, drug abuse, withdrawal, or rebound in the clinical pharmacology studies. The applicant relies on the reference product, monograph, literature, and experience with the active ingredients (codeine and chlorpheniramine) to evaluate these issues. COD-CPM-ER oral suspension is a Schedule III controlled product based on the codeine component. The risks of drug abuse potential and overdose are well-recognized for the codeine component. The labeling will reflect the risk of overdose and drug abuse potential.

7.7 Additional Submissions / Safety Issues

No additional submissions were provided, and no other safety issues were addressed.

8 Postmarket Experience

As this COD-CPM ER oral suspension has not been marketed, there is no postmarketing experience. However, the active ingredients, codeine and chlorpheniramine, have a long history of clinical use both individually and in combination. The current understanding of the safety and efficacy of these active ingredients and their clinical acceptability in practice come from postmarketing experience. Routine postmarketing surveillance would be beneficial for the product under review to monitor adverse events, particularly focusing on respiratory depression and any unexpected adverse events.

9 Appendices

9.1 Literature Review/References

The OTC monograph and the applicant's NDA are the only references used in this review.

9.2 Labeling Recommendations

At the time of this clinical review, labeling negotiations are ongoing. It appears that the applicant used the listed drug's label as the basis for this COD-CPM ER oral suspension. Because of this, there are many Agency recommendations to update the label to meet current Physician Labeling Rule (PLR) requirements and to be consistent with more recently approved cold and cough products. Below are highlights from the Agency's labeling recommendations, focused mainly on the clinical portions of the label.

- Indication and usage
    - The applicant's proposed indication needs to be revised. The Agency recommends the following:

      TUZISTRA XR is indicated for the relief of cough and symptoms associated with upper respiratory allergies or a common cold in adults 18 years of age and older.

- Boxed warning, Contraindications, Warnings and Precautions
    - Although this product is currently only indicated for adults, the boxed warning for codeine related to respiratory depression and death in children who receive codeine post-operatively and who are ultra-rapid metabolizers needs to be included. The Agency is concerned about this product's potential off-label use in children.
    - Similarly, information regarding codeine and the concern for respiratory depression and death in children also needs to be included in Sections 4 (Contraindications) and 5 (Warnings and Precautions). The specific risk with children needs to be discussed in a subsection labeled, "Section 5.1: Death Related to Ultra-Rapid Metabolism of Codeine to Morphine," and "Section 5.2: Respiratory Depression."
    - Other changes to the Warning and Precautions section include the following:
        - Drug Dependence should be added as a sub-heading (Section 5.3).

        - The section on Acute Abdominal Conditions should be revised to include the warning that use with anticholinergics may produce paralytic ileus.

- Dosage forms and strengths
    - Based on the Agency's CMC review and current practice that the label should be clear with what drug substances are actually contained in the drug product, the Agency recommends that the label be amended to include the dose of codeine and chlorpheniramine free base. The equivalent dose of codeine phosphate and chlorpheniramine maleate should also be included.
    - Please see the CMC review for more details regarding the Agency labeling recommendations for Section 3 of the USPI.

- Clearer patient instructions on dosing (e.g., with an oral dosing dispenser with accurate milliliter measurements) are recommended for several sections: Section 2.1 of Dosage and Administration, Section 5.8 regarding Dosing under Warnings and Precautions, Section 16 How Supplied/Storage and Handling, and Section 17 Patient Counseling Information.

- Adverse Reactions
    - All the adverse events listed under Section 5 Warning and Precautions needs to precede the general discussion on adverse reactions as a bulleted list.

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 individual 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 Schedule of Assessments

Table 12. Events Schedule for Study 3007116

PROCEDURE	SCREENING	STUDY (PERIODS 1 & 2)			END-OF-STUDY
		Day -1	Days 1-6	Day 7	
Informed consent	X				
Medical and medication histories	X	X			
ECG	X				X
Vital signs	X	X	X	X	X
Physical examination	X				X
Biochemistry, hematology, urinalysis	X				X
Serology	X				
Urine cotinine screen	X				
Urine drug screen	X	X			
Urine alcohol screen		X			
Pregnancy test (female subjects)	X	X			
Drug administration			X	X	
Predose blood sample collection for pharmacokinetic analysis			X	X	
Postdose blood sample collection for pharmacokinetic analysis				X	
Adverse events		X	X	X	X

Source: NDA 207768, Study 3007116 Clinical Study Report, Table 9.5.1.1, dated December 15, 2013; page 28 .

