

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207768Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**BIOPHARMACEUTICS REVIEW**  
**Office of New Drug Products**

NDA:	207768	Reviewer: Assadollah Noory, Ph.D.
Submission Date:	June 27, 2014	
Clinical Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)	Acting Quality Assessment Lead: Kelly Kitchens, Ph.D.
Applicant:	Tris Pharma, Inc.	Acting Branch Chief: Tapash Ghosh, Ph.D.
Trade Name:	Tuzistra™ XR	Acting Division Director: Paul Seo, Ph.D.
Generic Name:	Codeine Polistirex – Chlorpheniramine Polistirex	
Indication:	Relief of cough and (b) (4) (b) (4) other upper respiratory allergies in adults.	
Formulation/strengths:	Oral Suspension, Codeine Polistirex eq. to 20 mg codeine phosphate and Chlorpheniramine Polistirex eq. to 4 mg chlorpheniramine maleate per 5 mL	
Route of Administration:	Oral	

**Summary:**

Under the provisions of 505(b)(2), Tris Pharma submitted NDA 207-768 seeking approval for their Tuzistra™ XR (Codeine Polistirex eq. to 20 mg codeine phosphate and Chlorpheniramine Polistirex eq. to 4 mg chlorpheniramine maleate per 5 mL) Oral Suspension, for the relief of cough and (b) (4) upper respiratory allergies in adults. In support of the approval of this product, the Sponsor submitted dissolution study reports as part of the biopharmaceutics requirement characterizing the in vitro release profile of their product, including the effect of media pH, apparatus, rotation speed, and the alcohol dose dumping.

**Dissolution Methodology:**

The following dissolution test and specification is to be used for product release and quality control.

**Dissolution Methodology and Specification**

Apparatus	USP Apparatus II, Paddle Method	
Rotation Speed	50 rpm	
Medium	500 mL 0.1N HCl 1 <sup>st</sup> hour, add 400 mL of 0.2M Phosphate buffer, pH 6.8	
Temperature	37°C ±0.5°C	
Sampling Time	1, 3, and 12 hours	
Specifications	Codeine	1 hour: (b) (4) %
		3 hour: (b) (4) %
		12 hour: NLT (b) (4) %
	Chlorpheniramine	1 hour: NMT (b) (4) %
		3 hour: (b) (4) %
		12 hour: NLT (b) (4) %

The effect of alcohol on codeine and chlorpheniramine was evaluated in vitro using 0.1 N HCl media containing 0, 5, 10, 20, or 40% alcohol (v/v). The in vitro study demonstrated dose dumping potential of codeine in the presence of 40% alcohol. The Office of Clinical Pharmacology is requested to interpret this finding in light of the need for any in vivo alcohol dose dumping study with this drug product.

**RECOMMENDATION:**

**Dissolution Methodology:**

The following dissolution test and specification to be used for product release and quality control are found acceptable.

**Dissolution Methodology and Specification**

Apparatus		USP Apparatus II, Paddle Method
Rotation Speed		50 rpm
Medium		500 mL 0.1N HCl 1 <sup>st</sup> hour, add 400 mL of 0.2M Phosphate buffer, pH 6.8
Temperature		37°C ±0.5°C
Sampling Time		1, 3, and 12 hours
Specifications	Codeine	1 hour: (b) (4) %
		3 hour: (b) (4) %
		12 hour: NLT (b) (4) %
	Chlorpheniramine	1 hour: NMT (b) (4) %
		3 hour: (b) (4) %
		12 hour: NLT (b) (4) %

**In-vitro Alcohol Dose-dumping Potential:**

The effect of alcohol on codeine and chlorpheniramine was evaluated in vitro using 0.1 N HCl media containing 0, 5, 10, 20, or 40% alcohol (v/v). The in vitro study demonstrated dose dumping potential of codeine in the presence of 40% alcohol. The Office of Clinical Pharmacology is requested to interpret this finding in light of the need for any in vivo alcohol dose dumping study with this drug product.

Overall, from the Biopharmaceutics perspective, NDA 207768 for Tuzistra™ XR (Codeine Polistirex eq. to 20 mg codeine phosphate and Chlorpheniramine Polistirex eq. to 4 mg chlorpheniramine maleate per 5 mL) Oral Suspension is recommended for approval.

**Signature:**

Kelly M. Kitchens  
-S  
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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,  
ou=People,  
0.9.2342.19200300.100.1.1=2000336574, cn=Kelly  
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Kelly M. Kitchens, Ph.D.  
Acting Quality Assessment Lead  
Division of Biopharmaceutics  
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Tapash Ghosh, Ph.D.  
Acting Branch Chief  
Division of Biopharmaceutics  
Office of New Drug Products

cc. ANoory; JDuan; PSeo

## BACKGROUND

In support of this NDA, the Sponsor submitted a dissolution development report to study the effect of media pH, apparatus, rotation speed, and the alcohol dose dumping.

On June 27, 2014, Tris Pharma submitted an NDA 207768 for Tuzistra™, an ER oral suspension containing codeine polistirex (eq. to 20 mg codeine phosphate/5 mL) and chlorpheniramine polistirex (eq. to 4 mg chlorpheniramine maleate/per 5 mL). The Codeine Polistirex and Chlorpheniramine Polistirex (COD-CPM) Extended-Release (ER) oral suspension is designed to release over a 12-hour period. The two similar approved formulations (Codeprex™ NDA 021369 and Penntuss®, NDA 018928) have been discontinued.

The batches used in the two pilot and two pivotal pharmacokinetic studies are summarized in table below:

Table 1: Formulations Used in Pilot and Pivotal Pharmacokinetic Studies

Study	Study Objective	Batch #	Formulation Type
3006726	Formulation-finding	RD0478-023	Prototype Formulation 1 (Pilot 1)
3007132	Formulation-finding	RD0478-121	Prototype Formulation 2 (Pilot 2)
3007117	Pivotal comparative bioavailability versus reference product for single dose under fasted conditions and food effect	TB-121A	Intended Commercial Formulation (Test Product)
3007116	Pivotal comparative bioavailability versus reference product at steady state	TB-121A	Intended Commercial Formulation (Test Product)

## FORMULATION COMPOSITION

The product formulation composition is submitted to DMF 027314. A comparison between the active ingredient compositions of the proposed product and two previously marketed products are shown in the following table.

**Comparison between the Proposed Drug Product and currently Approved Drug Products:**

	<b>COD-CPM ER Oral Suspension</b>	<b>Penntuss®</b>	<b>Codeprex™ Pennkinetic®</b>
<b>Eq. Active Ingredient Strength (per 5 mL)</b>			
Codeine Base	(b) (4)	10 mg	20 mg
Chlorpheniramine Maleate	4 mg	4 mg	4 mg
<b>Eq. Active Ingredient in Single Adult Dose (10 mL)</b>			
Codeine Base	(b) (4)	20 mg	40 mg
Chlorpheniramine Maleate	8 mg	8 mg	8 mg

Inactive ingredients are: purified water, sodium polystyrene sulfonate, ethyl maltol, povidone, triacetin, polyvinyl acetate, polysorbate 80, citric acid, sodium citrate, sucrose, starch, D&C Red No. 30, glycerin, methylparaben, propylparaben, propyl gallate, xanthan gum, cherry flavor.

**PROPOSED DISSOLUTION TEST**



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### **DISCRIMINATING CAPABILITY OF THE DISSOLUTION METHOD**

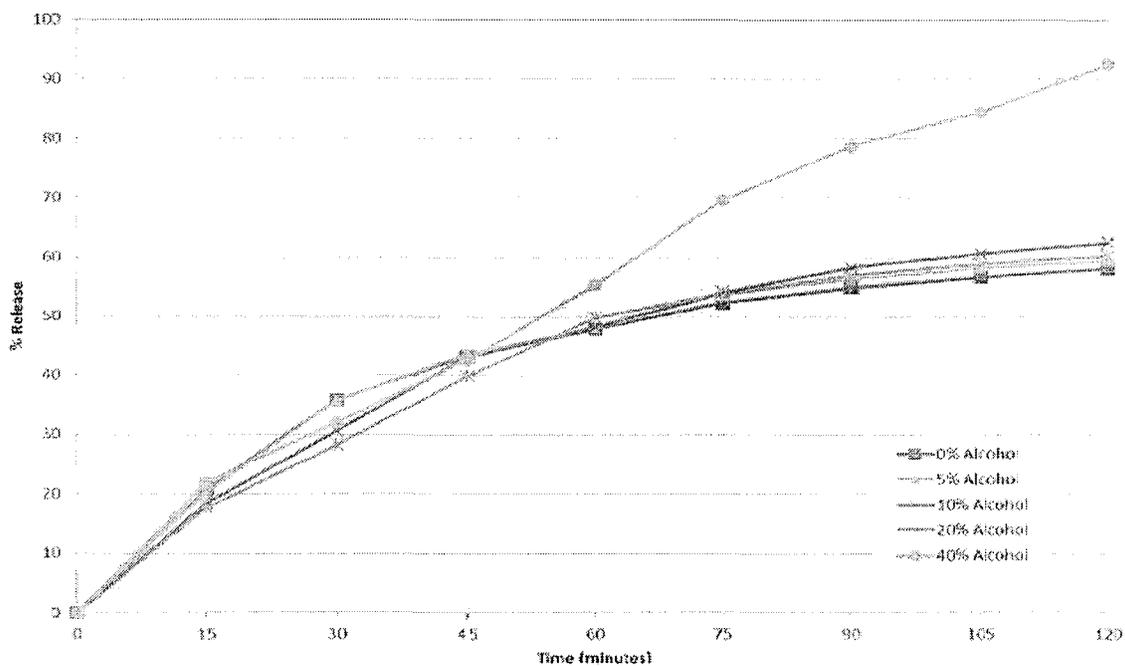
The ability of the dissolution method to detect changes in the formulation was evaluated using the paddle method 50 rpm and 500 mL 0.1N HCl for one hour followed by addition of 400 mL 0.2M NaH<sub>2</sub>PO<sub>4</sub>. Two suspensions [REDACTED] (b) (4) were tested to show the discriminating capability of the method. The table below shows the results.

