CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207768Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA CHEMISTRY CONSULTATION

Application number:	NDA 207768
Supporting document/s:	SD 1: Initial IND SD 7: Response to Nonclinical Information Request
Sponsor's letter date:	SD 1: 6/27/14 SD 7: 2/26/15
CDER stamp date:	SD 1: 6/30/14 SD 7: 2/27/15
Product:	Tuzistra XR (Codeine Polistirex + Chlorpheniramine Polistirex Extended Release Oral Suspension)
Indication:	Relief of cough and symptoms associated with upper respiratory allergies or a common cold
Sponsor:	Tris Pharma, Inc.
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer:	Matthew Whittaker, Ph.D.
Supervisor/Team Leader:	Timothy Robison, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Sadaf Nabavian

Template Version: September 1, 2010

TABLE OF CONTENTS

Table of Tables

Table of Figures

1 Executive Summary

1.1 Introduction

NDA 207768 was submitted on 6/30/14 under section 505(b)(2) of the FD& C Act to support marketing approval for Tuzistra XR (Codeine Polistirex and Chlorpheniramine Polistirex Extended Release Oral Suspension) as a (b) (4) for symptoms of upper respiratory allergies or the common cold. The reference product is Codeprex Pennkinetic Extended Release Oral Suspension (NDA 21369). The Tuzistra XR drug product (DP) labeling was recently recommended for approval from the nonclinical perspective (Whittaker, NDA 207768 Nonclinical Labeling Review, 3/17/15).

A nonclinical inquiry from CMC reviewer Ciby Abraham, Ph.D. was received via email on 2/16/15. The inquiry referenced the specification limits for two residual solvents (b) (4) in two excipients (b) (4) and (b) (4) Cherry Flavor (b) (4), respectively) in the DP as defined in Tris Pharma Inc.'s Drug Master File for Codeine and Chlorpheniramine (COD-CPM) extended release (ER) Oral Suspension (DMF 27314).

The maximum recommended human daily dose (MRHDD) for Tuzistra XR is 2 x 10 ml doses per 24 hours. Although the duration of dosing of this product is not explicitly defined, it is considered to be a chronic-intermittent use drug based on its indication. The safety of the proposed specification limits for (b) (4) is evaluated in this review.

1.2 Brief Discussion of Nonclinical Findings

(b) (4)

The (b) (4) excipient specification in DMF 27314 (section 3.2.P.4.1) originally listed the limit for the residual solvent (b) (4) as NMT (b) (4) ppm. The U.S. EPA considers (b) (4) to be a probable human carcinogen (Group B1). The maximum daily intake of (b) (4) was defined as (b) (4) g/day, thus resulting in a maximum daily intake of (b) (4) µg/day) that exceeded the Acceptable Daily Intake at 10 µg/day for mutagenic impurities in drugs administered on a chronic intermittent basis (ICH M7 Guidance: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (Step 4 Version, June 23, 2014)).

In response to an Information Request, Tris Pharma committed to lowering the specification for (b) (4) in the (b) (4) excipient to NMT (b) (4) ppm. The revised specification results in a maximum daily intake (equivalent to (b) (4) µg/day in the worst case scenario) that is less than the compound-specific Acceptable Daily Intake for (b) (4) µg/day). Therefore, the current (b) (4) specification in the (b) (4) excipient is considered to be adequate from the nonclinical perspective.

(b) (4)

The specification for the (b) (4) Cherry Flavor excipient in DMF 27314 (section 3.2.P.4.1) includes a limit of NMT (b) (4) ppm for the Class (b) (4) residual solvent (b) (4). The maximum daily intake of the (b) (4) Cherry Flavor excipient in the Tuzistra XR DP is (b) (4)

mg/day, resulting in a maximum daily (b) (4) intake of (b) (4) mg/day. This value is less than the (b) (4) mg per day limit for Class (b) (4) residual solvents. Therefore the current (b) (4) specification in the (b) (4) Cherry Flavor excipient is considered to be adequate from the nonclinical perspective.

1.3 Recommendations

1.3.1 Approvability

Tris Pharma's proposed limits of NMT (b) (4) ppm for (b) (4) in the (b) (4) excipient and NMT (b) (4) ppm for (b) (4) in the (b) (4) Cherry Flavor excipient in the Tuzistra XR drug product are considered safe from the nonclinical perspective.

2 Drug Information

2.1 Drug

Generic Name: Codeine Polistirex and Chlorpheniramine Polistirex Extended Release Oral Suspension

Code Name: Tuzistra XR

Chemical Name: Codeine phosphate + chlorpheniramine maleate + sodium polystyrene sulfonate

Molecular Formula/Molecular Weight

- Codeine phosphate: (b) (4) g/mol
- Chlorpheniramine maleate: 390.9 g/mol

Structure or Biochemical Description:

(b) (4)

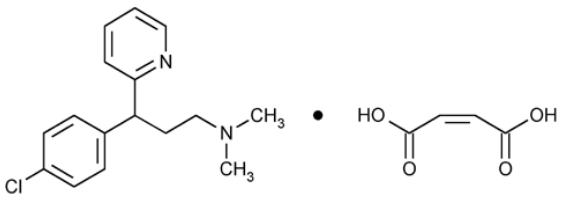


Figure 1. Chemical structures of codeine phosphate (left) and chlorpheniramine maleate (right).

The drug-polistirex complex is formed with each active ingredient plus sodium polystyrene sulfonate, which has the following structure:

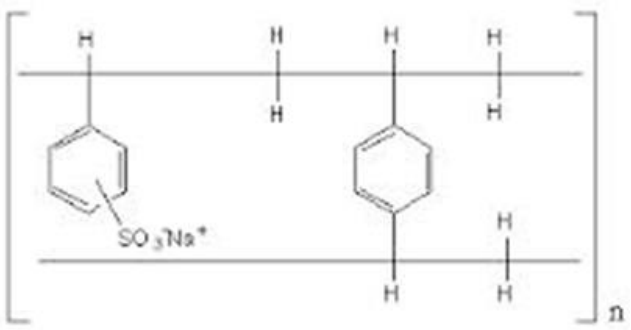


Figure 2. Chemical structure of sodium polystyrene sulfonate**.**

Pharmacologic Class

- Codeine phosphate: opiate antitussive
- Chlorpheniramine maleate: Histamine -1 (H1) receptor antagonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

	Sponsor	Description
DMF 27314	Tris Pharma, Inc.	Drug master file for Codeine Polistirex & Chlorpheniramine Polistirex ER Oral suspension

2.3 Drug Formulation

The drug product (DP) composition for Tuzistra XR is found in Table 1. All components of the DP formulation are within the limits of currently approved oral suspension drug products. The NDA 207768 nonclinical labeling review (Whittaker, 3/17/15) contains a detailed examination of excipient levels.

Table 1. Drug product composition of Tuzistra XR.

Ingredient	mg / 5 ml	mg/day
Codeine phosphate	20	80
Chlorpheniramine maleate	4	16
Sodium Polystyrene Sulfonate	(b) (4)	
Ethyl maltol		
Povidone		
Triacetin		

Ingredient	mg / 5 ml	mg/day
Polyvinyl acetate (b) (4)	(b) (4)	(b) (4)
Polysorbate 80		
Citric acid, (b) (4)		
Sodium citrate, (b) (4)		
Sucrose		
D & C Red n. 30 (b) (4)		
(b) (4)		
Glycerin		
Methylparaben		
Propylparaben		
Propyl gallate		
Xanthan gum		
Cherry flavor, (b) (4)		

2.4 Comments on Novel Excipients

There are no novel excipients in the DP formulation.