Table 13. Events Schedule for Study 3007117

PROCEDURE	SCREENING	STUDY PERIODS 1 & 2	END-OF-STUDY
Informed consent	X		
Medical and medication histories	X	X	
ECG	X		X
Vital signs	X	X	X
Physical examination	X		X
Biochemistry, hematology, urinalysis	X	X[2]	X
Serology	X		
Urine cotinine screen	X		
Urine drug screen	X	X	
Urine alcohol screen		X	
Pregnancy test (female subjects)	X	X	
Standard high-fat, high-calorie breakfast[2]		X	
Drug administration		X	
Blood sample collection for pharmacokinetic analysis		X	
Adverse events		X	X
Iron supplement distribution			X

[1] Additional hemoglobin and hematocrit testing was performed at check-in to Period 3 only.
[2] FDA standard high-fat, high-calorie breakfast meal administration for Treatment B only.
Source: NDA 207768, Study 3007117 Clinical Study Report, Table 9.5.1.1, dated April 23, 2014; page 26.

9.5 Financial Disclosure Review

Clinical Investigator Financial Disclosure Review

Application Number: NDA 207768

Submission Date(s): June 27, 2014

Applicant: Tris Pharma, Inc.

Product: Tuzistra XR (codeine polistirex and chlorpheniramine polistirex ER)

Reviewer: Suzette Peng, MD

Date of Review: March 26, 2015

Covered Clinical Study (Name and/or Number): Studies 3007116 and 300717

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 1		
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 3455): None		
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)): Not Applicable Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided: N/A	Yes ☐	No ☐ (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: N/A	Yes ☐	No ☐ (Request explanation from applicant)

Reviewer's Comments:
Tris Pharma, Inc. has adequately disclosed financial interests and/or arrangements with clinical investigators by submitting a signed Form 3454. It should be noted that, for the covered bioavailability studies 3007116 and 3007117, there was only one clinical investigator. The applicant certifies that these pivotal studies are not funded via variable compensation and that the sole clinical investigator does not hold any form of proprietary interest in the product.
Of note, the sole investigator did not have any disclosable financial interests/arrangements. Additionally, she did not require a certification of due diligence.

In summary, the disclosed financial interests/arrangements do not affect the approvability of the application.

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

/s/

SUZETTE W PENG
03/25/2015

JANET W MAYNARD
03/25/2015

Food and Drug Administration
Center for Drug Evaluation and Research
ODE II / DPARP / HFD-570
10903 New Hampshire Ave.
Silver Spring, MD 20993

MEMO TO FILE

Filing/Planning Review

NDA: 207,768

Reviewer: Suzette Peng, M.D., CDER/OND/DPARP

Submitted: June 30, 2014

Reviewed: August 11, 2014

Product: Codeine polistirex and chlorpheniramine polistirex ER oral suspension

Indication: Relief of cough and (b) (4) upper respiratory allergies in adults 18 years of age or older

Sponsor: Tris Pharma, Inc.

Submission: SEQ 0 (SDN 1)

Synopsis: The Sponsor has submitted a 505(b)(2) application for this product with support of the Cough/Cold OTC monograph (21 CFR 341) and reference list drug (RLD), Codeprex™ Pennkinetic® (UCB Inc., NDA 021369).

The attached Filing/Planning meeting presentation, dated August 5, 2014, summarizes the relevant regulatory history and a synopsis of this NDA submission. The Sponsor performed 2 pivotal bioavailability (BA) studies, comparing the drug product to an in-house manufactured codeine phosphate and chlorpheniramine maleate IR oral solution. The Sponsor is relying heavily on the RLD for the bulk of the efficacy and safety data, as well as the proposed label. Therefore, no new efficacy data are submitted. A safety assessment from the 2 pivotal BA studies is submitted.