[REDACTED TABLE]

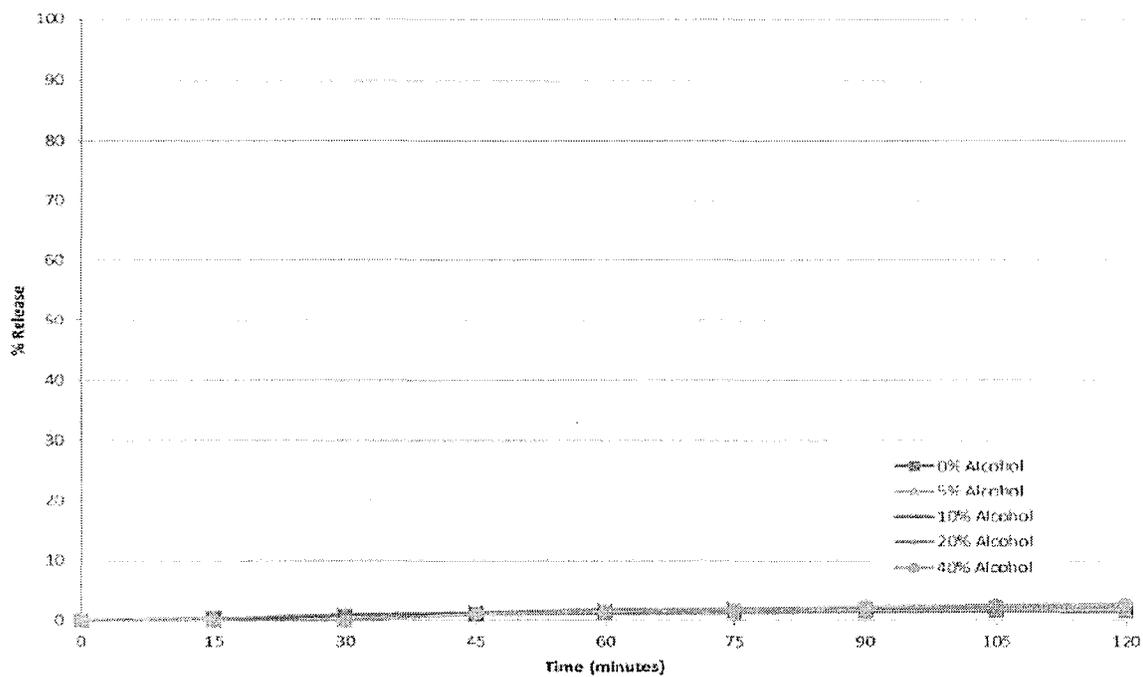
### **ALCOHOL DOSE DUMPING STUDY**

The effect of alcohol on codeine and chlorpheniramine was evaluated using lot TB-121A. Dissolution studies were performed in 0.1 N HCl media containing 0, 5, 10, 20, or 40% alcohol (v/v).

### Codeine



### Chlorpheniramine



The dissolution profiles for codeine indicate dose dumping in dissolution medium with 40% alcohol; the dissolution profile of chlorpheniramine is not influenced by presence of alcohol. This is

supported by the similarity factor, f2, reported in DMF 27314 indicating dose dumping of codeine in 40% alcohol.

Alcohol Concentration	f2 comparison with 0% Alcohol	
	Codeine	Chlorpheniramine
5%	92	98
10%	74	96
20%	72	95
40%	36	95

#### REVIEWER'S OVERALL ASSESSMENT

- The applicant provided sufficient information in support of the dissolution methodology for batch release and quality control of Tuzistra™ XR.
- The dissolution method is capable of detecting differences in the dissolution profiles of drug product with different formulation (i.e. different codeine polistirex coating levels and ingredients); the dissolution method assures at least (b) (4)% drug release for Codeine and a plateau for Chlorpheniramine release.
- The alcohol dose dumping study showed that dose dumping occurs in dissolution medium with 40% alcohol. This observation has been communicated with the Office of Clinical Pharmacology, which will determine if an in vivo alcohol study is needed for the drug product.

#### RECOMMENDATION

##### Dissolution Methodology:

The following dissolution test and specification to be used for product release and quality control are found acceptable.

##### Dissolution Methodology and Specification

Apparatus		USP Apparatus II, Paddle Method
Rotation Speed		50 rpm
Medium		500 mL 0.1N HCl 1 <sup>st</sup> hour, add 400 mL of 0.2M Phosphate buffer, pH 6.8
Temperature		37°C ±0.5°C
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		12 hour: NLT (b) (4)%
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**In-vitro Alcohol Dose-dumping Potential:**

The effect of alcohol on codeine and chlorpheniramine was evaluated in vitro using 0.1 N HCl media containing 0, 5, 10, 20, or 40% alcohol (v/v). The in vitro study demonstrated dose dumping potential of codeine in the presence of 40% alcohol. The Office of Clinical Pharmacology is requested to interpret this finding in light of the need for any in vivo alcohol dose dumping study with this drug product.

Overall, from the Biopharmaceutics perspective, NDA 207768 for Tuzistra™ XR (Codeine Polistirex eq. to 20 mg codeine phosphate and Chlorpheniramine Polistirex eq. to 4 mg chlorpheniramine maleate per 5 mL) Oral Suspension is recommended for approval.

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## CLINICAL PHARMACOLOGY REVIEW

NDA: 207768	Submission Date(s): 06/30/2015
Brand Name	TUZISTRA XR
Generic Name	Codeine/Chlorpheniramine ER Oral Suspension
Reviewer	Ritesh Jain, Ph.D.
Clinical Pharmacology Team Leader	Satjit Brar, Pharm.D. Ph.D.
OCP Division	Clinical Pharmacology -2
OND division	Division of Pulmonary, Allergy and Rheumatology Products
Sponsor	Tris Pharma
Submission Type; Code	NDA; Standard
Formulation; Strength(s)	10 mL (40 mg codeine phosphate and 8 mg chlorpheniramine maleate) every 12 hours, with or without food, not to exceed 2 doses (20 mL) in 24 hours
Proposed Indication	Relief of cough and <span style="background-color: gray; color: gray;">(b) (4)</span>  <span style="background-color: gray; color: gray;">upper</span> respiratory allergies in adults 18 years of age and older

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## 1 Executive Summary

### 1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP 2) have reviewed the clinical pharmacology data submitted under this NDA, and recommends approval.

### 1.2 Phase IV Commitments

None

### 1.3 Summary of Important Clinical Pharmacology Findings

#### 1.3.1 Background

In this application (NDA 207768), Tris Pharma is seeking the marketing approval for codeine polistirex and chlorpheniramine polistirex (COD-CPM) extended release (ER) oral suspension. The proposed COD-CPM ER oral suspension contains 20 mg codeine phosphate and 4 mg chlorpheniramine maleate per 5 mL.

The proposed product, COD-CPM ER oral suspension, is intended to provide adult patients, aged 18 years and over, with a combination of codeine and chlorpheniramine in a single product with a twice daily dosing frequency. The COD-CPM ER oral suspension is indicated for relief of cough and (b) (4)

(b) (4) upper respiratory allergies in adults. Both molecules codeine and chlorpheniramine are listed in the monograph for Combination Cough, Cold and Bronchodilator Drug Products. The monograph indicates that the two drugs are safe and efficacious at recommended doses independently and in combination.

Sponsor has submitted this application through 505(b) (2) pathway and is relying on the FDA's safety and efficacy findings from the following sources:

- i. reference product, Codeprex<sup>TM</sup> Pennkinetic<sup>®</sup>, NDA 021369;
- ii. OTC monographs for codeine phosphate 21 CFR 341.14(a)(2)(ii) and chlorpheniramine maleate in 21 CFR 341.12(c)

The clinical development program in this application comprised of two pivotal and two pilot clinical pharmacokinetic studies. Two pivotal clinical studies evaluated the relative bioavailability between COD-CPM ER oral suspension and a reference product following single and multiple dose administration. These pivotal studies also evaluated the effect of food on the proposed COD-CPM ER oral suspension. Currently, there are no immediate or extended release codeine/chlorpheniramine combination products approved via an NDA available on the market. Thus, the pivotal pharmacokinetics trials were conducted using an immediate release (IR) oral solution formulation of codeine phosphate and chlorpheniramine maleate (COD-CPM IR) extemporaneously manufactured by Tris Pharmaceutical.