2.5 Comments on Residual Solvents of Concern

(b) (4)

The (b) (4) excipient (b) (4) The original specification for this excipient in DMF 27314 (section 3.2.P.4.1) included a limit of NMT (b) (4) ppm for (b) (4) (Figure 3).

(b) (4)

The U.S. EPA considers (b) (4) to be a probable human carcinogen (Group B1). This classification includes agents for which the weight of evidence of carcinogenicity based on animal studies is "sufficient". However there is limited evidence of carcinogenicity from epidemiologic studies.

The maximum daily intake of (b) (4) was initially defined by the sponsor in DMF 27314 as (b) (4) g/day. The resulting maximum daily intake of (b) (4) in patients taking Tuzistra XR is calculated as follows:

(b) (4)

This amount exceeds the Acceptable Daily Intake of 10 µg/day for mutagenic impurities in drugs administered on a chronic intermittent basis as defined in ICH M7.

(b) (4)

The specification for the (b) (4) Cherry Flavor (b) (4) excipient in DMF 27314 includes a limit of NMT (b) (4) ppm for the residual solvent (b) (4) (Figure 4).

(b) (4)

(b) (4) residual solvent. Chemicals in this class are not known to present a human health hazard at levels normally accepted in pharmaceuticals. The ICH Q3C limit for Class (b) (4) residual solvents is (b) (4) mg per day.

2.8 Regulatory Background

A nonclinical information request was sent to Tris Pharma on 2/19/15 to request justification for the potential (b) (4) exposure in patients taking Tuzistra XR. The content of the request is excerpted below:

> NDA 207768 is currently under review. We have the following request for information:
>
> 1. The specification for the excipient (b) (4) found in DMF 27314 Section 3.2.P.4.1, includes a limit for (b) (4) of NMT (b) (4) ppm. Table 1 of DMF 27314 section 3.2.P.1 lists a total of (b) (4) per 20 ml of drug product (maximum daily dose). Therefore, the maximum total daily intake of (b) (4) would be:
>
> (b) (4)
>
> Provide justification for the safety of this level of (b) (4) µg/day) in the COD-CPM ER Suspension.

The sponsor provided a response on 2/27/15. The response included the following components:

(1) Clarification that the daily dose of [redacted]/20 ml Tuzistra XR and not [redacted]/20 ml.
(2) A commitment to lower the specification for [redacted] in [redacted] from [redacted] ppm to [redacted] ppm.
(3) An [redacted] risk assessment.

3 Studies Submitted

3.1 Studies Reviewed

Study Title	Date
Risk Assessment of [redacted] in an ER Oral Suspension Product	2/27/15

3.3 Previous Reviews Referenced

Review	Reviewer	Date
NDA 207768 Nonclinical Labeling Review	Matthew Whittaker, Ph.D.	3/17/2015

11 Integrated Summary and Safety Evaluation

11.1 Evaluation of residual solvent levels in excipients

Ethylene oxide

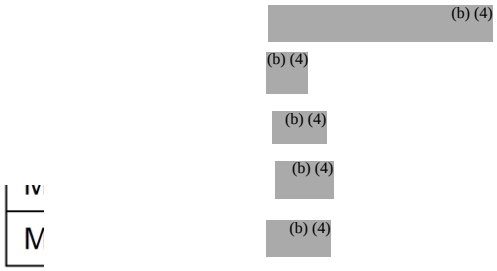
[redacted] The original specification for this excipient in DMF 27314 (section 3.2.P.4.1) included a limit of NMT [redacted] ppm for the residual solvent [redacted], a probable human carcinogen. Based on the amount of [redacted] in the Tuzistra XR DP, the maximum daily exposure to [redacted] was calculated to be [redacted] µg/day. The treatment duration for Tuzistra XR is defined as chronic-intermittent based on its indication as a [redacted] for symptoms of upper respiratory allergies or the common cold. The [redacted] µg/day [redacted] exposure exceeds the Acceptable Daily Intake of 10 µg/day for mutagenic impurities in drugs administered on a chronic intermittent basis as defined in ICH M7.

A nonclinical information request was sent to the sponsor on 2/19/15 to request justification for this level of (b) (4) exposure in the Tuzistra XR DP. Tris Pharma provided a response on 2/27/15. The response contained the following elements:

(1) The sponsor clarified that the reported amount of (b) (4) per 20 ml of DP in DMF 27314 was in error. The correct amount is (b) (4) per 20 ml DP. Tris has updated the DMF to correct this error.

(2) Tris Pharma provided data on the measured levels of (b) (4) in 4 lots of (b) (4) (Table 2). Based on the observed (b) (4) levels, the sponsor lowered the proposed specification from (b) (4) ppm to (b) (4) ppm. Tris committed to revising the current specification and submitting the revision to the DMF.

Table 2. (b) (4) levels in 4 lots of (b) (4).



(3) Tris Pharma also measured (b) (4) levels in a recently manufactured commercial scale optimization batch of Tuzistra XR (lot TS0003-001) drug product. (b) (4) testing was conducted according to USP 37/NF 32 Supplement 2 Chapter (b) (4) (b) (4). The Sponsor stated that there was no detectable (b) (4) in this lot of Tuzistra XR DP. However, the limit of detection for (b) (4) using this methodology was not defined by the sponsor, and is not listed in Chapter (b) (4). It is unclear why (b) (4) is detectable in the (b) (4) excipient but is not carried over to the final DP.

Based on items (1) and (2) above, the maximum daily exposure to (b) (4) is recalculated as follows:

(b) (4)

A compound-specific calculation of acceptable daily intake for (b) (4) was conducted according to the methods outlined in (b) (4) of ICH M7. Briefly, the lifetime daily dose resulting in tumor formation in 50% of animals (TD_{50}) in published rodent carcinogenicity studies was extrapolated to establish an (b) (4) dose resulting in a probability of 1:100,000 for tumor development in humans.

The publicly available Carcinogenicity Potency Database was queried for (b) (4)[1]. The entry references data from a total of 8 rodent carcinogenicity studies. (b) (4) was administered by the inhalation route in 7 studies and by oral gavage in 1 study. The database listed a TD_{50} of (b) (4) mg/kg for the oral gavage study[2] (conducted in rats) based on tumors of the stomach. This study was further examined given that the route of administration is consistent with that of Tuzistra XR. Rats were dosed twice per week for 25 months. The author states that tumors of the glandular stomach were observed "only rarely".

It appears that the TD_{50} value reported in the Carcinogenicity Potency Database was derived by combining the observed forestomach and glandular stomach tumors. Given that the dosing in the study (2 times per week) was considered inadequate and tumors of the rat forestomach are not relevant to humans, it was decided in concurrence with (b) (4), Ph.D. and (b) (4) Ph.D. that the (b) (4) mg/kg TD_{50} (email communication: 2/27/15 – 3/2/15) was not appropriate for calculation of an acceptable daily intake of (b) (4). The harmonic mean TD_{50} of (b) (4) mg/kg/day, derived from all rat carcinogenicity studies (oral and inhalation) with (b) (4), was used instead. This value is also used as an example in (b) (4) of the ICH M7 Guidance. Table 3 outlines the calculations involved in determining the acceptable daily intake for (b) (4) in Tuzistra XR.

