CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 9, 2015
From	Janet Maynard, MD, MHS
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	207,768
Applicant	Tris Pharma, Inc.
Date of Submission	June 30, 2014
PDUFA Goal Date	April 30, 2015
Proprietary Name / Established (USAN) names	TUZISTRA XR / Codeine polistirex and chlorpheniramine polistirex ER oral suspension
Dosage forms / Strength	Oral suspension (extended release) – codeine polistirex, which contains 14.7 mg of codeine (equivalent to 20mg codeine phosphate) and chlorpheniramine polistirex, which contains 2.8 mg of chlorpheniramine (equivalent to 4mg chlorpheniramine maleate) per 5 mL
Proposed Indication(s)	Relief of cough and (b) (4) upper respiratory allergies in adults 18 years of age and older.
Recommended Action:	Approval

1. Introduction

Tris Pharma, Inc. submitted this 505(b)(2) new drug application for codeine polistirex and chlorpheniramine polistirex extended-release (COD-CPM ER) oral suspension, equivalent to 20 mg codeine phosphate and 4 mg chlorpheniramine maleate per 5 mL on June 30, 2014. The proposed indication is for "relief of cough and (b) (4) upper respiratory allergies in adults 18 years of age and older."

This 505(b)(2) application relies on FDA's safety and effectiveness findings from the listed drug, Codeprex™ Pennkinetic® (NDA 021,369) and the over the counter (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 consisted of two pivotal and two pilot clinical pharmacokinetic studies. The 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. Since there are no immediate or extended release

codeine/chlorpheniramine combination products currently approved via an NDA available on the market, the pivotal pharmacokinetics studies were conducted using an immediate release (IR) oral solution formulation of codeine phosphate and chlorpheniramine maleate (COD-CPM IR) extemporaneously manufactured by Tris Pharma.

The bioavailability study submitted by the Applicant has established the bioequivalence of each component of their cough/cold combination oral suspension test drug product, codeine and chlorpheniramine, to each component of the respective reference drug. This review will outline the clinical pharmacology program used to support approval, as well as summarize applicable discipline-specific reviews.

2. Background

This 505(b)(2) application is for a combination containing codeine polistirex and chlorpheniramine polistirex, as an extended release oral suspension containing 14.7 mg of codeine (equivalent to 20mg codeine phosphate) and 2.8 mg of chlorpheniramine (equivalent to 4 mg chlorpheniramine maleate) per 5 mL. This formulation is being developed to provide patients and clinical practitioners with an alternative dose strength and formulation with a twice daily dosing regimen. The Applicant proposed a dosing regimen of 10 mL every 12 hours, with or without food, not to exceed 2 doses (20 mL) in 24 hours in adults 18 years of age and older.

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

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

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

There are currently no known marketed products containing a combination of codeine and chlorpheniramine as an ER formulation. Two similar products have been approved in the past:

- Fisons Corporation previously marketed Pentuss (NDA 18,928, approved on August, 14, 1985) containing 10 mg/5 mL of codeine and 4 mg/5 mL of chlorpheniramine. It was withdrawn from the market at the request of the holder of the application in 1996 for reasons unrelated to safety or efficacy (Federal Register Notice dated August 5, 1996, effective date September 4, 1996).

- Celltech Pharmaceuticals received approval for Codeprex Pennkinetic ER Suspension (NDA 21,369 approved on June, 21, 2004), containing codeine polistirex and chlorpheniramine polistirex equivalent to 20 mg codeine and 4 mg chlorpheniramine maleate, respectively in each 5 mL of product. The holder of the application requested withdrawal of approval of NDA 21,369 on February 21, 2007. The NDA was with withdrawn for reasons unrelated to safety or efficacy on March 30, 2007 (Federal Register Notice dated February 11, 2009).

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

Applicants can use any 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 14.7 mg of codeine (equivalent to 20 mg codeine phosphate) and 2.8 mg of chlorpheniramine (equivalent to 4 mg of chlorpheniramine maleate) per 5 mL.