This review will focus on the following two pivotal clinical pharmacology studies:

- **Study 3007117**, a single-dose, open-label, randomized, three-period, three-treatment crossover study conducted in 36 healthy adults to evaluate the relative bioavailability of COD-CPM ER Oral Suspension (Test Product) under fasted conditions against the COD-CPM IR solution (Reference Product), and to evaluate the effect of administration of the ER oral suspension with a high fat meal.
- **Study 3007116**, a multiple-dose, open-label, randomized, two-period, two-treatment crossover study conducted in 32 healthy adult subjects to establish the pharmacokinetic profile of the Test Product, in comparison with the COD-CPM IR solution (Reference Product), at steady state.

### 1.3.2 Results from Pivotal Clinical Pharmacology Trials

#### Single-Dose Bioequivalence (BE) Assessment

A comparison of systemic exposure ( $C_{max}$  and AUC) between the proposed COD-CPM ER oral suspensions (equivalent to 20 mg of codeine phosphate/4 mg of chlorpheniramine maleate per 5 mL) to an equivalent dose of a reference product (COD-CPM IR oral solution) was assessed in an open-label, randomized, three-period crossover, single dose fasted study.

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% (Table 1). 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 sharp peaks and provide slower drug release as compared to the IR product.

**Table 1: Geometric Mean, Ratios of Geometric Means and the 90% Confidence Intervals for the Pharmacokinetic Parameter of Codeine and Chlorpheniramine Following Single Dose Administration of Test (COD-CPM ER Suspension) and Reference Product (COD-CPM IR Solution) in Fasted Condition. (Study 3007117)**

Parameter	Codeine			90% Confidence Interval
	Geometric Mean <sup>a</sup>		%Ratio <sup>b</sup>	
	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
Chlorpheniramine				
Parameter	Geometric Mean <sup>a</sup>		%Ratio <sup>b</sup>	90% Confidence Interval
	Test	Ref		

<b>AUC<sub>last</sub> (ng·h/mL)</b>	267.1	307.1	86.9	83.4 - 90.7
<b>AUC<sub>inf</sub> (ng·h/mL)</b>	287.9	324.1	88.8	85.3 - 92.6
<b>C<sub>max</sub> (ng/mL)</b>	7.7	11.47	67.3	64.7 - 69.9

<sup>a</sup> 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

<sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref); Source: Study 3007117

### **Multiple-Dose Bioequivalence (BE) Assessment (Study 3007116)**

Multiple dose pharmacokinetics of COD-CPM ER suspension was assessed in study 3007116, which was a multiple-dose, two periods, two-treatment, randomized 2-way crossover study. In this study, twice daily administrations of 10 mL of COD-CPM ER suspension (20 mg codeine/4 mg chlorpheniramine; Test) and four times daily administration of 5 mL of COD-CPM IR solution (20 mg codeine/4 mg chlorpheniramine; Reference) for 7 days resulted in similar exposure and C<sub>max</sub> to both codeine and chlorpheniramine at Day 7.

At steady state, for both codeine and chlorpheniramine, the 90% CIs for the test/reference ratios of the geometric means for both C<sub>max</sub> and AUC<sub>0-12hr</sub> were within the BE limits of 80%-125% (Table 2). Therefore, at steady state the pharmacokinetic parameters were bioequivalent between the test and the reference product.

**Table 2: 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 Condition.**

Parameter	Codeine			90% Confidence Interval
	Geometric Mean <sup>a</sup>		%Ratio <sup>b</sup>	
	Test	Ref		
<b>AUC<sub>0-12</sub> (ng·h/mL)</b>	367.9	412.9	89.1	85.1 – 93.3
<b>C<sub>max</sub> (ng/mL)</b>	61.5	65.5	93.9	87.8 – 100.5
Parameter	Chlorpheniramine			90% Confidence Interval
	Geometric Mean <sup>a</sup>		%Ratio <sup>b</sup>	
	Test	Ref		
<b>AUC<sub>0-12</sub> (ng·h/mL)</b>	365.3	376.3	97.1	91.8-102.6
<b>C<sub>max</sub> (ng/mL)</b>	35.8	36.2	98.7	92.8-105.1

<sup>a</sup> 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

<sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref);

Source: Study 3007116

### **Food-Effect**

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.

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 (Table 3). 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%. Thus, 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 a reference formulation in this application. Similar exposure data with COD-CPM ER formulation in the presence of food to that with COD-CPM IR solution in fasted state suggests 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.

**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 Under Fed and Fasted Condition**

Parameter	Codeine			90% Confidence Interval
	Geometric Mean <sup>a</sup>		%Ratio <sup>b</sup>	
	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 <sup>a</sup>		%Ratio <sup>b</sup>	
	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

<sup>a</sup> Geometric Mean based on Least Squares Mean of log transformed parameter values

<sup>b</sup> Ratio(%) = Geometric Mean (Fed)/Geometric Mean (Fasted)

Source: Study 3007117

### **Dose Dumping**

The influence of alcohol on the drug release profiles for codeine and chlorpheniramine from COD-CPM ER suspension was assessed via *in vitro* dissolution studies. The range of alcohol concentrations in the dissolution medium ranged from 0 to 40%. The sponsor claimed that high (40%) concentrations of alcohol may have some impact on the release of codeine from the proposed formulation. For further details, refer to Biopharmaceutics review by Dr. Assadollah Noory.

In conclusion, from clinical pharmacology aspect, this NDA application is approvable.

## 2 Question-Based Review (QBR)

### 2.1 General Attributes of the Drug and Drug Product

The proposed product, COD-CPM ER oral suspension, is intended to provide adult patients aged 18 years and over with a combination of codeine and chlorpheniramine in a single product with a twice daily dosing frequency for the relief of symptoms that occur with the common cold, allergies, (b) (4)

Codeine and chlorpheniramine both molecules are listed in the monograph for Combination Cough, Cold and Bronchodilator Drug Products. Typical adult doses of codeine for pain relief are 30 to 60 mg every 4 to 6 hours, to a maximum of 240 daily, whereas the antitussive dose is lower at 10 to 20 mg every 4 to 6 hours, to a maximum daily dose of 120 mg. Adult doses for chlorpheniramine varies according to the indication. Adult dose for cold and rhino conjunctivitis symptoms is 4 mg chlorpheniramine maleate every 4 to 6 hours, higher doses (8 to 20 mg) may be required for more severe allergic reactions. Lower doses (2 mg every 4 to 6 hours) have also been demonstrated to be effective as part of a combination treatment for rhinitis and the common cold.

#### 2.1.1 *What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?*

**Drug Substance:** The active ingredients in COD-CPM ER oral suspension are codeine and chlorpheniramine. Codeine has been used widely in the United States for many years as a cough suppressant and for pain relief. Chlorpheniramine is also a well-known active pharmaceutical ingredient used as an antihistamine.

**Drug Product:** COD-CPM ER oral suspension is an (b) (4) oral suspension of (b) (4) codeine polistirex and chlorpheniramine maleate. The composition of the proposed product is shown in Table 4.

**Table 4: Composition of the Proposed Codeine-Chlorpheniramine Extended Release Suspension**

Ingredients	Quantity (mg/5mL)
(b) (4) USP	(b) (4)
Chlorpheniramine Maleate, USP	4
Sodium Polystyrene Sulfonate, USP	(b) (4)
Ethyl Maltol, USP	(b) (4)
Codeine Phosphate, USP	20
Povidone, USP	(b) (4)
Triacetin, USP	(b) (4)
Polyvinyl Acetate (b) (4)	(b) (4)
Polyvinyl Acetate (b) (4)	(b) (4)
Povidone (b) (4)	(b) (4)
Sodium Lauryl Sulfate (b) (4)	(b) (4)
Polysorbate 80, NF	(b) (4)
Citric Acid (b) (4) USP	(b) (4)
Sodium Citrate (b) (4) USP	(b) (4)
Sucrose, NF	(b) (4)
D&C Red No. 30 (b) (4)	(b) (4)
(b) (4) Starch (b) (4)	(b) (4)
Glycerin, USP	(b) (4)
Methylparaben, NF	(b) (4)
Propylparaben, NF	(b) (4)
Propyl Gallate, NF	(b) (4)
Xanthan Gum, NF	(b) (4)
Cherry Flavor (b) (4)	(b) (4)
(b) (4)	(b) (4)
Purified Water, USP	(b) (4)
(b) (4)	(b) (4)

**2.1.2 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and Biopharmaceutics of the drug?**

COD-CPM ER Oral Suspension is being developed by Tris Pharma Inc. to provide the new dosage form which will allow dosing at 12 hour intervals. Conventional immediate release (IR) products containing codeine and/or chlorpheniramine usually have to be administered every 4 to 6 hours. In the past three decades, two extended-release drug products containing codeine and chlorpheniramine have been approved in the United States (US):

- Pentuss<sup>®</sup> (Fisons, NDA 018928, containing codeine, 10 mg free base equivalents, and chlorpheniramine, 2.8 mg free base equivalents, per 5 mL), and
- Codeprex<sup>™</sup> Pennkinetic<sup>®</sup> (UCB Inc., NDA 021369, containing codeine, 20 mg, free base equivalents, and chlorpheniramine, 2.8 mg free base equivalents, per 5 mL).