- To derive the (b) (4) dose resulting in tumor formation in 1:100,000 rats, the established TD_{50} (tumor probability 1:2) was divided by 50,000 to arrive at a value of (b) (4) µg/kg/day.
- The human Tumor Dose 1:100,000 was calculated using an average human weight of 50 kg, resulting in a value of (b) (4) µg/person/day.
- Given that Tuzistra XR will be administered on a (b) (4) ICH M7 (b) (4) was consulted to establish a less-than-lifetime acceptable intake for (b) (4) in Tuzistra XR. The hypothetical total number of treatment days of Tuzistra XR in a lifetime was estimated as 30 days per year * 70 years = 2,100 treatment days.
- The equation for acceptable daily intake of (b) (4) in Tuzistra XR is as follows:

(b) (4)

[1] http://toxnet.nlm.nih.gov/cpdb/chempages (b) (4) html

(b) (4)

Table 3. Summary of calculations for determination of Acceptable Daily Intake for (b) (4) in Tuzistra XR.

Rat TD_{50}[a]	**Rat Tumor dose 1:100,000 [b]**	**Human Tumor dose 1:100,000[c]**	**Total # of lifetime COD-CPM-ER treatment days[d]**	**Acceptable daily intake for (b) (4) in Tuzistra XR**
(b) (4) mg/kg/day	(b) (4) µg/kg/day	(b) (4) µg/person/day	2,100	(b) (4) µg/person/day

[a] Carcinogenicity Potency Database: http://toxnet.nlm.nih.gov/cpdb/chempages
[b] Divide TD_{50} by 50,000 to get tumor dose in 1:100,000 animals
[c] (b) (4) µg/kg/day * (b) (4) (average weight) = (b) (4) µg/person/day
[d] (30 days/year) * 70 years = 2,100 days
[e] Acceptable daily exposure: (b) (4) µg * (365 days/yr *70 years) / 2100 days = (b) (4) µg

The limit of detection for (b) (4) in the Tuzistra XR DP is not known at this time. However, even if (b) (4) was present at the (b) (4) ppm limit in the (b) (4) excipient and the entire amount of (b) (4) was carried over to the DP, the daily (b) (4) µg/day) would be less than the acceptable daily intake calculated in Table 3. Therefore, Tris Pharma's current specification for (b) (4) in the (b) (4) excipient is considered acceptable from the nonclinical perspective.

(b) (4)

The specification for the (b) (4) Cherry Flavor (b) (4) excipient lists the limit for the residual solvent (b) (4) as NMT (b) (4) ppm. (b) (4) is a Clas (b) (4) residual solvent. The ICH Q3C limit for Class (b) (4) residual solvents is (b) (4) mg/day or less. The maximum daily intake of the (b) (4) Cherry Flavor excipient in the Tuzistra XR DP is (b) (4) mg/day. The maximum daily intake of (b) (4) is calculated as follows:

(b) (4)

This value is less than the (b) (4) mg per day limit, thus supporting the safety of the proposed specification.

11.2 Overall Recommendation

Tris Pharma's proposed limits of NMT (b) (4) ppm for (b) (4) in the (b) (4) excipient and NMT (b) (4) ppm for (b) (4) in the (b) (4) Cherry Flavor excipient in the Tuzistra XR drug product are considered safe from the nonclinical perspective.

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

/s/

MATTHEW T WHITTAKER
03/23/2015

TIMOTHY W ROBISON
03/23/2015
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	207768
Supporting document/s:	Supporting Document 1
Applicant's letter date:	6/27/14
CDER stamp date:	6/30/14
Product:	Tuzistra XR (Codeine Polistirex + Chlorpheniramine Polistirex Extended Release Oral Suspension)
Indication:	Relief of cough and symptoms associated with upper respiratory allergies or a common cold
Applicant:	Tris Pharma, Inc.
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer:	Matthew Whittaker, Ph.D.
Supervisor/Team Leader:	Timothy Robison, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Sadaf Nabavian

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 207768 are owned by Tris Pharma or are data for which Tris Pharma has obtained a written right of reference. Any information or data necessary for approval of NDA 207768 that Tris Pharma does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 207768.

TABLE OF CONTENTS

Table of Tables

Table of Figures

1 Executive Summary

1.1 Introduction

NDA 207768 was submitted on June 30, 2014 under section 505(b)(2) of the FD& C Act to support marketing approval for Tuzistra XR (Codeine Polistirex and Chlorpheniramine Polistirex Extended Release Oral Suspension) as a (b) (4) for symptoms of upper respiratory allergies or the common cold. The reference product is Codeprex Pennkinetic Extended Release Oral Suspension (NDA 21369). Each 5 ml of Tuzistra XR is comprised of 20 mg codeine phosphate ((b) (4) mg codeine free base) and 4 mg chlorpheniramine maleate (2.8 mg chlorpheniramine free base) bound to styrene-divinylbenzene copolymer. The maximum recommended human daily dose (MRHDD) is 10 ml every 12 hours in adult patients 18 years of age and older.

1.2 Brief Discussion of Nonclinical Findings

There were no nonclinical studies submitted in support of this NDA. The nonclinical review of the Tuzistra XR labeling is limited to the following sections: Indications and Usage, sections 8 (Use in Specific Populations) and 13 (Nonclinical Toxicology). The Pharmacology Review for the reference product (NDA 21369) was consulted to establish exposure multiples between toxic doses for codeine and chlorpheniramine reported in nonclinical studies and their respective doses at the proposed MRHDD for Tuzistra XR. The labeling is generally consistent with the labeling for Codeprex. However, exposure multiples were revised in all relevant nonclinical sections.

1.3 Recommendations

1.3.1 Approvability

Tuzistra XR (Codeine Polistirex and Chlorpheniramine Polistirex Extended Release Oral Suspension) is recommended for approval from the nonclinical perspective.

1.3.2 Additional Nonclinical Recommendations

Labeling recommendations are provided in Section **1.3.3**. There are no other nonclinical recommendations or outstanding issues at this time.

1.3.3 Recommended Labeling Edits

The recommended text for the nonclinical sections of the Tuzistra XR prescribing information is provided below.

INDICATIONS AND USAGE
Tuzistra XR is a combination of codeine phosphate, an opiate antitussive, and chlorpheniramine maleate, a histamine-1 (H1) receptor antagonist indicated for relief of cough and symptoms associated with upper respiratory allergies or a common cold.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C
Teratogenic Effects

There are no adequate and well-controlled studies of Tuzistra™ XR in pregnant women.

Reproductive toxicity studies have not been conducted with Tuzistra XR; however, studies are available with individual active ingredients or related active ingredients. Because animal reproduction studies are not always predictive of human response, Tuzistra XR should be used during pregnancy only if the benefit justifies the potential risk to the fetus.

Codeine:

Codeine has embryolethal and fetotoxic effects in rats. In a study in which pregnant rats were dosed throughout organogenesis, a dose approximately 20 times the maximum recommended human daily dose (MRHDD; on a mg/m^2 basis at an oral maternal dose of 120 mg/kg/day) increased resorptions and decreased fetal weight; however, these effects occurred in the presence of maternal toxicity.

In studies in which rabbits and mice were dosed throughout organogenesis, codeine at doses approximately 9 and 45 times the MRHDD (on a mg/m^2 basis at 30 and 600 mg/kg/day, respectively) produced no adverse developmental effects.