As no IR or ER codeine and chlorpheniramine combination products are currently marketed, the relative BA assessments were conducted using a codeine and chlorpheniramine combination IR solution manufactured by the Applicant as the reference product. This issue was discussed during pre-submission meetings and was considered acceptable.

Regulatory history

Written responses were issued for pre-investigational new drug application (pre-IND) (b) (4) on September 14, 2012. The responses provided general advice on the Chemistry, Manufacturing, and Controls (CMC), nonclinical, and clinical development plan for 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 listed drug would need to be a specific drug, not just the OTC monograph 21 CFR 341. It was agreed that an IR solution of codeine and chlorpheniramine manufactured by the Applicant, was reasonable for use as the reference product. The Agency generally agreed with the proposed single-dose and multi-dose dose PK studies to demonstrate bioequivalence between the test product and the reference product. The Agency noted that internal deliberations were still ongoing as to whether products for allergic rhinitis and cold indications would need to be studied in the pediatric population, and separate studies in pediatrics may be

needed to support approval of the product in children. Lastly, the Agency agreed that no further toxicology studies were required for safety assessments of the active ingredients. Follow-up questions regarding CMC and clinical pharmacology questions were addressed on October 26, 2012 at a meeting between the Applicant and the Agency on October 26, 2012, to discuss four, similar development programs.

The Applicant submitted IND (b) (4) for COD-CPM ER oral suspension on July 29, 2013 and was allowed to proceed.

On December 3, 2013, the Applicant submitted an initial PSP (iPSP), which requested a full waiver of studies for all pediatric groups. The Agency responded to the iPSP on February 26, 2014 (b) (4) Of note, during review of the NDA, it was determined that the application did not trigger PREA. See Section 10 for additional discussion regarding pediatric issues.

During the filing meeting, 2 review issues were determined and communicated to the Applicant, i.e., a statistically relevant food effect on the codeine component of the ER tablet and lower plasma concentrations of codeine with the ER tablet versus reference in the 6-12 hours period of the dosing interval (See Section 5). After completion of the review of the submitted data, both these issues are now considered addressed and there are no pending review issues from a clinical pharmacology perspective.

3. CMC/Device

- **General product quality considerations**

The proposed product is a reddish pink colored viscous suspension of codeine polistirex and chlorpheniramine polistirex. Each 5 mL of the proposed product contains 14.7 mg codeine base (equivalent to 20 mg of codeine phosphate) and 2.8 mg of chlorpheniramine base (equivalent to 4 mg of chlorpheniramine maleate) per 5 mL. The inactive ingredients are purified water, sodium polystyrene sulfonate, ethyl maloti, povidone, triacetin, polyvinyl acetate, polysorbate 80, citric acid, sodium citrate, sucrose, starch, D&C Red No.30, glycerin, methylparaben, propylparaben, propyl gallate, xanthan gum, and cherry flavor.

Table 1 compares the composition (strengths) of the COD-CPM ER oral suspension in this application, as well as other products. A major difference between products is the dosage strength of the codeine base.

Table 1: 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

Source: Dr. Suzette Peng's clinical review dated March 25, 2015

The first of two drug substances, chlorpheniramine maleate is manufactured by (b) (4) and is referenced in DMF# (b) (4). This DMF was reviewed on December 16, 2014 and found to be adequate for this NDA.

The second drug substance, codeine phosphate is manufactured by (b) (4) and is referenced in DMF# (b) (4). This DMF was reviewed on February 18, 2015 and found to be adequate for this NDA.

The drug product, Tuzistra XR is an extended-release oral suspension that contains codeine polistirex and chlorpheniramine polistirex. Tuzistra XR is manufactured by Tris Pharma, Inc. All of the required CMC data, including manufacturing method, process controls, release specifications, batch analysis, and stability data is referenced in DMF 027314, which was reviewed on March 19, 2015 and found to be adequate.

The drug product suspension will be placed in a 16 oz. amber (b) (4) modern round container (b) (4) with a proposed expiry of 24 months at 20°C to 25°C with excursions permitted to 15° to 30°C.