COD-CPM ER Oral Suspension contains the equivalent of 20 mg codeine phosphate, equivalent to (b) (4) codeine base, per 5 mL of suspension, providing a concentration of codeine between that provided in Codeprex™ and Penntuss®. The concentration of chlorpheniramine is the same in all three products.

Both extended release drug products are currently not marketed and the NDAs for both have been delisted. Thus, in the pivotal trials, pharmacokinetic assessments were conducted using an extemporaneously prepared immediate release (IR) oral solution formulation of codeine phosphate and chlorpheniramine maleate (COD-CPM IR) manufactured by Tris Pharmaceutical.

**2.1.3 *What is the mechanism of action, proposed therapeutic indication and dosage recommendation for Zutistra XR suspension?***

**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.

**Proposed Indication:** Indicated for the relief of cough and (b) (4) upper respiratory allergies in adults 18 years of age and older.

**Dosage:** COD-CPM ER suspension should be orally administered in a dose of 10 mL every 12 hours, with or without food, not to exceed 2 doses (20 mL) in 24 hours.

**2.1.4 *Is any OSI (Office of Scientific Investigation) inspection requested for any of the clinical studies?***

The OSI inspection was requested for multiple dose steady state relative bioavailability study (Study 3007116). OSI review team recommended accepting the data of this relative bioavailability study without on-site inspection at clinical and bioanalytical sites (Worldwide Clinical Trials Early Phase Services, LLC, San Antonio, TX and (b) (4)). The OSI recommendation was based on their recent satisfactory inspections of these facilities without any significant irregularities. Please refer to OSI memo DARRTS dated 11/05/2014 for further details.

## 2.2 General Clinical Pharmacology

### 2.2.1 *What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?*

To support the efficacy and safety of COD-CPM ER oral suspension in this NDA, Sponsor is relying on the Agency's previous findings of efficacy and safety from the reference product, Codeprex™ Pennkinetic®, NDA 021369, and the monograph for Combination Cough, Cold and Bronchodilator Drug Products.

The clinical development program for COD-CPM ER oral suspension is therefore comprised of pharmacokinetic studies intended to establish relative bioavailability between COD-CPM ER oral suspension and a reference product. At the present time, there are no immediate or extended release codeine/chlorpheniramine combination products approved via an NDA available on the market and so the pharmacokinetic assessments were conducted in comparison to an immediate release oral solution of codeine phosphate and chlorpheniramine maleate manufactured by Tris, for investigational purpose only.

Two pivotal clinical studies were then conducted to support the development and registration of the COD-CPM ER suspension (Test Product):

- **Study 3007117**, a single-dose, open-label, randomized, three-period, three-treatment crossover study conducted in 36 healthy adults to evaluate the relative bioavailability of COD-CPM ER Oral Suspension (Test Product) under fasted conditions against the COD-CPM IR solution (Reference Product), and to evaluate the effect of administration of the ER oral suspension with a high fat meal.
- **Study 3007116**, a multiple-dose, open-label, randomized, two-period, and two-treatment crossover study conducted in 32 healthy adult subjects to establish the pharmacokinetic profile of the Test Product, in comparison with the COD-CPM IR solution (Reference Product), at steady state.

### 2.2.2 *Are the active moieties in the plasma appropriately identified and measured?*

Yes. Please refer to the section 2.4 for details of the bioanalytical method.

### 2.2.3 *Is the systemic exposure after single administration of the test product COD-CPM ER suspension comparable to that after the administration of the reference product COD-CPM IR solution?*

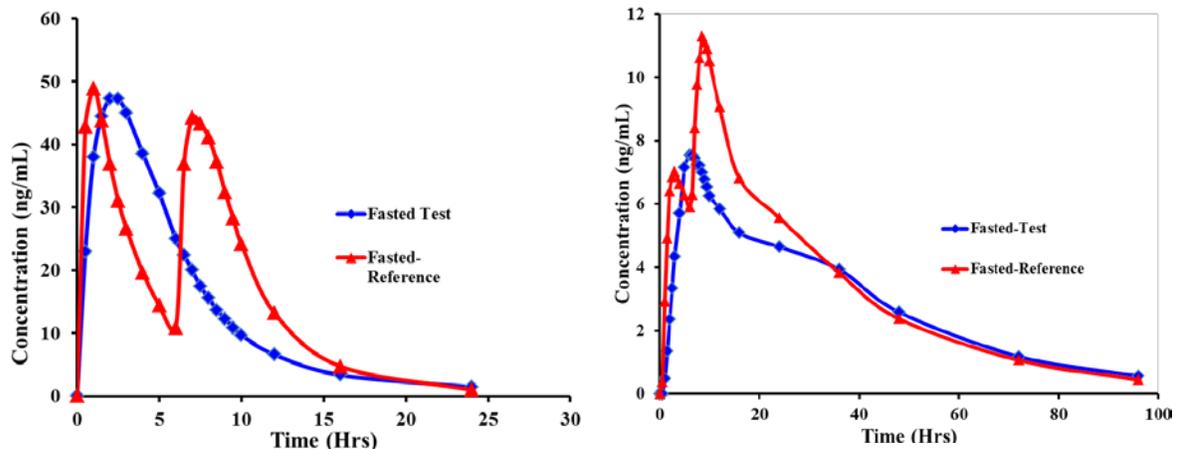
In this application, study 3007117 evaluated the oral bioavailability of a single dose of 10 mL of test product COD-CPM ER oral suspension (equivalent to 20 mg of codeine phosphate/4 mg of chlorpheniramine maleate per 5 mL) to an equivalent dose of a reference product COD-CPM IR oral solution manufactured by Tris Pharma, Inc.

Study 3007117 was a single-dose, three period, open-label, randomized, 3-way crossover study. In this study, subjects under fasting condition received one single dose of test product (COD-CPM ER suspension) and two single doses of reference product (COD-CPM IR solution). A total of 36 subjects participated in the study and 32 of those subjects completed all three study periods.

Mean codeine and chlorpheniramine plasma concentration-time profiles are shown in Figure 1. Mean and statistical analysis of the PK parameters for codeine and chlorpheniramine are shown in Table 5.

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% (Table 5). 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).

**Figure 1: Mean Codeine (Left) and Chlorpheniramine (Right) Plasma Concentration-Time Profile Following Single Dose Administration of Test Product (10 mL COD-CPM ER Suspension) and Two Doses (Q6h) of Reference Product (5 mL COD-CPM IR Solution) Under Fasting Condition**



**Table 5: 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) in Fasted Condition. (Study 3007117)**

Parameter	Codeine			90% Confidence Interval
	Geometric Mean <sup>a</sup>		%Ratio <sup>b</sup>	
	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

<b>C<sub>max</sub> (ng/mL)</b>	49.5	53.9	91.7	85.3 - 98.5
<b>T<sub>1/2</sub> (Hr)</b>	5.0	3.01		
<b>Parameter</b>	<b>Chlorpheniramine</b>			<b>90% Confidence Interval</b>
	<b>Geometric Mean<sup>a</sup></b>		<b>%Ratio<sup>b</sup></b>	
	<b>Test</b>	<b>Ref</b>		
<b>AUC<sub>last</sub> (ng·h/mL)</b>	267.1	307.1	86.9	83.4 - 90.7
<b>AUC<sub>inf</sub> (ng·h/mL)</b>	287.9	324.1	88.8	85.3 - 92.6
<b>C<sub>max</sub> (ng/mL)</b>	7.7	11.4	67.3	64.7 - 69.9
<b>T<sub>1/2</sub> (Hr)</b>	21.5	19.6		

<sup>a</sup> 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

<sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref); Source: Study 3007117

***Reviewer's Comment:*** In this study ER product showed lower C<sub>max</sub> for chlorpheniramine as compared to IR product. Typically, the ER product is expected to have lower C<sub>max</sub>, since the ER product is designed to reduce the sharp peaks and provide slower drug release as compared to the IR product. Moreover, in the multiple dose study the C<sub>max</sub> for chlorpheniramine was with the BE limits of 80%-125%

#### **2.2.4 Is the systemic exposure after multiple administration (steady-state) of the test product COD-CPM ER suspension comparable to that after the administration of the reference product COD-CPM IR solution?**

Multiple dose pharmacokinetics of COD-CPM ER suspension was assessed in study 3007116, which was a multiple-dose, two-period, two-treatment, randomized 2-way crossover study.

The objective of this study was to compare the rate of absorption and oral bioavailability of a COD-CPM ER oral suspension (test) and COD-CPM IR oral solution (reference) manufactured by Tris Pharma, Inc., when administered under fasted steady-state conditions.