No clinical deficiencies were identified with this submission.

Action Taken: The submitted 505(b)(2) application is fileable.

Appendix 1. Clinical Filing Checklist for a New NDA/BLA
Appendix 2. Filing/Planning Meeting Presentation, August 5, 2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 207,768 **Applicant: Tris Pharma, Inc.** **Stamp Date: June 30, 2014**

Drug Name: codeine polistirex and chlorpheniramine polistirex ER oral suspension **NDA/BLA Type: 505(b)(2)**

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		The primary safety information is extrapolated from the reference drug. The Sponsor does provide a clinical summary of safety based on the safety data from the PK studies. Therefore, it is reasonable that the ISS is not submitted.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		X		Similarly, the primary efficacy information is extrapolated from the reference drug. It is also reasonable that the ISE is not submitted.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			A "benefits and risks conclusions" is located in section 2.5.6 of the Clinical Overview.
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If	X			505(b)(2) – The

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Application is a 505(b)(2) and if appropriate, what is the reference drug?				reference drug is Codeprex Pennkinetic, which is currently discontinued.
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	Dose-ranging studies were not requested by the Division.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? The following are the 2 pivotal BA studies: Pivotal BA Study #1 (Study 3007116) – multi-dose, 2-period, t-way crossover study to evaluate the BA of test formulation of codeine polistirex and chlorpheniramine polistirex ER oral suspension compared to an equivalent dose of a reference product codeine phosphate and chlorpheniramine maleate IR oral solution under fasted stead-state conditions Pivotal BA Study #2 (Study 3007117) – single-dose, 3-period, open-label, randomized, 3-way crossover study to evaluate the effect of food on a test formulation of codeine polistirex and chlorpheniramine polistirex ER oral suspension and to evaluate the relative BA of the test formulation compared to an equivalent dose of a reference product (codeine phosphate and chlorpheniramine maleate IR solution) under fasted conditions				There are no efficacy studies. Rather, the Sponsor submits 2 pilot PK studies to support early formulation development. Then, 2 pivotal BA studies were performed on the ER product that the Sponsor will bring to market.
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	Efficacy studies were not required for this 505(b)(2).
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			PK parameters – rate of absorption and oral bioavailability
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	Studies performed in the US.
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			Primary safety data are extrapolated from the reference drug. In addition, the Sponsor

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					provides the safety information from their BA studies.
19.	Has the applicant submitted adequate information to assess the arythmogenic 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			The Sponsor uses the reference drug for the primary safety data.
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			Total 68 subjects were exposed from the BA studies.
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
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	There were no deaths and no AE-related drop-outs.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
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			(b) (4) The Sponsor also submits the agreed iPSP.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?				
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S.			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).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	population?				
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	No efficacy studies were performed.
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			The Sponsor has submitted multiple CRFs. However, there were no deaths, SAEs, or dropouts secondary to AEs.
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			1 form?
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			Description of ethical conduct of study in individual study reports.

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.

N/A

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

No clinical review issues

Suzette Peng, MD	August 4, 2014
Reviewing Medical Officer	Date
Janet Maynard, MD, MHS	August 4, 2014
Clinical Team Leader	Date

File name: Clinical Filing Checklist for NDA 207768

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Received: June 30, 2014
PDUFA: April 30, 2015

NDA 207768
Codeine Polistirex and Chlorpheniramine Polistirex ER Oral Suspension

MO: Suzette Peng, MD
TL: Janet Maynard, MD, MHS
Filing meeting
August 5, 2014

1

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Outline

- Sponsor: Tris Pharma, Inc.
- Product: codeine polistirex and chlorpheniramine polistirex (COD-CPM) ER oral suspension
- Formulation: 20mg codeine phosphate and 4mg chlorpheniramine maleate
-
- Proposed Indication: Relief of cough and (b) (4) upper respiratory allergies in adults 18 years of age and older
- Pivotal bioavailability studies: 3007116 and 3007117
- **Application fileable: Yes**
- Issues: None