Chlorpheniramine:

A retrospective study found a small, but statistically significant, association between maternal use of chlorpheniramine and inguinal hernia and eye or ear anomalies in children. Other retrospective studies have found that the frequency of congenital anomalies, in general, was not increased among offspring of women who took chlorpheniramine during pregnancy. The significance of these findings to the therapeutic use of chlorpheniramine in human pregnancy is not known.

In studies with chlorpheniramine in which pregnant rats and rabbits were dosed throughout organogenesis, oral doses up to approximately 25 and 30 times the MRHDD on a mg/m^2 basis, respectively, produced no adverse developmental effects. However, when mice were dosed throughout pregnancy, a dose approximately 9 times the MRHDD (on a mg/m^2 basis at an oral maternal dose of 20 mg/kg/day) was embryolethal, and postnatal survival was decreased when dosing was continued after parturition. Embryolethality was also observed when male and female rats were dosed with approximately 9 times the MRHDD (on a mg/m^2 basis at an oral parental dose of 10 mg/kg/day) prior to mating.

Nonteratogenic Effects

Codeine:

Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and reproductive studies have not been conducted with Tuzistra™ XR Extended-Release Suspension; however, published information is available for the individual active ingredients or related active ingredients.

Codeine:

Carcinogenicity studies were conducted with codeine. In 2 year studies in F344/N rats and B6C3F1 mice, codeine showed no evidence of tumorigenicity at dietary doses up to 70 and 400 mg/kg/day, respectively (approximately 10 and 30 times, respectively, the MRHDD on a mg/m^2 basis).

Codeine was not mutagenic in the *in vitro* bacterial reverse mutation assay or clastogenic in the *in vitro* Chinese hamster ovary (CHO) cell chromosomal aberration assay.

Fertility studies with codeine have not been conducted.

Chlorpheniramine:

In 2-year studies in F344/N rats and B6C3F1 mice, chlorpheniramine maleate showed no evidence of tumorigenicity when administered 5 days/week at oral doses up to 30 and 50 mg/kg/day, respectively (approximately 25 and 20 times, respectively, the MRHDD on a mg/m^2 basis).

Chlorpheniramine maleate was not mutagenic in the *in vitro* bacterial reverse mutation assay or the *in vitro* mouse lymphoma forward mutation assay. Chlorpheniramine maleate was clastogenic in the *in vitro* CHO cell chromosomal aberration assay.

Chlorpheniramine maleate had no effects on fertility in rats and rabbits at oral doses approximately 25 and 30 times the MRHDD on a mg/m^2 basis, respectively.

2 Drug Information

2.1 Drug

Generic Name: Codeine Polistirex and Chlorpheniramine Polistirex Extended Release Oral Suspension

Code Name: Tuzistra XR

Chemical Name: Codeine phosphate + chlorpheniramine maleate + sodium polystyrene sulfonate

Molecular Formula/Molecular Weight

- Codeine phosphate: (b) (4) g/mol
- Chlorpheniramine maleate: 390.9 g/mol

Structure or Biochemical Description:

(b) (4)

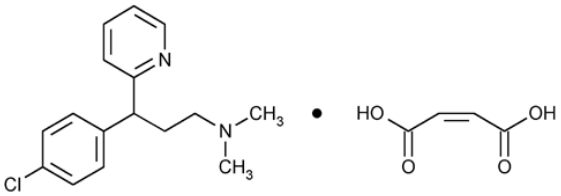


Figure 1. Chemical structures of codeine phosphate (left) and chlorpheniramine maleate (right).

The drug-polistirex complex is formed with each active ingredient plus sodium polystyrene sulfonate, which has the following structure:

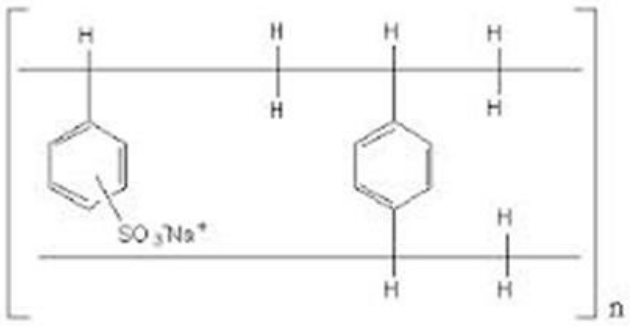


Figure 2. Chemical structure of sodium polystyrene sulfonate.

Pharmacologic Class

- Codeine phosphate: opiate antitussive
- Chlorpheniramine maleate: Histamine -1 (H1) receptor antagonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

	Sponsor	Description
DMF 27314	Tris Pharma, Inc.	Drug master file for Codeine Polistirex & Chlorpheniramine Polistirex ER Oral suspension
IND (b) (4)	Tris Pharma, Inc.	Codeine Polistirex and Chlorpheniramine Polistirex ER Suspension
NDA 21369	UCB, Inc.	Reference product: Codeprex Pennkinetic (discontinued)

2.3 Drug Formulation

All components of the Tuzistra XR drug product (DP) formulation are within the limits of currently approved oral suspension drug products. The sodium polystyrene sulfonate content was evaluated on a mg/day basis (

Table 1). The limits for the other excipients in the DP (Table 2) are based on levels found in approved oral suspension products (FDA Inactive Ingredient Database). These values are listed on a percentage (weight/volume) basis.

Table 1. Tuzistra XR sodium polystyrene content comparison with amount in an approved oral suspension drug product.

Ingredient	mg/5 ml	mg/day (per 20 ml)	Inactive ingredient limit (mg/day)
Sodium polystyrene sulfonate	(b) (4)	(b) (4)	(b) (4)
(b) (4)			

Table 2. Comparison of excipient levels in Tuzistra XR with amounts in approved oral suspension drug products

Ingredient	mg / 5 ml	% (w/v)	Inactive ingredient limit (% w/v)
Ethyl maltol	(b) (4)	(b) (4)	(b) (4)
Povidone			
Triacetin			

Ingredient	mg / 5 ml	% (w/v)	Inactive ingredient limit (% w/v)
Polyvinyl acetate (b) (4)	(b) (4)		
Polysorbate 80			
Citric acid, (b) (4)			
Sodium citrate, (b) (4)			
Sucrose			
D & C Red n. 30 (b) (4)			
(b) (4)			
Glycerin			
Methylparaben			
Propylparaben			
Propyl gallate			
Xanthan gum			
Cherry flavor, (b) (4)			

2.4 Comments on Novel Excipients

There are no novel excipients in the Tuzistra XR drug product formulation.

2.5 Comments on Impurities/Degradants of Concern

Discussion of safety concerns with regard to impurities or residual solvents is beyond the scope of the current labeling review.

2.6 Proposed Clinical Population and Dosing Regimen

Tuzistra XR is indicated for relief of cough and symptoms associated with upper respiratory allergies or a common cold in adults 18 years of age and older. The MRHDD is 10 ml every 12 hours, not to exceed 20 ml in 24 hours.

2.7 Regulatory Background

A pre-IND file for codeine polistirex and chlorpheniramine polistirex extended release from Tris Pharma, Inc. (pIND (b) (4)) was initiated on 6/8/12. Preliminary FDA comments in response to the sponsor's pre-IND meeting questions were sent on 9/14/12. The pre-IND meeting was subsequently cancelled. The nonclinical question and response are excerpted below:

Nonclinical question:

Question 8: In this 505(b)(2) application, Tris will reference the Agency's previous findings of nonclinical safety for codeine and chlorpheniramine maleate which provided the basis for inclusion in the OTC monographs of these drug substances. Does the Agency agree that no other nonclinical studies are required for NDA submission and subsequent product approval?