See review by Dr. Ciby Abraham dated March 24, 2015 for additional details. Adequate information to support the manufacture, controls, and quality of the drug substances and drug products is provided in referenced DMFs for the Drug Substances and the Drug Product. Therefore, from the CMC standpoint, this application is recommended for approval.

- **Facilities review/inspection**

All the reviews and inspections have been completed and are acceptable. Please refer to the CMC review by Dr. Ciby Abraham dated March 24, 2015, for additional details. The Office of Compliance issued an overall recommendation of Acceptable for the application on February 20, 2015.

- **Product Quality Microbiology**

The proposed product is a non-sterile, (b) (4) oral suspension. On February 13, 2015, microbiology review of DMF 27314 found the DMF adequate to support approval of this NDA. For complete details, see review by Dr. Jessica Cole, dated February 13, 2015.

- **Other notable issues (resolved or outstanding)**

The CMC review team has concluded that the application may be approved from a CMC perspective.

4. Nonclinical Pharmacology/Toxicology

- **General nonclinical pharmacology/toxicology considerations**

No new nonclinical pharmacology/toxicology studies were required or performed for this application. There are no outstanding toxicology issues. See the pharmacology/toxicology review by Dr. Matthew Whittaker dated March 17, 2015 for complete details.

- **Other notable issues (resolved or outstanding)**

The pharmacology/toxicology review team has concluded that the application may be approved from a pharmacology/toxicology perspective.

5. Clinical Pharmacology/Biopharmaceutics

The Applicant performed four clinical pharmacology studies: two pilot studies and two pivotal studies. This review will focus on the pivotal studies, 3007117 and 3007116, which 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 pharmacokinetic studies were conducted using an immediate release (IR) oral solution formulation of codeine phosphate and chlorpheniramine maleate (COD-CPM IR) manufactured by Tris Pharmaceutical.

Study 3007117

Study 3007117 was 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.

Treatment A: Test Product (Fasted), Dose = 1 x 10 mL (20 mg/4 mg per 5 mL) at 0 hour, ER Oral Suspension

Treatment B: Test Product (Fed), Dose = 1 x 10 mL (20 mg/4 mg per 5 mL) at 0 hour, ER Oral Suspension

Treatment C: Reference Product (Fasted), Dose = 1 x 5 mL (20 mg/4 mg per 5 mL) at 0 and 6 hour, IR Oral Solution

The treatment phases were separated by washout periods of at least 7 days. 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 2 below.

Table 2: 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: Study 3007117

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 3 below.

Table 3: 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: Study 3007117

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 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.

Study 3007116

Study 3007116 was a multiple-dose, open-label, randomized, two-period, and two-treatment crossover study conducted in 32 healthy adult subjects to establish the pharmacokinetic profile of the Test Product, in comparison with the COD-CPM IR solution (Reference Product), at steady state.

Treatment A: Test Product (Fasted), Dose = 1 x 10 mL (20 mg/4 mg per 5 mL) twice daily on Days 1-6 and once on Day 7, ER Oral Suspension

Treatment B: Reference Product (Fasted), Dose = 1 x 5 mL (20 mg/4 mg per 5 mL) four times daily on Days 1-6 and twice on Day 7, IR Oral Solution

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. 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 Table 4 below.

Table 4: 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)