2

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

COD-CPM ER Oral Suspension

- 2 ER products in the last 3 decades
  - Codeprex™ Pennkinetic®, NDA 021369 ***Reference Product***
  - Pentuss®, NDA 01898
- Supportive evidence
  - Safe and efficacious antitussive and antihistamine drug products
    - Codeine phosphate in 21 CFR 341.14(a)(2)(ii) OTC monograph
    - Chlorepheniramine maleate in 21 CFR 341.12(c) OTC monograph
  - Dosing
    - Codeine phosphate in 21 CFR 341.74(d)(ii)
    - Chlorpheniramine maleate in 21 CFR 341.72(d)(3)
  - Use in combination in 21 CFR 341.40(d)

3

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Regulatory History

- **October 2012, Pre-IND meeting**
  - 505(b)(2) acceptable
  - Reference specific drug, not OTC monograph
  - Acceptable to use labeling similar to Codeprex Pennkinetic
  - No further toxicology studies are required
  - Codeine phosphate and chlorpheniramine IR solution prepared in-house appropriate as reference product
  - Single-dose 3-way crossover and a steady state BA/BE PK studies acceptable
  - Pediatric requirements under discussion

4

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Regulatory History

- **October 2012**
  - CMC response on stability requirements
- **December 2012**
  - Sponsor response to CMC regarding stability requirements
- **July 2013, IND (b) (4) submission**
  - August 2013 CMC IR
  - September 18, 2013, *Study may proceed* letter
- **December 2013, request for proprietary name review, Tuzistra XR**
  - June 2014, proprietary name acceptable

5

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Clinical Development

Study	Study Design	Study Product	Subjects	Duration of Treatment
3006726	SD, OL, R, 2-period crossover study to compare rate of absorption and oral BA of test ER oral suspension to equivalent IR oral solution	Test: ER Oral Suspension 10mL once at 0hr (20mg/4mg per 5mL) Reference: IR Oral Solution (20mg/4mg per 5mL) 5mL at 0h and 6h	14 healthy subjects	18 days
3007132	SD, OL, R, 2-period crossover study to compare rate of absorption and oral BA of test ER oral suspension to equivalent IR oral solution	Test: ER Oral Suspension 10mL once at 0hr (20mg/4mg per 5mL) Reference: IR Oral Solution (20mg/4mg per 5mL) 5mL at 0h and 6h	14 healthy subjects	18 days
3007116 **(Pivotal)**	MD, 2-period, 2-treatment, 2-way crossover study to compare rate of absorption and oral BA of test to equivalent oral dose of reference	Test: ER Oral Suspension, 20mg/4mg per mL Reference: IR Oral Solution (20mg/4mg per mL)	32 healthy subjects	27 days
3007117 **(Pivotal)**	SD, 3-period, OL, 3-way crossover study to compare BA of test under fasted and fed conditions and to evaluate relative BA of test to reference	Test: ER Oral Suspension 10mL once at 0hr (20mg/4mg per 5mL) Reference: IR Oral Solution (20mg/4mg per 5mL)	32 healthy subjects (36 enrolled)	32 days

6

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Clinical Development

- **Test product** (pivotal studies)
  - 20mg codeine phosphate and 4mg chlorpheniramine maleate per 5 mL, ER suspension
  - 1 dose is 10 mL
- **Reference product**
  - 20mg codeine phosphate and 4mg chlorpheniramine maleate per 5 mL, IR solution, ***prepared in-house***
  - 1 dose is 5 mL

7

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Study 3007117

- SD, OL, R, 3-period, 3-treatment crossover study
- Subjects received each of the following treatments
  - 1 single dose (0 hr) of the test formulation following an overnight fast of at least 10 hours
  - 1 single dose (0 hr) of the test formulation following an overnight fast of at least 10 hours, then consumption of a FDA-defined standard high-fat, high-calorie breakfast meal
  - 2 single-dose administrations (0hr and 6hr) of the reference product following an overnight fast of at least 10 hours
- Each 0hr drug administration separated by 14-day washout
- 32 healthy volunteers (36 enrolled)