FDA Response: We agree that no further toxicology studies are required for the safety assessments of the active ingredients (codeine phosphate and chlorpheniramine maleate) of the drug product.

Additional comments pertaining to qualification of inactive ingredients in the drug product were also included in the response. The sponsor adequately addressed all of these comments.

3 Studies Submitted

3.1 Studies Reviewed

No nonclinical studies were submitted or required for NDA 207768.

3.3 Previous Reviews Referenced

Review	Date	Reviewer
NDA 21369 (Codeprex) Pharmacology Review	6/21/2004	Timothy Robison, Ph.D.
IND [redacted] (b) (4) (Codeine polistirex and chlorpheniramine maleate) Preliminary Pharmacology/Toxicology Safety Review	8/28/2013	Carol Rivera-Lopez, Ph.D.

11 Integrated Summary and Safety Evaluation

11.1 Labeling Evaluation

The MRHDD for Tuzistra XR is 2 x 10 ml doses per 24 hours. The amounts of codeine and chlorpheniramine free base present at this dose were calculated in terms of mg/m^2 (Table 3) in order to establish exposure multiples relative to toxic doses in nonclinical studies.

The labeling for the reference product (Codeprex) included exposure margins that were calculated based on the amount of codeine free base and chlorpheniramine maleate at the MRHDD (Table 3). The listed exposure multiples for codeine in Tuzistra XR differ from those in the Codeprex labeling due to (1) The codeine strength in Tuzistra XR (b) (4) mg per 5 ml) is lower than that of the reference product (20 mg per 5 ml) and (2) the FDA's current practice of using 60 kg average human body weight rather than the 50 kg value used in the preparation of the Codeprex label.

The listed exposure multiples for chlorpheniramine in Tuzistra XR differ from those in the Codeprex labeling due to (1) the chlorpheniramine present at the MRHDD in Tuzistra XR is calculated based on the amount of chlorpheniramine free base rather than chlorpheniramine maleate and (2) the FDA's current practice of using 60 kg average human body weight in calculation of MRHDD rather than the 50 kg value used in the preparation of the Codeprex label.

Table 3. MRHDD values for the active pharmaceutical ingredients in Tuzistra XR. The bottom half of the table presents the values used in exposure multiple calculation for the reference product (Codeprex).

	Component	Amount per 5 ml dose (mg)	Maximum dose per day[1] (mg)	Adult weight (kg)	mg/kg	Km (mg/m^2)	**mg/m^2**
Tuzistra XR	Codeine (free base)	(b) (4)	**62.4**	60	1.04	37	**38.5**
	Chlorpheniramine (free base)	2.8	**11.2**	60	0.19	37	**6.9**
Reference Product	Codeine (free base)	20	**80**	50	1.60	37	**59.2**
	Chlorpheniramine maleate	4	**16**	50	0.32	37	**11.8**

[1] Maximum daily dose is 20 ml/day

Reported exposure multiples between animal and human codeine and chlorpheniramine doses are calculated as follows: (Human Equivalent Dose (HED) in nonclinical species) / (MRHDD). The revised MRHDD values led to increased values for exposure multiples for both codeine (Table 4) and chlorpheniramine (Table 5). The exposure multiples for codeine and chlorpheniramine in Tuzistra XR and in Codeprex are shown in each table to allow for comparison.

Table 4. Exposure multiples for **codeine** in Tuzistra XR vs. reference product

Row	Species	Route	Dose (mg/kg/d)	K_m [a] (kg/m^2)	HED (mg/m^2)	Exposure multiple (HED/MRHDD[b])				Comments
						Tuzistra XR		Reference Product (Codeprex)		
						Dose Ratio	Rounded value	Dose Ratio	Rounded value	
Carcinogenicity										
1	Mouse	Oral	400	3	1200	31.2	30	20.3	20	No evidence of tumorigenicity
2	Rat	Oral	70	6	420	10.9	10	7.1	7	No evidence of tumorigenicity
Reproduction and Fertility										
3	NA									Fertility studies have not been conducted with codeine
Teratogenicity										
4	Mouse	Oral	600	3	1800	46.8	45	30.4	30	No effects up to highest dose tested
5	Rat	Oral	120	6	720	18.7	20	12.2	10	▲resorptions, ▼fetal weight at HD
6	Rabbit	Oral	30	12	360	9.4	9	6.1	6	No effects up to highest dose tested

[a] FDA Guidance for Industry: Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers
[b] MRHDD for codeine: Tuzistra XR = 38.5 mg/m^2 ; Codeprex = 59.2 mg/m^2

Table 5. Exposure multiples for **chlorpheniramine** in Tuzistra XR vs. reference product

Row	Species	Route	Dose (mg/kg/d)	K_m[a] (kg/m^2)	HED (mg/m^2)	Exposure multiple (HED/MRHDD[b])				Comments
						Tuzistra XR		Reference Product (Codeprex)		
						Dose Ratio	Rounded value	Dose Ratio	Rounded value	
Carcinogenicity										
1	Mouse (male)	Oral	50	3	150	21.7	20		15	No evidence of tumorigenicity at up to 50 mg/kg/day
2	Rat (male)	Oral	30	6	180	26.1	25		15	No evidence of tumorigenicity: 5 days/week dosing
Reproduction and Fertility										
3	Rat	Oral	-	6	-	24	25	20	20	The label for Codeprex referenced the labeling for NDA 12152 (Ornade Spansule Capsules) for reproduction and fertility data. The Tuzistra XR exposure multiple is derived by multiplying the Codeprex exposure multiple (20) by a factor of (60/50) to account for the current FDA practice of using 60 kg as average human weight rather than 50 kg.
4	Rabbit	Oral	-	12	-	30	30	25	25	The Tuzistra XR exposure multiple is derived by multiplying the Codeprex exposure multiple (25) by a factor of (60/50) to account for the current FDA practice of using 60 kg as average human weight rather than 50 kg.

Row	Species	Route	Dose (mg/kg/d)	K_m [a] (kg/m^2)	HED (mg/m^2)	Exposure multiple (HED/MRHDD[b])				Comments
						Tuzistra XR		Reference Product (Codeprex)		
						Dose Ratio	Rounded value	Dose Ratio	Rounded value	
Teratogenicity										
5	Rat	Oral	-	6	-	24	25	20	20	The sources of rat and rabbit teratology studies with chlorpheniramine maleate that are noted in the labeling for NDA 12152 are not known.
6	Rabbit	Oral	-	12	-	30	30	25	25	See above
7	Mouse	Oral	20	3	60	8.69	9	5.1	5	Embryolethality: Study from 1968 (Swiss Webster Mice): Drug treatment in this study was extended before and after the period of organogenesis and there was no examination of fetuses: referenced in the Codeprex Pharmacology review.
8	Rat	Oral	10	6	60	8.69	9	5.1	5	Embryolethality: Study from 1965; NDA 12152; referenced in the Codeprex Pharmacology review

[a] FDA Guidance for Industry: Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers
[b] MRHDD for codeine: Tuzistra XR = 6.9 mg/m^2 ; Codeprex = 11.8 mg/m^2

11.2 Labeling Recommendations

The complete labeling recommendations pertaining to nonclinical data in the Prescribing Information for Tuzistra XR are presented below. The Sponsor's text is from their draft Prescribing Information dated October 3, 2014. Reference is made within the FDA revised text (in blue font) to the location in Table 4 or Table 5 where specific exposure multiple values are calculated.