In this study, subjects were randomized to receive one of the following treatments:

- Two single-dose (10 mL) administrations of a test formulation of COD-CPM ER oral suspension (equivalent to 20 mg of codeine and 4 mg of chlorpheniramine)

phosphate in each 5 mL) at 0 and 12 hours on Days 1 through 6 (inclusive), and one single-dose administration of the test formulation at 0 hour on Day 7.

- Four single dose administrations of the reference product, COD-CPM IR oral solution (20 mg/4 mg 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.

In the study, the first drug administration on each study day occurred after a minimum 10-hour overnight fast. In addition, each treatment was separated by a washout period of at least 14 days.

Steady state mean codeine and chlorpheniramine plasma concentration-time profiles are shown in Figure 2. Mean and statistical analysis of the PK parameters for codeine and chlorpheniramine are shown in Table 6.

At steady state, both for codeine and chlorpheniramine, the 90% CIs for the test/reference ratios of the geometric means for both  $C_{max}$  and  $AUC_{0-12hr}$  were within the BE limits of 80%-125% (Table 6). Therefore, at steady state the pharmacokinetic parameters were bioequivalent between the test and the reference product.

**Table 6: 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 Condition.**

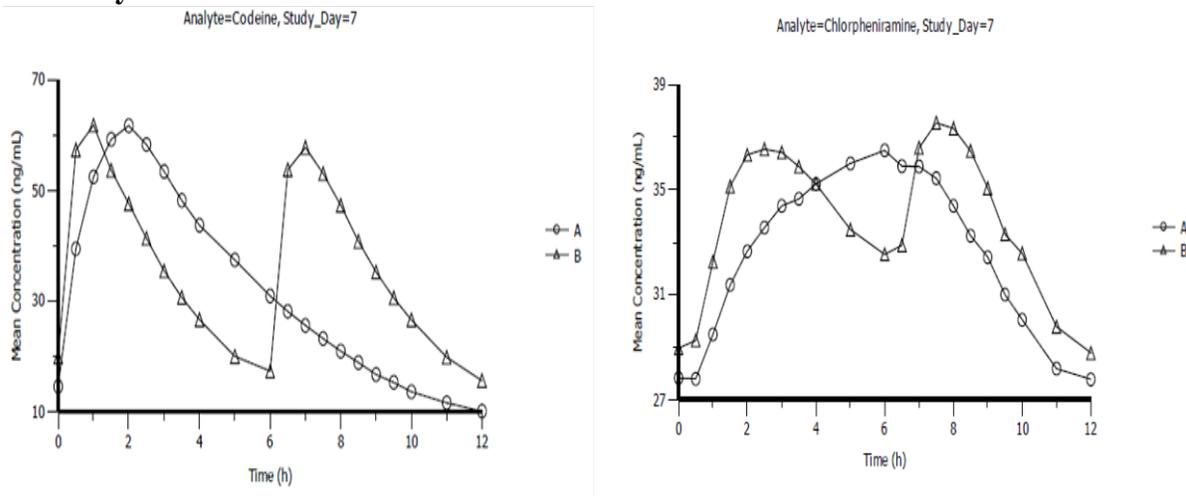
Parameter	Codeine			90% Confidence Interval
	Geometric Mean <sup>a</sup>		%Ratio <sup>b</sup>	
	Test	Ref		
$AUC_{0-12}$ (ng·h/mL)	367.9	412.9	89.1	85.1 – 93.3
$C_{max}$ (ng/mL)	61.5	65.5	93.9	87.7-100.5
$C_{min}$ (ng/mL)	9.4	14.5	64.4	60.8-68.3
$C_{avg}$ (ng/mL)	30.6	34.4	89.1	85.1-93.2
Parameter	Chlorpheniramine			90% Confidence Interval
	Geometric Mean <sup>a</sup>		%Ratio <sup>b</sup>	
	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

<sup>a</sup> 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

<sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref);

Source: Study 3007116

**Figure 2: Mean Codeine (Left) and Chlorpheniramine (Right) Plasma Concentration-Time Profile Following Multiple Dose Administration of Test Product (COD-CPM ER Suspension) and Reference Product (COD-CPM IR Solution) Under Fasting Condition for 7 Days**



**Reviewer's Comment:** At steady state, both for codeine and chlorpheniramine,  $C_{max}$  and AUC were bioequivalent between the ER and IR product. 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 40 mg every 12 hours (total daily dose of 80 mg). Since much lower doses of codeine are 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 of symptoms associated with the common cold (the desired indication) and thus, Tuzistra XR does not rely solely on codeine for its indicated benefit. Thus lowered  $C_{min}$  values for codeine between hours of 9-12 are of limited relevance.

## 2.3 General Biopharmaceutics

### 2.3.1 *Is the to-be-marketed formulation used in the pharmacokinetic studies?*

Yes, the Sponsor used proposed to be marketed formulation in the pivotal bioavailability and food effect study.

### 2.3.2 *What is the effect of food on the bioavailability of codeine and chlorpheniramine from the proposed COD-CPM ER product?*

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 state.

Steady state mean codeine and chlorpheniramine plasma concentration-time profiles are shown in Figure 3. Mean and statistical analysis of the PK parameters for codeine and chlorpheniramine are shown in Table 7.

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 (Table 7). 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%. Thus 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 a reference formulation in this application. Similar exposure data with COD-CPM ER formulation in the presence of food to that with COD-CPM IR solution in fasted state suggests that the increased exposures in the presence of food are within the allowed monograph range.

**Table 7: 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 Condition**

Parameter	Codeine			90% Confidence Interval
	Geometric Mean <sup>a</sup>		%Ratio <sup>b</sup>	
	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 <sup>a</sup>		%Ratio <sup>b</sup>	
	Fed	Fasted		

<b>AUC<sub>inf</sub> (ng·h/mL)</b>	284.2	288.8	98.4	93.8-103.2
<b>C<sub>max</sub> (ng/mL)</b>	6.4	7.7	83.6	78.5-89.0

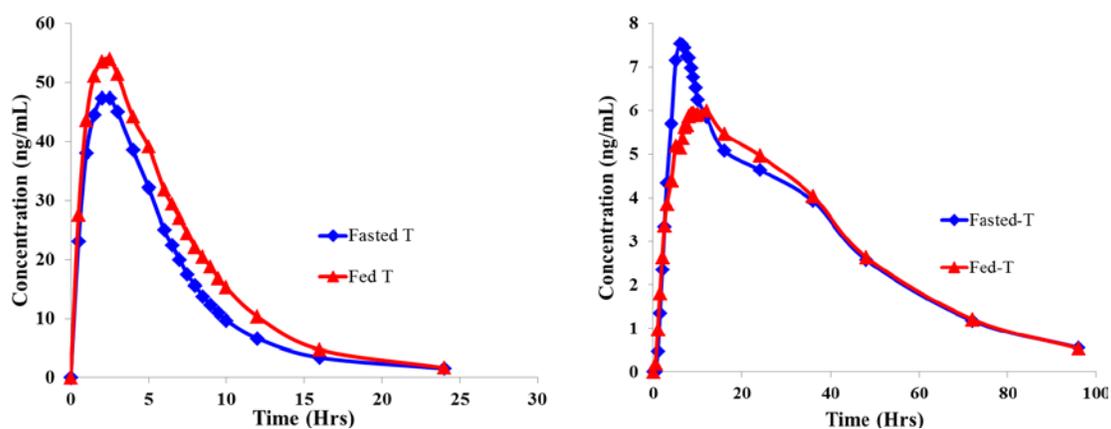
<sup>a</sup> Geometric Mean based on Least Squares Mean of log transformed parameter values

<sup>b</sup> Ratio(%) = Geometric Mean (Fed)/Geometric Mean (Fasted)

Source: Study 3007117

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

**Figure 3: Mean Codeine (Left) and Chlorpheniramine (Right) Plasma Concentration-Time Profile Following Administration of Test Product Under Fed (High Fat Meal) and Fasting Condition**



**Reviewer's Comment:** In this study, in the presence of food an increase in exposure ~25% (AUC<sub>inf</sub>) for codeine was observed. However, from the same single dose study, head to head comparison of AUC<sub>inf</sub> of the ER oral suspension under fed state to the IR oral solution under fasting condition showed similar exposure with geometric means for AUC<sub>inf</sub> within the BE limits of 80%-125% (90%CI=102.7-112.7, point estimate 107.6). Thus increased exposure of codeine with high fat meal is comparable to IR formulation in the fasted state and thus within the allowed monograph range; hence does not raise any safety concerns.

### 2.3.3 What is the dose dumping potential of the proposed COD-CPM ER product?

The influence of alcohol on the drug release profiles for codeine and chlorpheniramine from COD-CPM ER Oral Suspension was assessed via *in vitro* dissolution studies. The range of alcohol concentrations in the dissolution medium ranged from 0 to 40%. The sponsor claimed that high (40%) concentrations of alcohol may have some impact on the release of codeine from the proposed formulation. For further details please refer to Biopharmaceutics review by Dr. Assadollah Noory.