8

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Study 3007117

- Study objectives
  - To evaluate the bioavailability of test formulation under both fasted and fed conditions
  - To evaluate the relative bioavailability of test formulation to an equivalent dose of reference product under fasted conditions
- PK endpoints
  - C_{max}, T_{max}, C_{last}, T_{last}, λ_z, $T_{1/2}$, AUC_{last}, AUC_{inf}, AUC_{Extrap}(%)
- Safety
  - Adverse events
  - Clinical laboratory results, vital signs, ECG, physical findings

9

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Study 3007116

- MD, OL, R, 2-period, 2-treatment crossover study
- Subjects received each of the following treatments
  - Test formulation
    - 2 single-dose administrations at 0hr and 12hr on Days 1-6
    - 1 single-dose administration at 0hr on Day7
  - Reference product
    - 4 single-dose administrations at 0hr, 6hr, 12hr, and 18hr on Days 1- 6
    - 2 single-dose administrations at 0hr and 6hr on Day 7
- Each treatment period was separated by a 14-day washout after the 0hr dose on Day 7
- 32 healthy subject (32 enrolled)

10

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Study 3007116

- Study objective
  - To compare the rate of absorption and oral bioavailability of test formulation to an equivalent dose of reference product under fasted steady-state conditions
- PK endpoints
  - C_{max}, C_{min}, T_{max}, T_{min}, Flux, Swing, C_{avg}, AUC_{0-12}
- Safety
  - Adverse events
  - Clinical laboratory results, vital signs, ECG, physical findings

11

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Safety: Codeprex Pennkinetic

Warnings

- Respiratory depression
- Head injury and increased intracranial pressure
- Acute abdominal conditions
- Obstructive bowel disease
- Respiratory conditions

12

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Safety: Exposure

Treatment	Number of Doses	Single Codeine/ Chlorpheniramine Dose	Total Codeine/ Chlorpheniramine Dosed
Study 3007117			
A: COD-CPM ER Oral Suspension (fasted) (Test Product)	1	40 mg/8 mg	40 mg/8 mg
B: COD-CPM ER Oral Suspension (fed) (Test Product)	1	40 mg/8 mg	40 mg/8 mg
C: Codeine Phosphate and Chlorpheniramine Maleate Reference IR Product (fasted)	2	20 mg/4 mg	40 mg/8 mg
Study 3007116			
A: COD-CPM ER Oral Suspension (fasted) (Test Product)	13a	40 mg/8 mg	520 mg/104 mg
B: Codeine Phosphate and Chlorpheniramine Maleate Reference IR Product (fasted)	26b	20 mg/4 mg	520 mg/104 mg

[a] Over 7 days with 2 doses/day on Days 1 through 6 and 1 dose on Day 7
[b] Over 7 days with 4 doses/day on Days 1 through 6 and 2 doses on Day 7

Clinical Summary of Safety, Table 3, page 4.

13

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Safety

- No deaths
- No severe or serious AEs
- No withdrawals secondary to AEs
- No clinically significant abnormalities in vital signs, ECG, or clinical laboratory evaluation

14

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Safety: Study 3007117

	Treatment A (Test Product [fasted]) N = 34	Treatment B (Test Product [fed]) N = 34	Treatment C (Reference Product [fasted]) N = 34
	No. Adverse Events	No. Adverse Events	No. Adverse Events
Abdominal pain	1	--	--
Upper abdominal pain	--	--	1
Gastrointestinal hypomobility	1	--	--
Viral URTI*	--	1	--
Dizziness	--	--	2 (mild) 1 (moderate)
Headache	2	--	1
Presyncope	1 (moderate)	--	1
Epistaxis	--	1	--
Hiccups	--	1	--
Rash	--	--	1 (moderate)
Orthostatic hypotension	--	--	1

Upper Respiratory Tract Infection
No Serious Adverse Events were reported
All Adverse Events were mild unless otherwise reported

- Total 16 TEAEs in 9 subjects
- Most common AEs
  - Headache (2), Presyncope (1)
- No food effect on safety

Clinical Overview, Table 7, page 19.