INDICATIONS AND USAGE

Sponsor's text

(b) (4)

FDA Revised text

TUZISTRA XR is a combination of codeine phosphate, an opiate antitussive, and chlorpheniramine maleate, a histamine-1 (H1) receptor antagonist indicated for relief of cough and symptoms associated with upper respiratory allergies or a common cold.

The Established Pharmacologic Class (EPC) text phrase for codeine is "opioid agonist". However, "opiate antitussive" is used in the labeling for Tuzistra XR to remain consistent with the labeling for the reference product Codeprex. For chlorpheniramine, the EPC is "histamine-1 (H1) receptor antagonist"

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Sponsor's text

(b) (4)

The format and content of Section 8.1 were not changed as this NDA is not required to conform to the guidelines of the Pregnancy and Lactation Labeling Rule (PLLR). The NDA was submitted (6/30/14) prior to the Rule's implementation (December, 2014).

The language in Section 8.1 is generally consistent with the language in the reference product. The changes introduced are only in the exposure multiples. The rationale behind the exposure multiple adjustments include: (1) decreased strength of codeine free base in Tuzistra relative to the reference product, (2) use of chlorpheniramine free base values at the MRHDD for Tuzistra XR rather than chlorpheniramine maleate in the Codeprex label, and (3) the FDA's current practice of using an average human weight of 60 kg rather than 50 kg.

Actual study data for rat and rabbit fertility and teratogenicity studies with chlorpheniramine were not available. The Pharmacology Review for Codeprex (Robison, 2004) referenced the labeling for NDA 12152 (Ornade Spansule Capsules) for reproduction and fertility data to establish exposure multiples for chlorpheniramine. Exposure multiple values for chlorpheniramine in Tuzistra XR were referenced from the Codeprex labeling. These values were multiplied by a factor of 1.2 to account for the use of 60 kg human weight rather than the 50 kg value used in the preparation of the Codeprex label.

FDA Revised text

8.1 Pregnancy

Pregnancy Category C

Teratogenic Effects

There are no adequate and well-controlled studies of Tuzistra™ XR in pregnant women.

Reproductive toxicity studies have not been conducted with Tuzistra XR; however, studies are available with individual active ingredients or related active ingredients. Because animal reproduction studies are not always predictive of human response, Tuzistra XR should be used during pregnancy only if the benefit justifies the potential risk to the fetus.

Codeine:

Codeine has embryolethal and fetotoxic effects in rats. In a study in which pregnant rats were dosed throughout organogenesis, a dose approximately **20 times** [Table 4, Row 5] the maximum recommended human daily dose (MRHDD; on a mg/m^2 basis at an oral maternal dose of 120 mg/kg/day) increased resorptions and decreased fetal weight; however, these effects occurred in the presence of maternal toxicity.

In studies in which rabbits and mice were dosed throughout organogenesis, codeine at doses approximately **9** [Table 4, Row 6] and **45** [Table 4, Row 4] times the MRHDD (on a mg/m^2 basis at 30 and 600 mg/kg/day, respectively) produced no adverse developmental effects.

Chlorpheniramine:

A retrospective study found a small, but statistically significant, association between maternal use of chlorpheniramine and inguinal hernia and eye or ear anomalies in children. Other retrospective studies have found that the frequency of congenital anomalies, in general, was not increased among offspring of women who took chlorpheniramine during pregnancy. The significance of these findings to the therapeutic use of chlorpheniramine in human pregnancy is not known.

In studies with chlorpheniramine in which pregnant rats and rabbits were dosed throughout organogenesis, oral doses up to approximately **25** [Table 5, Row 5] and **30 times** [Table 5, Row 6] the MRHDD on a mg/m^2 basis, respectively, produced no adverse developmental effects. However, when mice were dosed throughout pregnancy, a dose approximately **9 times** [Table 5, Row 7] the MRHDD (on a mg/m^2 basis at an oral maternal dose of 20 mg/kg/day) was embryolethal, and postnatal survival was decreased when dosing was continued after parturition. Embryolethality was also observed when male and female rats were dosed with approximately **9 times** [Table 5, Row 8] the MRHDD (on a mg/m^2 basis at an oral parental dose of 10 mg/kg/day) prior to mating.

Nonteratogenic Effects

Codeine:

Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose.

13 NONCLINICAL TOXICOLOGY

Sponsor's text

(b) (4)

[redacted]

FDA Revised text

The language in Section 13 is generally consistent with the language in the reference product. The changes introduced to the exposure multiples have been described previously.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and reproductive studies have not been conducted with Tuzistra™ XR Extended-Release Suspension; however, published information is available for the individual active ingredients or related active ingredients.

Codeine:

Carcinogenicity studies were conducted with codeine. In 2 year studies in F344/N rats and B6C3F1 mice, codeine showed no evidence of tumorigenicity at dietary doses up to 70 and 400 mg/kg/day, respectively (approximately **10** [Table 4, Row 2] and **30 times** [Table 4, Row 1], respectively, the MRHDD on a mg/m^2 basis).

Codeine was not mutagenic in the *in vitro* bacterial reverse mutation assay or clastogenic in the *in vitro* Chinese hamster ovary (CHO) cell chromosomal aberration assay.

Fertility studies with codeine have not been conducted.

Chlorpheniramine:

In 2-year studies in F344/N rats and B6C3F1 mice, chlorpheniramine maleate showed no evidence of tumorigenicity when administered 5 days/week at oral doses up to 30 and 50 mg/kg/day, respectively

(approximately **25** [Table 5, Row 2] and **20 times** [Table 5, Row 1], respectively, the MRHDD on a mg/m^2 basis).

Chlorpheniramine maleate was not mutagenic in the *in vitro* bacterial reverse mutation assay or the *in vitro* mouse lymphoma forward mutation assay. Chlorpheniramine maleate was clastogenic in the *in vitro* CHO cell chromosomal aberration assay.

Chlorpheniramine maleate had no effects on fertility in rats and rabbits at oral doses approximately **25** [Table 5, Row 3] and **30 times** [Table 5, Row 4] the MRHDD on a mg/m^2 basis, respectively.

11.3 Overall Recommendations

NDA 207768 is recommended for approval from the nonclinical perspective. There are no outstanding nonclinical issues and no further nonclinical studies are recommended.

12 Appendix/Attachments

1. IND (b) (4) (Codeine Polistirex and Chlorpheniramine Polistirex ER Suspension) Preliminary Pharmacology/Toxicology Safety Review dated August 28, 2013

DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS (DPARP)
PRELIMINARY PHARMACOLOGY/TOXICOLOGY SAFETY REVIEW

IND: (b) (4)
Sponsor: Tris Pharma, Inc.
Drug: Codeine Polistirex and Chlorpheniramine Polistirex ER oral suspension
Indication: (b) (4) relief of cough, (b) (4) upper respiratory allergies, or allergic rhinitis.
Drug Class: Antitussive (codeine)/antihistamine (chlorpheniramine)
Review Completion Date: August 28, 2013

Clinical Studies Safe to Proceed: Yes

The proposed clinical studies (Protocols 3007117 and 3007116) are considered safe to proceed from the nonclinical perspective.