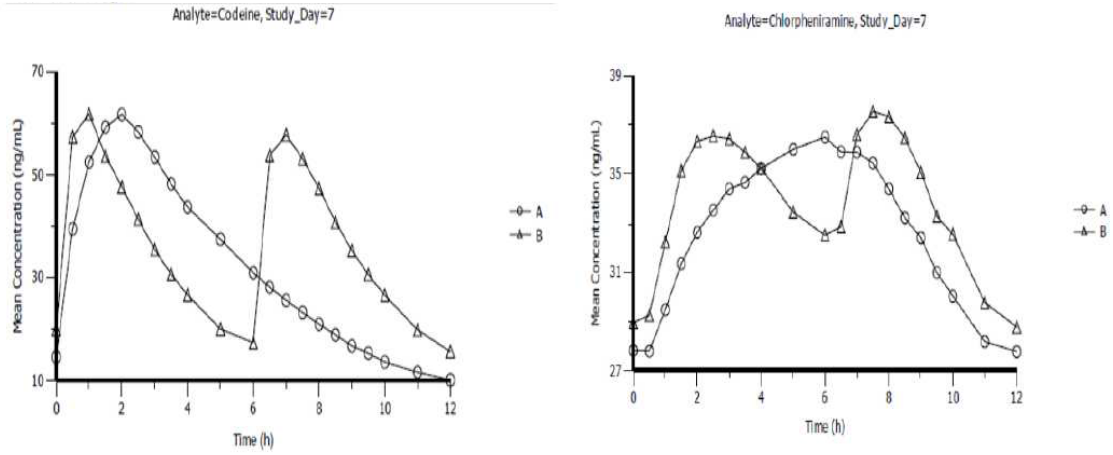
Parameter	Codeine			90% Confidence Interval
	Geometric Mean [a]		%Ratio [b]	
	Test	Ref		
AUC_{0-12} (ng·h/mL)	367.9	412.9	89.1	85.1 – 93.3
C_{max} (ng/mL)	61.5	65.5	93.9	87.7-100.5
C_{min} (ng/mL)	9.4	14.5	64.4	60.8-68.3
C_{avg} (ng/mL)	30.6	34.4	89.1	85.1-93.2
Parameter	**Chlorpheniramine**			**90% 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: Study 3007116

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%. 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 (see figure below). 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 is 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.

Figure 1: 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



Source: Dr. Jain's clinical pharmacology review

See the review by Dr. Ritesh Jain dated March 3, 2015 for further details.

The Applicant 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 alcohol dose dumping. 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. Please see the biopharmaceutics review by Dr. Assadollah Noory for additional details. The product label will indicate that concurrent use of Tuzistra XR with alcohol should be avoided because additional impairment of central nervous system performance may occur. Overall, from the Biopharamcaeutics perspective, the application is recommended for approval.

The clinical pharmacology and biopharmaceutics review teams have concluded that the application may be approved from their perspectives.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

The application relies on a bioavailability comparison and the OTC monograph. Thus, no clinical efficacy studies were conducted.

8. Safety

The safety of the product is based on establishing bioequivalence of the proposed product to the reference products. In addition, the Applicant provided a Summary of Clinical Safety including reference to the monograph and the safety data from the clinical pharmacology studies. Dr. Peng has concluded that there were no new safety signals in the submitted data, and I concur.

9. Advisory Committee Meeting

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

10. Pediatrics

During review of this application and discussion at the Pediatric Review Committee (PeRC) meeting on March 4, 2015, it was determined that the application does not trigger the Pediatric Research Equity Act (PREA) because it does not include a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. Of note, the Sponsor did have an Agreed Pediatric Study Plan (PSP). See Section 2 for additional background on the regulatory history of the Applicant's pediatric plan. Codeine antitussive labeling (21 CFR 341.74(d)(ii)) goes down to age 6 years of age with professional labeling down to 2 years of age (21 CFR 341.90(c). Chlorpheniramine maleate labeling goes down to age 6 (21 CFR 341.72(d)(3)).

While the safety and effectiveness of specific doses of codeine and chlorpheniramine have been established in the monograph in children ages 6 to 18 years of age, there are safety concerns related to combination of two long-acting, sedating medications in children. Further, there are concerns regarding the risk of respiratory depression associated with the use of codeine in children. Codeine products now contain a boxed warning regarding the risk of respiratory depression and death that have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to CYP2D6 polymorphism. All cough/cold products containing codeine will carry the same warning. A search of FDA's Adverse Event Reporting System (AERS) database between 1969 to May 1, 2012 identified 13 cases of pediatric death (n=10) or overdose (n=3) associated with codeine. Three of the cases were reported in the setting of respiratory tract infection. In view of these safety concerns, the Applicant will need to establish the appropriate dose of the proposed product in children if the Applicant wants to seek approval in children. Pharmacokinetic (PK) data for adequate dose selection and additional safety data in the pediatric population will be needed to support approval in children. (b) (4)