15

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Safety: Study 3007116

	Treatment A (Test Product) N=32 subjects		Treatment B (Reference Product) N=32 subjects	
	No. AE's	No. Subjects (%)	No. AE's	No. Subjects (%)
Vertigo	--	--	1	1 (3.1%)
Abdominal pain	1	1 (3.1%)	--	--
Constipation	6 mild	6 (18.8%)	8 mild	6 (18.8%)
	4 moderate	3 (9.4%)	8 moderate	8 (25.0%)
Gastroesophageal reflux	--	--	1	1 (3.1%)
Back pain	1 mild	1 (3.1%)	1 mild	1 (3.1%)
	1 moderate	1 (3.1%)	--	--
Muscle spasms	1	1 (3.1%)	1	1 (3.1%)
Dizziness	--	--	2	2 (6.3%)
Headache	2	2 (6.3%)	3	3 (9.4%)
Presyncope	--	--	1 mild	1 (3.1%)
	1 moderate	1 (3.1%)	--	--
Somnolence	--	--	4	4 (12.5%)
Nasal congestion	--	--	1	1 (3.1%)
Nausea	1	1 (3.1)	1	1 (3.1)
Oral discomfort	--	--	1	1 (3.1%)
Thirst	--	--	1	1 (3.1%)
Viral URTI*	2	2 (6.3%)	2	2 (6.3%)
Total	20	--	36	--

Upper respiratory tract infection
No Serious Adverse Events were reported
All Adverse events were mild unless otherwise indicated
Source: Table 14.3.4 Clinical Report: Study Protocol 3007116

- Total 56 AEs in 22 subjects
- Most common AEs
  - Constipation (10), HA (2), abdominal pain (1), nausea (1)

Clinical Overview, Table 8, page 20.

16

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Pediatric Plan

- **December 2013, iPSP submission**
  - Request for full waiver of studies for all pediatric groups
- **February 2014, Agency response to iPSP**
  - (b) (4)
  - (b) (4)
  - (b) (4)

17

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Pediatric Plan

- **March 2014, revised iPSP submitted**
- **May 2014, Agency response to revised iPSP**
  - (b) (4)
- **May 2014, updated Agreed iPSP submitted**
- **June 3, 2014, review of Agreed iPSP complete**
- **NDA submission**
  - (b) (4)
  - Agreed iPSP

18

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Preliminary Conclusions

- Application is fileable from a clinical perspective
- Standard review priority
- No need for Advisory Committee Meeting
- As summarized by the Sponsor, COD-COM ER Oral Suspension appears to have an adequately favorable risk-benefit profile
  - Comparable bioavailability to 2 doses of IR combination of codeine phosphate and chlorpheniramine maleate
  - No new safety concerns
  - Currently no ER codeine and chlorpheniramine products on the market

19

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Major Labeling Issues

- The majority of the label is taken from the reference product drug label
- Indications and Usage
  - Common Cold and Respiratory Allergies
- Adverse reactions
  - Includes events from clinical PK studies
- Pharmacokinetics
  - Extensive data including figures

20

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Midcycle Deliverables

- Safety results
  - Common AEs
  - AEs of interest

Consults

- Recommend OSI inspection
  - BE study is pivotal
  - Reference solution of codeine phosphate and chlorpheniramine prepared in house

21

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Questions?

22

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Back-up

[redacted]

23

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Safety: Codeprex Pennkinetic

Precautions

- Caution when prescribing to patients with narrow-angle glaucoma, asthma or prostate hypertrophy
- Codeine may aggravate constipation
- Special risk patients
  - Elderly or debilitated
  - Severe hepatic or renal impairment
  - Hypothyroidism, Addison's disease
  - Prostate hypertrophy or uretheral stricture
  - Poss bility of respiratory depression
- Cough reflex
- Marked drowsiness and impaired mental/physical abilities when performing potentially hazardous tasks such as driving a car or operating machinery
- Do not dilute with fluids or mix with other drugs
- Antihistamines may cause excitability, especially in children

24

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

/s/

SUZETTE W PENG
08/18/2014

JANET W MAYNARD
08/18/2014