## 2.4 Analytical

### 2.4.1 *How are the active moieties identified and measured in the plasma/serum?*

Quantitation of plasma codeine and chlorpheniramine concentrations were determined using validated high-performance liquid chromatography with tandem mass spectrometry (HPLC/MS/MS).

### 2.4.2 *What bioanalytical methods are used to assess concentrations?*

#### **Codeine:**

Codeine was determined in human plasma samples according to Worldwide Clinical Trials LLC (WCT) procedure ATM-1903, Original. The method validation was finalized and reported under WCT DCN 1004376. The method used in this study was validated for a range of 1.00 to 500 ng/mL, based on the analysis of 0.200 mL of plasma.

Human plasma containing codeine and the internal standard, codeine-D<sub>6</sub>, is extracted using solid phase extraction (SPE). The eluent is evaporated, reconstituted, and an aliquot is injected onto a Sciex API 4000 mass spectrometer equipped with an HPLC column. The peak area of the m/z 300→165 codeine product ion is measured against the peak area of the m/z 306→165 codeine-D<sub>6</sub> internal standard product ion.

#### **Chlorpheniramine:**

Human plasma samples were analyzed for chlorpheniramine according to WCT procedure ATM-1904, Revision 1. The method validation was finalized and reported under WCT DCN 1004199.

Human plasma containing chlorpheniramine and the internal standard, chlorpheniramine-D<sub>6</sub>, was extracted with an organic solvent mixture (liquid-liquid extraction). An aliquot of the extract was injected onto a Sciex API 5000 or API 4000 LC-MS-MS equipped with an HPLC column. The peak area of the m/z 275→230 chlorpheniramine product ion was measured against the peak area of the m/z 281→230 chlorpheniramine-D<sub>6</sub> internal standard product ion.

A brief summary of the different bioanalytical methods used is shown in the Table 8 and Table 9 below. Accepted validation indicates that method met the FDA guidance “Bioanalytical Method Validation” recommendations, and was therefore acceptable.

**Table 8: Assay Validation Results for Codeine**

<b>Information Requested</b>	<b>Data<sup>‡</sup></b>
<b>Analyte</b>	Codeine
<b>Internal standard (IS)</b>	Codeine-D6
<b>Method description</b>	ATM-1903; Solid Phase extraction; Sciex API 4000 LC-MS-MS; Masterfile 1004376
<b>Limit of quantitation</b>	1.00 ng/mL
<b>Average recovery of drug (%)</b>	79.16
<b>Average recovery of IS (%)</b>	78.35
<b>Standard curve concentrations (ng/mL)</b>	1.00 to 500 ng/mL
<b>QC concentrations (ng/mL)</b>	3.00, 35.0, 400
<b>QC Intraday precision range (%)</b>	1.9 to 4.3
<b>QC Intraday accuracy range (%)</b>	-5.5 to 1.1
<b>QC Interday precision range (%)</b>	2.7 to 3.9
<b>QC Interday accuracy range (%)</b>	-3.3 to -0.6
<b>Bench-top stability (hrs)</b>	32 hours @ room temperature
<b>Codeine Stock stability (days)</b>	35 days @ 4°C and 23 hours @ room temperature @ 5.00 µg/mL; 35 days @ 4°C and 27 hours @ room temperature @ 10.0 ng/mL
<b>Codeine Phosphate Stock stability (days)</b>	35 days @ 4°C and 20 hours @ room temperature @ approximately 200 µg/mL; 35 days @ 4°C and 26 hours @ room temperature @ 10.0 ng/mL
<b>Processed stability (hrs)</b>	168 hours @ 4°C
<b>Freeze-thaw stability (cycles)</b>	7 cycles
<b>Long-term storage stability (days)</b>	89 days @ -20°C; pending @ -70°C
<b>Dilution integrity</b>	2500 ng/mL diluted 10-fold
<b>Selectivity</b>	No interfering peaks noted in blank plasma samples

<sup>‡</sup>Note: Data presented is based on the original validation report.

**Table 9: Assay Validation Results for Chlorpheniramine**

<b>Information Requested</b>	<b>Data</b>
<b>Analyte</b>	Chlorpheniramine
<b>Internal standard (IS)</b>	Chlorpheniramine –D6
<b>Method description</b>	ATM-1904; Liquid-liquid extraction; Sciex API 5000 LC-MS-MS or Sciex API 4000 LC-MS-MS; Masterfile 1004199
<b>Limit of quantitation</b>	0.250, ng/mL
<b>Average recovery of drug (%)</b>	66.80
<b>Average recovery of IS (%)</b>	66.19
<b>Standard curve concentrations (ng/mL)</b>	0.250 to 50.0 ng/mL
<b>QC concentrations (ng/mL)</b>	0.750, 10.0, 40.0
<b>QC Intraday precision range (%)</b>	1.0 to 4.4 <sup>a</sup> ; 2.3 to 3.3 <sup>b</sup> ; 1.3 to 2.7 <sup>c</sup>
<b>QC Intraday accuracy range (%)</b>	-5.5 to 14.0 <sup>a</sup> ; 4.5 to 9.2 <sup>b</sup> ; 3.5 to 11.1 <sup>c</sup>
<b>QC Interday precision range (%)</b>	3.3 to 4.7
<b>QC Interday accuracy range (%)</b>	-2.0 to 9.0
<b>Bench-top stability (hrs)</b>	24 hours @ room temperature
<b>Stock stability (days)</b>	968 days @ 4°C; 16 hours @ room temperature @ 200µg/mL; 51 days @ 4°C and 24 hours @ room temperature @ 2.50 ng/mL
<b>Processed stability (hrs)</b>	215 hours @ room temperature
<b>Freeze-thaw stability (cycles)</b>	6 cycles
<b>Long-term storage stability (days)</b>	116 days @ -20°C and -70°C
<b>Dilution integrity</b>	250 ng/mL diluted 10-fold
<b>Selectivity</b>	No interfering peaks noted in blank plasma samples

### **3 DETAILED LABELING RECOMMENDATION**

At the time of writing this review, the labeling discussion is ongoing and the reader is referred to the final approved label for the final labeling recommendations.

## 4 APPENDIX

### 4.1 OCP FILING MEMO

#### CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

<b>Office of Clinical Pharmacology</b>				
<i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA/BLA Number	207768		Brand Name	TUZISTRA XR
OCP Division (I, II, III, IV, V)	II		Generic Name	Codeine-Chlorpheniramine ER Oral Suspension
Medical Division	Pulmonary, Allergy, and Rheumatology Products		Drug Class	Antitussive and Antihistamine
OCP Reviewer	Ritesh Jain, Ph.D.		Indication(s)	Relief of cough and (b) (4)  (b) (4) upper respiratory allergies in adults 18 years of age and older
OCP Team Leader	Satjit Brar, Pharm.D., Ph.D.		Dosage Form	oral suspension
Pharmacometrics Reviewer			Dosing Regimen	10 mL (40 mg codeine phosphate and 8 mg chlorpheniramine maleate) every 12 hours, with or without food, not to exceed 2 doses (20 mL) in 24 hours
Date of Submission	06/30/2014		Route of Administration	Oral
Estimated Due Date of OCP Review	03/26/2015		Sponsor	Tris Pharma
Medical Division Due Date	04/02/2015		Priority Classification	Standard
PDUFA Due Date	04/30/2015			
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement 090808

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

single dose:				
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD -</b>				
Phase 2:				
Phase 3:				
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
Absolute bioavailability				
Relative bioavailability -	X	2		Study 3007116, Study 3007117
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose dumping				
<b>III. Other CPB Studies</b>				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
<b>Total Number of Studies</b>		2		

On initial review of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction			X	

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement 090808

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

	information?				
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	X			
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	X			
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

**Yes** \_\_\_\_\_

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement 090808

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.  
None

Ritesh Jain, Ph.D.	08/13/2014
<hr/>	
Reviewing Clinical Pharmacologist	Date
Satjit Brar, Pharm.D., Ph.D.	08/13/2014
<hr/>	
Team Leader/Supervisor	Date

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for  
NDA\_BLA or Supplement 090808

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

### **Background:**

Sponsor, Tris Pharma, is developing a combination product which is an extended release (ER) oral suspension of codeine phosphate and chlorpheniramine maleate (20 mg codeine phosphate and 4 mg chlorpheniramine maleate per 5 mL). The proposed drug product is intended to provide the new dosage strength with an extended drug release that allows dosing at 12 hour intervals.

The proposed product is indicated for relief of cough and [REDACTED] (b) (4) [REDACTED] upper respiratory allergies in adults.

In the past, two extended-release drug products containing codeine and chlorpheniramine have been approved in the United States (US):

- Pentuss® (Fisons, NDA 018928, containing codeine, 10 mg free base equivalents, and chlorpheniramine, 2.8 mg free base equivalents, per 5 mL),
- Codeprex™ Pennkinetic® (UCB Inc., NDA 021369, containing codeine, 20 mg, free base equivalents, and chlorpheniramine, 2.8 mg free base equivalents, per 5 mL).