As the proposed product does not trigger PREA, (b) (4)

11. Other Relevant Regulatory Issues

- **Inspections**

Office of Scientific Investigation (OSI) inspection was requested for the multiple dose steady state relative bioavailability study (Study 3007116). The Division of Bioequivalence and GLP Compliance (DBGLPC) recommended 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), for Study 3007116. The clinical site has been inspected four times during the last two years. The most recent inspection assures that WCT conducted study 3007116 without significant

irregularities. The analytical site has been inspected multiple times during the last two years. The inspectional outcomes provide assurance that the site conducted the analysis of samples from study 3007116 without significant irregularities. Thus, OSI recommended that the data from study 3007116 be accepted for review without onsite inspections of the clinical site and analytical site.

- **Compliance with Good Clinical Practices**

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

- **Financial Disclosures**

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

- **Any other outstanding regulatory issues**—Not applicable

12. Labeling

- **Proprietary Name**

The proposed trade name is "Tuzistra XR" and was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and found to be acceptable on September 19, 2014.

- **Physician Labeling**

The Applicant submitted a label in Physician's Labeling Rule (PLR) format. The label was revised to be consistent with other similar cough and cold combination products, such as Zutripro, Vituz, and Codeprex. Changes were made to the Indication section to reflect the population for which it would be used, those with respiratory tract symptoms due to the common cold and respiratory allergies. Further, a boxed warning was added to describe the risk of respiratory depression and death that have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to CYP2D6 polymorphism. Additionally, the Warnings and Precautions were updated to reflect the risk of dose-related respiratory depression and drug dependence.

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

use the strength of the base for both drug substances which would be consistent with USP <1121> Monograph "Naming Policy for Salt Drug Substances in Drug Products." Therefore, the label notes that the proposed drug is codeine polistirex and chlorpheniramine polistirex extended release oral suspension with strengths expressed as 14.7mg codeine and 2.8mg chlorpheniramine. A statement of equivalence to the respective codeine phosphate and chlorpheniramine maleate salts is included in the package insert. Labeling discussions are ongoing with the Applicant at the time of this review

- **Carton and Immediate Container Labels**

A detailed review of the carton and immediate container labels was conducted by the individual disciplines of the Division in consultation with the Division of Medication Error Prevention and Analysis. Labeling discussions are ongoing at the time of this review.

- **Patient Labeling and Medication Guide**

The Applicant included a patient package insert in the proposed labeling. Labeling discussions are ongoing at the time of this review.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of this application. The Applicant's clinical pharmacology program has established the bioequivalence of their proposed product to the individual reference product. In establishing bioequivalence, the program is able to rely on previous Agency determinations of the safety and efficacy of codeine phosphate and chlorpheniramine maleate in the proposed combination product for (b) (4) relief of cough (b) (4) associated with common cold when administered to adults 18 years of age and older at a dose 10 mL every 12 hours by mouth. Therefore, the recommendation is for Approval for the adult population.

- **Risk Benefit Assessment**

The overall risk and benefit assessment of the proposed codeine and chlorpheniramine combination product, based on establishing bioequivalence to the individual reference product suggests favorable risk benefit for these individual ingredients for the adult (18 years and older) population. Since respiratory depression associated with fatalities from the use of codeine has been reported for younger patients (patients under 18 years of age) additional PK and safety data to support the appropriate dose in the pediatric population are necessary prior to extending the indication to the pediatric population for this combination codeine/chlorpheniramine product for the proposed indication.

- **Recommendation for Postmarketing Risk Management Activities**

Postmarketing risk evaluation and management strategies are not recommended on the basis of this submission.

- **Recommendation for other Postmarketing Study Commitments**

Postmarketing requirements and commitments are not recommended on the basis of this submission.

- **Recommended Comments to Applicant**

Not applicable.

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/s/

JANET W MAYNARD
04/09/2015