Center for Drug Evaluation and Research

APPLICATION NUMBER:
21-369

PHARMACOLOGY

PHARMACOLOGY/TOXICOLOGY COVER SHEET
Chemistry Consult - Addendum

NDA number: NDA 21-369
Date/type of submission: December 19, 2003/Complete Response to the February 13, 2002 Approvable Letter
Request date: April 22, 2004 (Addendum to Review dated May 21, 2004) - Review of protocols for in vitro genotoxicity tests provided in the submission dated June 4, 2004.
Sponsor: Celltech Pharmaceuticals, Inc.
755 Jefferson Road
P.O. Box 31766
Rochester, NY

Reviewer name: Timothy W. Robison, Ph.D.
Division name: Division of Pulmonary and Allergy Drug Products
HFD: 570
Review completion date: June 9, 2004

Drug: Codeprex™ Extended-Release Suspension (Codeine/Chlorpheniramine Extended-Release Suspension)

Drug class: Antitussive/antihistamine

Indication: For the temporary relief of [redacted] cough, and runny nose, sneezing, itching of the nose or throat, and itchy watery eyes, as may occur with the common cold, inhaled irritants, hay fever, or other upper respiratory allergies.

Route of administration: Oral

Response to Chemistry Consult Requested by Vibhakar J. Shah, Ph.D.

Description of the Consult: [redacted] has been identified as a degradation product in Codeprex Extended-Release Suspension. [redacted]

In a submission dated June 4, 2004, the sponsor agreed to limit levels of [redacted] to NMT [redacted] (current LOQ) in the drug product. Further, the sponsor agreed in a Phase 4 commitment to conduct two in vitro genetic toxicology tests [redacted] and provided protocols for these two tests. Per agreement, study reports for these two genetic toxicology tests will be provided to the Division within 6 months.

2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

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/s/

Timothy Robison
6/9/04 04:00:26 PM
PHARMACOLOGIST

Joseph Sun
6/9/04 04:26:03 PM
PHARMACOLOGIST
I concur.

PHARMACOLOGY/TOXICOLOGY COVER SHEET
Chemistry Consult

NDA number: NDA 21-369
Date/type of submission: December 19, 2003/Complete Response to the February 13, 2002 Approvable Letter
Request date: April 22, 2004
Sponsor: Celltech Pharmaceuticals, Inc.
755 Jefferson Road
P.O. Box 31766
Rochester, NY

Reviewer name: Timothy W. Robison, Ph.D.
Division name: Division of Pulmonary and Allergy Drug Products
HFD: 570
Review completion date: May 21, 2004

Drug: Codeprex™ Extended-Release Suspension (Codeine/Chlorpheniramine Extended-Release Suspension)

Drug class: Antitussive/antihistamine

Indication: For the temporary relief of ——————→cough, and runny nose, sneezing, itching of the nose or throat, and itchy watery eyes, as may occur with the common cold, inhaled irritants, hay fever, or other upper respiratory allergies.

Route of administration: Oral

Response to Chemistry Consult Requested by Vibhakar J. Shah, Ph.D.

Description of the Consult:

3 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Alternatively, additional testing could be performed in consultation with the Division to potentially alleviate concerns.

Reviewer signature: _____
Timothy W. Robison, Ph.D.

Supervisor signature: Concurrence - _____
Joseph Sun, Ph.D.

Non-Concurrence - _____
(see memo attached)

cc: list:
NDA 21-369 Division File, HFD-570
YuC, HFD-570
ShahV, HFD-820
LostrittoR, HFD-820
ChowdhuryB, HFD-570
Gilbert-McClainL, HFD-570
LeeC, HFD-570
SunC, HFD-570
McGovernT, HFD-570
RobisonT, HFD-570

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/s/

Timothy Robison
5/21/04 10:34:40 AM
PHARMACOLOGIST

Joseph Sun
5/21/04 12:34:58 PM
PHARMACOLOGIST
I concur.

PHARMACOLOGY AND TOXICOLOGY REVIEW

NDA #: 21-369

Product Name: Codeprex™ Extended-Release Suspension

Sponsor: Celltech Pharmaceuticals, Inc.

Indication: For the temporary relief of _____ cough, and runny nose, sneezing, itching of the nose or throat, and itchy watery eyes, as may occur with the common cold, inhaled irritants, hay fever, or other upper respiratory allergies.

Division: Pulmonary and Allergy Drug Products

Reviewer: Timothy W. Robison, Ph.D.

Date: April 8, 2004

APPEARS THIS WAY
ON ORIGINAL

PHARMACOLOGY/TOXICOLOGY COVER SHEET

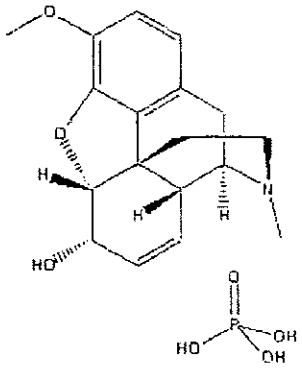
NDA number: 21-369
Review number: #04
Sequence number/date/type of submission: #000/December 19, 2003/Complete Response to the February 13, 2002 Approvable Letter
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Celltech Pharmaceuticals, Inc.
755 Jefferson Road
P.O. Box 31766
Rochester, NY
Manufacturer for drug substance: Same