Safety Assessment

Introduction

This review evaluates the nonclinical safety of codeine and chlorpheniramine in support of two clinical protocols (3007117 and 3007116) submitted by Tris Pharma under IND (b) (4). Tris Pharma has developed a 12-hour extended release oral suspension of codeine and chlorpheniramine complexed with sodium polystyrene sulfonate (b) (4). This product is being developed for the (b) (4) relief of cough (as may occur with the common cold (b) (4) upper respiratory allergies, (b) (4)

The sponsor proposes to perform a single-dose clinical pharmacokinetic study to assess bioavailability of the extended-release oral suspension under fasted and fed conditions against an immediate release oral solution (reference product) under fasted conditions. In addition, the sponsor proposed a multiple-dose study to demonstrate the bioavailability of the extended-release oral suspension against the immediate release oral solution (reference product) under fasted conditions. Both studies will be conducted in healthy adult volunteers.

Codeine is an opioid analgesic indicated for the relief of mild to moderately severe pain and for the symptomatic relief of cough, alone or in combination with other antitussives or expectorants. It is a recognized monograph drug under 21 CFR 341.74(d)(ii) [doses not to exceed 60 mg in 24 hours for children 6-12 years of age or 120 mg for patients ≥ 12 years of age]. Chlorpheniramine is an antihistamine indicated for the temporary relief of allergic symptoms (e.g., rhinorrhea, sneezing, itching eyes, oronasopharyngeal irritation or itching, lacrimation) caused by histamine release. It is also a recognized monograph drug under 21 CFR 341.72(d)(3) [doses not to exceed 12 mg in 24 hours for children 6-12 years of age or 24 mg for patients ages ≥ 12 years of age]. The combination of these two drugs is permitted under 21 CFR 341.40(d); Combination Cough, Cold and Bronchodilator Drug Products. In addition, two extended-release drug products containing codeine and chlorpheniramine have been approved in the US (NDAs 18928 and 21369), although they are currently discontinued.

No nonclinical studies were submitted with this IND. The sponsor references FDA's general findings of safety and efficacy for the two active ingredients from the reference listed drug (RLD) Codeprex Pennkinetic® under NDA 21369.

Regulatory History

A pre-IND meeting request was submitted by the sponsor and preliminary comments were sent on September 14th, 2012. The pre-IND meeting was cancelled subsequently.

Nonclinical question:

Question 8: In this 505(b)(2) application, Tris will reference the Agency's previous findings of nonclinical safety for codeine and chlorpheniramine maleate which provided the basis for inclusion in the OTC monographs of these drug substances. Does the Agency agree that no other nonclinical studies are required for NDA submission and subsequent product approval?

FDA Response: We agree that no further toxicology studies are required for the safety assessments of the active ingredients (codeine phosphate and chlorpheniramine maleate) of the drug product. Please refer to our comments below regarding qualification of inactive ingredients.

Additional nonclinical comments:

- Provide a quantitative description of the drug product composition for appropriate safety assessment of the inactive ingredients of the drug product, including polistirex. We remind you that use of any novel excipient or excipients exceeding levels in currently US approved oral products will need to be qualified for safety prior to initiating any clinical studies as described in Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients (May 2005).

- Provide a quantitative description of the chemical composition of the 'Flavor' you will be using in the drug product formulation. Provide a safety assessment of each of the components of the 'Flavor'. Alternatively you may provide appropriate justification for the safe use of the 'Flavor' in the drug product.

- Provide structures of impurities and degradants of the drug substance and drug product in your NDA that exceed permittable levels. Monitor impurities and degradation products of all active ingredients and refer to the ICH Guidance for qualification of drug impurities in drug substances [ICH Q3A(R)] and degradants in drug products [ICH Q3B(R)] for possible qualification requirements. Impurities or degradants that are identified as structural alerts should be at or below acceptable qualification thresholds for genotoxic and carcinogenic impurities as described in the draft FDA Guidance for Industry, Genotoxic and Carcinogenic Impurities in Drug Substances and Drug Products: Recommended Approaches (December 2008).

Clinical Protocols

Protocol number 3007117 is for a single-dose, open-label, randomized, three-period, three-treatment crossover study in healthy adult subjects. In this study, subjects will receive the following treatments (one treatment per period): one single dose of the investigational drug product following an overnight fast of at least 10 hours (fasting state), one single dose of the investigational drug following an overnight fast of at least 10 hours and consumption of a high-

calorie breakfast meal (fed state), or two single-dose administrations (0 hour and 6 hours) of the reference drug (immediate release formulation) following an overnight fast of at least 10 hours. Pregnant or breastfeeding women will be excluded from this study.

The objectives of this study are to evaluate the bioavailability of the extended-release formulation of codeine and chlorpheniramine (20 mg codeine/4 mg chlorpheniramine per 5 mL) under both fasted and fed conditions, and to evaluate the relative bioavailability of this extended-release investigational drug product to an equivalent dose of an immediate release product under fasted conditions.

Protocol number 3007116 is for a multiple-dose, open-label, randomized, two-period, two-treatment crossover study in healthy adult volunteers. Subjects will receive the following: two single-dose administrations of the investigational drug product (20 mg codeine/4 mg chlorpheniramine per 5 mL) at 0 hours and 12 hours daily for 7 days [total 40 mg codeine/8 mg chlorpheniramine daily]; or four single-dose administrations of the reference product (20 mg codeine/4 mg chlorpheniramine per 5 mL immediate release formulation) at 0, 6, 12, and 18 hours daily for 7 days [total of 80 mg codeine/16 mg chlorpheniramine daily]. Pregnant or breastfeeding women will be excluded from this study. The first drug administration on each study day will occur after a minimum 10-hour overnight fast.

The objective of the multiple-dose study is to compare the rate of absorption and oral bioavailability of the extended-release investigational drug to an equivalent oral dose of the immediate release reference product when administered under fasted steady-state conditions. Both products will be manufactured by Tris Pharma, Inc.

Previous Clinical Experience

Codeine and chlorpheniramine have extensive clinical experience as mono-products and also as a combination.

Codeine is an opioid analgesic (related to morphine) indicated 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. It is a recognized monograph drug under 21 CFR 341.74(d)(ii) [doses not to exceed 60 mg in 24 hours for children 6-12 years of age or 120 mg for patients ≥ 12 years of age].

Chlorpheniramine is an antihistamine indicated for the temporary relief of allergic symptoms (e.g., rhinorrhea, sneezing, itching eyes, oronasopharyngeal irritation or itching, lacrimation) caused by histamine release. It is also a recognized monograph drug under 21 CFR 341.72(d)(3) [doses not to exceed 12 mg in 24 hours for children 6-12 years of age or 24 mg for patients ages ≥ 12 years of age].

The combination of these two drugs is permitted by 21 CFR 341.40(d), Combination Cough, Cold and Bronchodilator Drug Products. Further, two extended-release drug products containing codeine and chlorpheniramine have been approved in the US (NDAs 18928 and 21369), although they are currently discontinued. The sponsor will rely on the Agency's previous findings of clinical efficacy to support approval of the drug product under this IND.

In addition to the extensive clinical experience, the sponsor conducted two pilot PK studies (3006726 and 3007132) to assess the bioavailability of codeine and chlorpheniramine after administration of the extended-release formulation compared to the immediate-release formulation. According to the sponsor, the most common adverse events reported in study

3006726 were headache, somnolence, and nausea. The most common adverse event reported in study 3007132 was nasal congestion. Refer to Dr. Xu Wang's clinical review for additional details.