Both the extended release drug product is currently not marketed and the NDAs for both the products have been delisted. There are, however, 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 the Cold, Cough, Allergy, Bronchodilator, And Asthmatic Drug Products For Over-The-Counter Human Use monograph and so none have been approved via a New Drug Application (NDA) mechanism.

Sponsor has submitted this application as a 505(b) (2) pathway and is relying on the FDA's safety and efficacy findings that provided:

- i. basis of approval for reference product, Codeprex™ Pennkinetic®, N021369;
- ii. supportive evidence to include codeine phosphate in 21 CFR 341.14(a)(2)(ii) and chlorpheniramine maleate in 21 CFR 341.12(c) OTC monographs as safe and efficacious antitussive and antihistamine drug products, respectively, when administered according to dosing in 21 CFR 341.74(d)(ii) for codeine phosphate, and in 21 CFR 341.72(d)(3) for chlorpheniramine maleate, as well as the permitted - use of these active ingredients in combination (21 CFR 341.40(d)).

The clinical development program in this application comprised of two pivotal pharmacokinetic studies intended to establish relative bioavailability between ER oral suspension and a reference product. At the present time, there are no immediate or extended release codeine/chlorpheniramine combination products approved via an NDA available on the market and so the pharmacokinetic assessments were conducted in comparison to an immediate release (IR) oral solution (codeine phosphate/Chlorpheniramine maleate) manufactured by Tris, for investigational purpose only.

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement 090808

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Please refer to slides below for further details. The review will focus on the two pivotal studies

- Study 3007117: single dose pharmacokinetic and food effect study
- Study 3007116: multiple dose pharmacokinetic study comparing ER formulation to IR formulation.



### Filing Meeting NDA 207768 Codeine + Chlorpheniramine ER Oral Suspension Tris Pharma

Clinical Pharmacology Review Team

Ritesh Jain

Satjit Brar (Team Leader)



### Summary

- This NDA is fileable from a Clinical Pharmacology perspective.
- Single-dose bioavailability study
  - Similar exposure (AUC) between IR (reference) and ER (test) product.
  - $C_{max}$  for chlorpheniramine was lower with ER product.
- Multiple-dose bioavailability study
  - Similar  $C_{max}$  and AUC between ER and IR product.
- Food effect study: In the presence of food
  - Lower  $C_{max}$  for chlorpheniramine
  - Higher AUC for codeine

2

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement 090808

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

### Indication and Usage

#### Formulation:

- o Codeine-Chlorpheniramine ER Oral Suspension, equivalent to 20 mg codeine phosphate and 4 mg chlorpheniramine maleate per 5 mL

#### Indication and Usage:

- o Indicated for the relief of cough and (b) (4) respiratory allergies in adults 18 years of age and older.
- o TUZISTRA XR should be orally administered in a dose of 10 mL every 12 hours, with or without food, not to exceed 2 doses (20 mL) in 24 hours

3

### Regulatory History

- 10/26/2012 Pre-IND meeting
  - FDA Agreed on single dose and multiple dose BA/BE studies.
- 07/29/2013 IND submission
- Two discontinued extended-release drug products containing codeine and chlorpheniramine have been approved in US in the past
  - **Penntuss® (Fisons, NDA 018928)**
  - **Codeprex™ Pennkinetic® (UCB Inc., NDA 021369)**

Comparison between the Proposed Drug Product and currently Approved Drug Products:

	COD-CPM ER Oral Suspension	Penntuss®	Codeprex™ Pennkinetic®
eq. Active Ingredient Strength (per 5 mL)			
Codeine Base	(b) (4)	10 mg	20 mg
Chlorpheniramine Maleate	4 mg	4 mg	4 mg
eq. Active Ingredient in Single Adult Dose (10 mL)			
Codeine Base	(b) (4)	20 mg	40 mg
Chlorpheniramine Maleate	8 mg	8 mg	8 mg

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement 090808

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement



U.S. Food and Drug Administration  
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## Background: Clinical Program Summary

### Submission Pathway:

To support this 505(b)(2) application Sponsor is relying on the Agency's previous findings of efficacy and safety from

- Codeprex™ Pennkinetic®, (NDA021369)
- Monographs

### Reference Product:

- No immediate or extended release codeine/chlorpheniramine combination products approved via an NDA available on the market.
- In this NDA, Immediate release (IR) oral solution (codeine phosphate/chlorpheniramine maleate) manufactured by in house by Tris, were used as reference product.



U.S. Food and Drug Administration  
Protecting and Promoting Public Health

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## Background: Clinical Program Summary

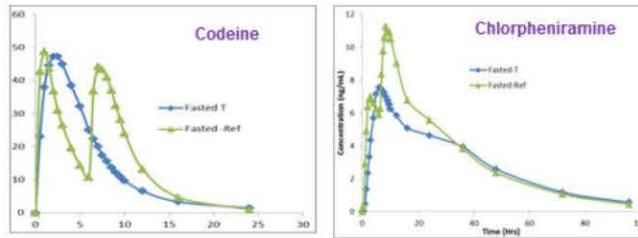
Two pivotal clinical studies to support the new ER product (Test Product):

- **Study 3007117:**
  - Single dose study relative bioavailability comparing ER and IR formulation
  - Food Effect Study
- **Study 3007116:**
  - Multiple dose relative bioavailability study comparing ER and IR formulation

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement 090808

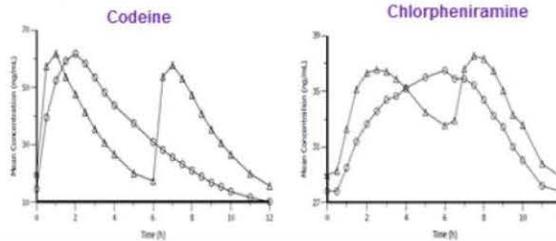
# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

## Single Dose PK Study: Lower $C_{max}$ for Chlorpheniramine



	Codeine % Ratio ER/IR (90 % CI)	Chlorpheniramine % Ratio ER/IR (90 % CI)	
$C_{max}$	91.67 (85.33-98.48)	<b>67.27 (64.73-69.90)</b>	
$AUC_{inf}$	85.60 (82.09-89.25)	88.85 (85.26-92.58)	7

## Multiple Dose PK Study: BE met for $AUC$ and $C_{max}$



	Codeine % Ratio ER/IR (90 % CI)	Chlorpheniramine % Ratio ER/IR (90 % CI)	
$C_{max}$	93.90 (87.77-100.46)	98.75 (92.77-105.11)	
$AUC_{0-12 \text{ hrs}}$	89.09 (85.10-93.27)	97.08 (91.82-102.65)	8

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement 090808

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RITESH JAIN  
03/03/2015

SATJIT S BRAR  
03/04/2015

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

**Office of Clinical Pharmacology**

*New Drug Application Filing and Review Form*

General Information About the Submission

	Information		Information
NDA/BLA Number	207768	Brand Name	TUZISTRA XR
OCP Division (I, II, III, IV, V)	II	Generic Name	Codeine-Chlorpheniramine ER Oral Suspension
Medical Division	Pulmonary, Allergy, and Rheumatology Products	Drug Class	Antitussive and Antihistamine
OCP Reviewer	Ritesh Jain, Ph.D.	Indication(s)	Relief of cough and runny nose, sneezing, (b) (4) upper respiratory allergies in adults 18 years of age and older
OCP Team Leader	Satjit Brar, Pharm.D., Ph.D.	Dosage Form	oral suspension
Pharmacometrics Reviewer		Dosing Regimen	10 mL (40 mg codeine phosphate and 8 mg chlorpheniramine maleate) every 12 hours, with or without food, not to exceed 2 doses (20 mL) in 24 hours
Date of Submission	06/30/2014	Route of Administration	Oral
Estimated Due Date of OCP Review	03/26/2015	Sponsor	Tris Pharma
Medical Division Due Date	04/02/2015	Priority Classification	Standard
PDUFA Due Date	04/30/2015		

***Clin. Pharm. and Biopharm. Information***

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement 090808

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

single dose:				
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD -</b>				
Phase 2:				
Phase 3:				
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>				
<b>Relative bioavailability -</b>	X	2		Study 3007116, Study 3007117
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>				
<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>				
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		2		

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

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction			X	

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement 090808

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	information?				
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	X			
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	X			
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

**Yes** \_\_\_\_\_

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement 090808

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.  
None

Ritesh Jain, Ph.D.

08/13/2014

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Reviewing Clinical Pharmacologist

Date

Satjit Brar, Pharm.D., Ph.D.

08/13/2014

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Team Leader/Supervisor

Date

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

## **Background:**

Sponsor, Tris Pharma, is developing a combination product which is an extended release (ER) oral suspension of codeine phosphate and chlorpheniramine maleate (20 mg codeine phosphate and 4 mg chlorpheniramine maleate per 5 mL). The proposed drug product is intended to provide the new dosage strength with an extended drug release that allows dosing at 12 hour intervals.

The proposed product is indicated for relief of cough [REDACTED] (b) (4)

[REDACTED] upper respiratory allergies in adults.

In the past, two extended-release drug products containing codeine and chlorpheniramine have been approved in the United States (US):

- Pentuss® (Fisons, NDA 018928, containing codeine, 10 mg free base equivalents, and chlorpheniramine, 2.8 mg free base equivalents, per 5 mL),
- Codeprex™ Pennkinetic® (UCB Inc., NDA 021369, containing codeine, 20 mg, free base equivalents, and chlorpheniramine, 2.8 mg free base equivalents, per 5 mL).

Both the extended release drug product is currently not marketed and the NDAs for both the products have been delisted. There are, however, 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 the Cold, Cough, Allergy, Bronchodilator, And Antiasthmatic Drug Products For Over-The-Counter Human Use monograph and so none have been approved via a New Drug Application (NDA) mechanism.

Sponsor has submitted this application as a 505(b) (2) pathway and is relying on the FDA's safety and efficacy findings that provided:

- i. basis of approval for reference product, Codeprex™ Pennkinetic®, N021369;
- ii. supportive evidence to include codeine phosphate in 21 CFR 341.14(a)(2)(ii) and chlorpheniramine maleate in 21 CFR 341.12(c) OTC monographs as safe and efficacious antitussive and antihistamine drug products, respectively, when administered according to dosing in 21 CFR 341.74(d)(ii) for codeine phosphate, and in 21 CFR 341.72(d)(3) for chlorpheniramine maleate, as well as the permitted - use of these active ingredients in combination (21 CFR 341.40(d)).

The clinical development program in this application comprised of two pivotal pharmacokinetic studies intended to establish relative bioavailability between ER oral suspension and a reference product. At the present time, there are no immediate or extended release codeine/chlorpheniramine combination products approved via an NDA available on the market and so the pharmacokinetic assessments were conducted in comparison to an immediate release (IR) oral solution (codeine phosphate/Chlorpheniramine maleate) manufactured by Tris, for investigational purpose only.

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement 090808

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Please refer to slides below for further details. The review will focus on the two pivotal studies:

- Study 3007117: single dose pharmacokinetic and food effect study
- Study 3007116: multiple dose pharmacokinetic study comparing ER formulation to IR formulation.



U.S. Food and Drug Administration  
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## Filing Meeting

NDA 207768

Codeine + Chlorpheniramine ER Oral Suspension

Tris Pharma

Clinical Pharmacology Review Team

Ritesh Jain

Satjit Brar (Team Leader)



U.S. Food and Drug Administration  
Protecting and Promoting Public Health

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## Summary

- This NDA is fileable from a Clinical Pharmacology perspective.
- Single-dose bioavailability study
  - Similar exposure (AUC) between IR (reference) and ER (test) product.
  - $C_{max}$  for chlorpheniramine was lower with ER product.
- Multiple-dose bioavailability study
  - Similar  $C_{max}$  and AUC between ER and IR product.
- Food effect study: In the presence of food
  - Lower  $C_{max}$  for chlorpheniramine
  - Higher AUC for codeine

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File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for  
NDA\_BLA or Supplement 090808

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement



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## Indication and Usage

### Formulation:

- o Codeine-Chlorpheniramine ER Oral Suspension, equivalent to 20 mg codeine phosphate and 4 mg chlorpheniramine maleate per 5 mL

### Indication and Usage:

- o Indicated for the relief of cough (b) (4)  
(b) (4)  
(b) (4) respiratory allergies in adults 18 years of age and older.
- o TUZISTRA XR should be orally administered in a dose of 10 mL every 12 hours, with or without food, not to exceed 2 doses (20 mL) in 24 hours

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## Regulatory History

- 10/26/2012 Pre-IND meeting
    - FDA Agreed on single dose and multiple dose BA/BE studies.
  - 07/29/2013 IND submission
- 
- Two discontinued extended-release drug products containing codeine and chlorpheniramine have been approved in US in the past
    - **Penntuss® (Fisons, NDA 018928)**
    - **Codeprex™ Pennkinetic® (UCB Inc., NDA 021369)**

Comparison between the Proposed Drug Product and currently Approved Drug Products:

	COD-CPM ER Oral Suspension	Penntuss®	Codeprex™ Pennkinetic®
eq. Active Ingredient Strength (per 5 mL)			
Codeine Base	(b) (4)	10 mg	20 mg
Chlorpheniramine Maleate	4 mg	4 mg	4 mg
eq. Active Ingredient in Single Adult Dose (10 mL)			
Codeine Base	(b) (4)	20 mg	40 mg
Chlorpheniramine Maleate	8 mg	8 mg	8 mg

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## Background: Clinical Program Summary

### Submission Pathway:

To support this 505(b)(2) application Sponsor is relying on the Agency's previous findings of efficacy and safety from

- Codeprex™ Pennkinetic®, (NDA021369)
- Monographs

### Reference Product:

- No immediate or extended release codeine/chlorpheniramine combination products approved via an NDA available on the market.
- In this NDA, Immediate release (IR) oral solution (codeine phosphate/chlorpheniramine maleate) manufactured by in house by Tris, were used as reference product.



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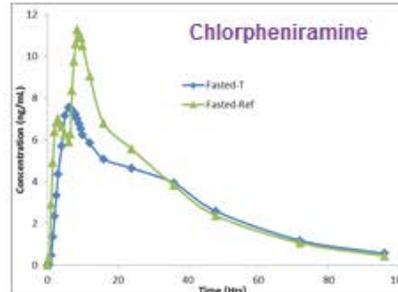
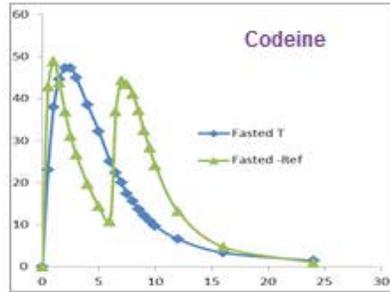
## Background: Clinical Program Summary

Two pivotal clinical studies to support the new ER product (Test Product):

- **Study 3007117:**
  - Single dose study relative bioavailability comparing ER and IR formulation
  - Food Effect Study
- **Study 3007116:**
  - Multiple dose relative bioavailability study comparing ER and IR formulation

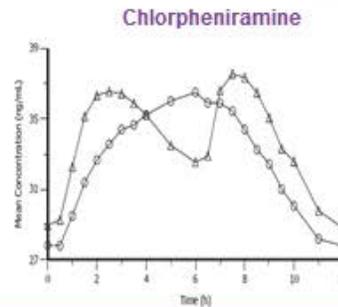
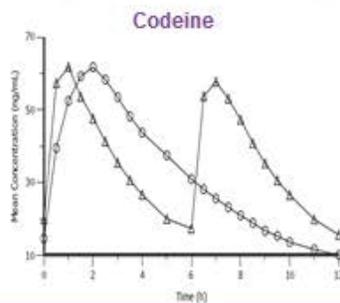
# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

## Single Dose PK Study: Lower $C_{max}$ for Chlorpheniramine



	Codeine % Ratio ER/IR (90 % CI)	Chlorpheniramine % Ratio ER/IR (90 % CI)	
$C_{max}$	91.67 (85.33-98.48)	<b>67.27 (64.73-69.90)</b>	
$AUC_{inf}$	85.60 (82.09-89.25)	88.85 (85.26-92.58)	7

## Multiple Dose PK Study: BE met for $AUC$ and $C_{max}$



	Codeine % Ratio ER/IR (90 % CI)	Chlorpheniramine % Ratio ER/IR (90 % CI)	
$C_{max}$	93.90 (87.77-100.46)	98.75 (92.77-105.11)	
$AUC_{0-12 \text{ hrs}}$	89.09 (85.10-93.27)	97.08 (91.82-102.65)	8

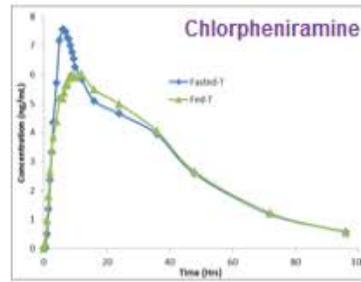
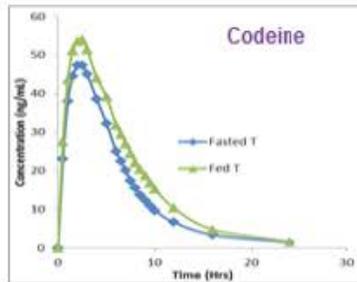
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## Food Effect Study:



	Codeine % Ratio ER/IR (90 % CI)	Chlorpheniramine % Ratio ER/IR (90 % CI)
$C_{max}$	112.66 (103.53-122.60)	83.59 (78.49-89.02)
$AUC_{inf}$	125.46 (118.80-132.49)	98.42 (93.87-103.19)



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## Conclusion and Mid-cycle Deliverables

- This NDA is fileable from Office of Clinical Pharmacology standpoint.
- DSI inspection: **Study 3007116** (Multiple Dose BA study between Test vs Reference)
- Will complete the review of both studies by mid-cycle.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RITESH JAIN  
08/14/2014

SATJIT S BRAR  
08/14/2014