Drug Formulation

The investigational drug product is a 12-hour extended-release oral suspension containing 20 mg codeine phosphate and 4 mg chlorpheniramine maleate per 5 mL. The CMC information was not submitted under this IND but a letter of authorization was submitted for Tris Pharma's DMF 027314. In addition, the two active ingredients were already reviewed under DMF (b) (4) (codeine phosphate) and DMF (b) (4) (chlorpheniramine maleate). The quantitative composition (mg/5 mL) of the investigational product is presented below in Table 1 (excerpted from the sponsor's submission under DMF 027314).

Table 1: Quantitative Composition of the Investigational Drug Product.

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

The levels of all the excipients are qualified for oral administration. However, a CMC information request was sent to the sponsor on August 13, 2013 to request letters of reference from the manufacturers of the non-compendial excipients (*i.e.*, resins, flavoring, and sweeteners) so that the quantitative composition could be evaluated.

The sponsor's response was received on August 15th, 2013 and included all the information necessary to fully evaluate the safety of all the non-compendial excipients. The safety of the "cherry flavor" listed on Table 1 above was already evaluated under DMF (b) (4) and was found

adequate. In addition, the other non-compendial ingredients are considered *generally recognized as safe* (GRAS) and, therefore there is no safety concern for their use.

The impurity levels in the investigational drug product were evaluated by Dr. Eugenia Nashed. All the specifications are maintained at no more than (NMT) (b) (4), except for (b) (4) (an impurity from codeine that contains a structural alert), which is at NMT (b) (4)%. Although this is above the ICH limit for qualification, it was already determined under DMF (b) (4) that the proposed specification of NMT (b) (4)% (b) (4) is safe from the nonclinical perspective. For additional details, refer to Dr. Nashed's CMC review.

Summary of Nonclinical Information

No new nonclinical studies were submitted with this IND. The sponsor references FDA's general findings of safety and efficacy for the two active ingredients from the reference listed drug (RLD) Codeprex Pennkinetic® under NDA 21369. The following nonclinical information was obtained from Codeprex Pennkinetic® approved label (August 2006):

> ***Carcinogenesis, Mutagenesis, Impairment of Fertility***
>
> *Although studies with Codeprex to evaluate carcinogenic, mutagenic or impairment of fertility potential have not been conducted, published data are available for the active ingredients.*
>
> *Codeine*
>
> *In 2-year studies in F344/N rats and B6C3F1 mice, codeine showed no evidence of tumorigenicity at dietary doses up to 70 and 400 mg/kg/day, respectively (approximately 8 and 20 times, respectively, the maximum recommended daily dose for adults and children on a mg/m2 basis).*
>
> *Codeine was not mutagenic in the* in vitro *bacterial reverse mutation assay or clastogenic in the* in vitro *Chinese hamster ovary (CHO) cell chromosomal aberration assay.*
>
> *Fertility studies with codeine have not been conducted.*
>
> *Chlorpheniramine*
>
> *In 2-year studies in F344/N rats and B6C3F1 mice, chlorpheniramine maleate showed no evidence of tumorigenicity when administered 5 days/week at oral doses up to 30 and 50 mg/kg/day, respectively (approximately 15 times the maximum recommended dose for adults and children on a mg/m2 basis).*
>
> *Chlorpheniramine maleate was not mutagenic in the* in vitro *bacterial reverse mutation assay or the* in vitro *mouse lymphoma forward mutation assay. Chlorpheniramine maleate was clastogenic in the* in vitro *CHO cell chromosomal aberration assay.*
>
> *In rats and rabbits, oral doses of chlorpheniramine maleate up to approximately 20 and 25 times the human dose on a mg/m2 basis, respectively, did not impair fertility.*
>
> ***Pregnancy***
>
> *Pregnancy Category C.*
>
> *Teratogenic Effects*
>
> *Although animal reproductive studies with Codeprex™ Pennkinetic® (codeine polistirex and chlorpheniramine polistirex) Extended-Release Suspension have not been conducted, published data are available which address reproductive toxicity of the active ingredients.*

Codeine

In a study in which pregnant rats were dosed throughout organogenesis, an oral dose of 120 mg/kg/day (approximately 10 times the maximum recommended daily dose for adults on a mg/m2 basis) increased resorptions and decreased fetal weight; however, these effects occurred in the presence of maternal toxicity. In studies in which rabbits and mice were dosed throughout organogenesis, oral doses up to 30 and 600 mg/kg/day, respectively (approximately 6 and 30 times, respectively, the maximum recommended daily dose for adults on a mg/m2 basis), produced no adverse developmental effects.

Chlorpheniramine

In studies in which pregnant rats and rabbits were dosed throughout organogenesis, oral doses up to approximately 20 and 25 times the maximum recommended daily dose for adults on a mg/m2 basis, respectively, produced no adverse developmental effects. However, when mice were dosed throughout pregnancy, an oral dose of 20 mg/kg/day (approximately 5 times the maximum recommended daily dose for adults on a mg/m2 basis) was embryolethal, and postnatal survival was decreased when dosing was continued after parturition. Embryolethality was also observed when male and female rats were dosed prior to mating with 10 mg/kg/day (approximately 5 times the maximum recommended daily dose for adults on a mg/m2 basis).

In conclusion, although no nonclinical studies were conducted to support the proposed clinical protocol, codeine and chlorpheniramine are recognized monograph drugs and their safety has been previously characterized. Therefore, no additional studies are needed to support the proposed clinical protocols.

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

/s/

CAROL M RIVERA-LOPEZ
08/28/2013

MARCIE L WOOD
08/28/2013
I concur

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

/s/

MATTHEW T WHITTAKER
03/17/2015

TIMOTHY W ROBISON
03/17/2015
I concur

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

NDA Number: 20-7768 **Applicant:** Tris Pharma, Inc. **Stamp Date:** 6/30/14

Drug Name: Tuzistra XR**;** Codeine Polistirex and Chlorpheniramine Polistirex (COD-CPM) Extended Release oral suspension **NDA Type:** 505(b)(2)

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		The pharmacology/toxicology section is comprised of an overview of the publicly available information on the toxicity of codeine phosphate and chlorpheniramine. Pdf files of references are included with the initial NDA submission.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			Not applicable. The codeine phosphate/chlorpheniramine maleate combination is to be administered according to the guidelines in 21 CFR Part 341.40 (d), "Cold, cough, allergy, bronchodilator, and antiasthmatic drug products for over- the-counter use; Permitted combinations of active ingredients".
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable. Sodium polystyrene sulfonate USP (b) (4) is included as an inactive ingredient in the proposed DP formulation. The sponsor provides a literature review to qualify the amount of this component in the DP in DMF 027314.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?			Not applicable. No animal studies with the proposed drug product were conducted in support of this NDA. The oral route of administration is consistent with that of the reference product Codeprex™ (NDA 021369).

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	Comment
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			Not applicable. No pharmacology or toxicology studies were conducted with the proposed drug product.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		The proposed labeling is in Physician Labeling Rule (PLR) format.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		To be determined in consultation with the reviewing chemist.
11	Has the applicant addressed any abuse potential issues in the submission?	X		Codeine phosphate is to be administered according to dosing outlined in 21 CFR 341.74(d)(ii)
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? *Yes*

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

The NDA is fileable from the pharmacology/toxicology perspective.

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

There are no potential review issues at this time.

Matthew Whittaker 8/5/14

Reviewing Pharmacologist Date

Timothy Robison 8/5/14

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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

/s/

MATTHEW T WHITTAKER
08/05/2014

TIMOTHY W ROBISON
08/05/2014
I concur