Reviewer name: Timothy W. Robison, Ph.D.
Division name: Pulmonary and Allergy Drug Products
HFD #: 570
Review completion date: April 8, 2004

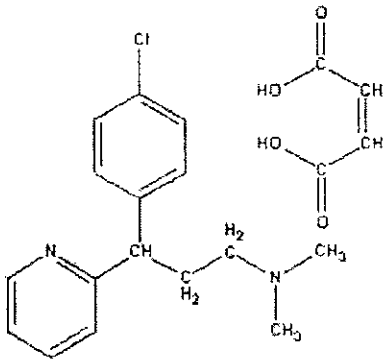
Drug:

Trade name: Codeprex™ Extended-Release Suspension
Generic name (list alphabetically): Codeine/Chlorpheniramine Extended-Release Suspension
Code name:
Chemical name:
Codeine phosphate, (5α,6α)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol, phosphate (1:1) (salt), hemihydrate;
Chlorpheniramine maleate, γ-(4-chlorophenyl)-N,N-dimethyl-2-pyridinepropanamine, (Z)-2-butenedioate
CAS registry number: Codeine Phosphate (41444-62-6); Chlorpheniramine Maleate (113-92-8)
Mole file number:
Molecular formula/molecular weight:
Codeine phosphate $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$ / 406.37
Chlorpheniramine maleate $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ / 390.87

Structure:
Codeine phosphate:



Chlorpheniramine maleate:



Relevant INDs/NDAs/DMFs:

IND 54,892 (Codeine/chlorpheniramine extended-release suspension from Celltech Pharmaceuticals Inc., of Rochester, NY).

NDA 18-928 (Penntuss® Suspension (Controlled release codeine polistirex with chlorpheniramine polistirex) from Fisons Corporation of Rochester, NY).

NDA 19-111 (Tussionex® Pennkinetic® (hydrocodone polistirex and chlorpheniramine polistirex) Extended-Release Suspension from Celltech Pharmaceuticals Inc., of Rochester, NY).

Drug Products containing codeine (NDA 8-306 and NDA 12-575)

Drug Products containing chlorpheniramine (NDA 6-921, NDA 7-638, NDA 8-826, NDA 12-152, NDA 13-397, NDA 13-764, NDA 14-968, NDA 17-369, NDA 18-099, NDA 18-556, NDA 18-747, NDA 19-428, NDA 19-746)

DMFs ——————————————

Drug class: Antitussive/antihistamine

Indication: For the temporary relief of ——— cough, and runny nose, sneezing, itching of the nose or throat, and itchy watery eyes, as may occur with the common cold, inhaled irritants, hay fever, or other upper respiratory allergies.

Clinical formulation: Codeine/chlorpheniramine extended-release suspension, an oral suspension product, is an aqueous suspension of coated codeine polistirex and chlorpheniramine maleate. "This product uses an ——— resin and Pennikinetic® technology, a patented process for binding of drugs to ion exchange resins and applying a water insoluble semi-permeable membrane coating to impart the extended release properties of the suspension. This system allows for the extended-release delivery of water-soluble active pharmaceutical ingredients in a suspension form. Drug substances used in the manufacture of the codeine/chlorpheniramine extended-release suspension are codeine phosphate and chlorpheniramine maleate, USP." The composition of the Codeine/chlorpheniramine extended-release suspension is shown below.

Ingredients	mg/10 mL
Dye, D&C Red #33 Certified	
Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF	
Sucrose, NF	
Glycerin, USP	
Propylene Glycol, USP	
Methylparaben, NF	
Propylparaben, NF	
Xanthan Gum, NF	
Citric Acid (Anhydrous), USP	
Edetate Disodium, USP	
Flavor, Artificial Cherry Cream ———	
Polysorbate 80, NF	
Coated Codeine Polistirex	
Chlorpheniramine Maleate, USP	
Water, Purified, USP	

[1]Based on anhydrous basis

[2]Input quantities vary slightly based on assay of resin bound codeine. The total amount of coated codeine polistirex is equivalent to 40 mg of codeine base. The calculation is based on the following equation:

Coated Codeine Polistirex = (40 mg)(100) / (% Assay)

Route of administration: Oral

Proposed use: The final formulation is an aqueous suspension containing codeine (40 mg/10 mL) and chlorpheniramine maleate (8 mg/10 mL). For adolescents ≥12 years of age and adults, the product is to be administered as a 10 mL (2 teaspoons) dose every 12 hr. For children ages 6 to under 12, the product is to be administered as a 5 mL (1 teaspoon) dose every 12 hr.

Product	Formulation	Dosage Regimen	Total Daily Dose
Codeine/chlorpheniramine Extended Release Suspension	40 mg / 8 mg per 10 mL	Adolescents ≥12 years and adults: 40 mg / 8 mg (2 teaspoons) q 12 hr	80 mg / 16 mg
		Children, ages 6 to under 12: 20 mg / 4 mg (1 teaspoon) q 12 hr	40 mg / 8 mg

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

APPEARS THIS WAY
ON ORIGINAL

Executive Summary

I. Recommendations

A. Recommendation on Approvability
From a nonclinical standpoint, the application is recommended for approval.

B. Recommendation for Nonclinical Studies
None.

C. Recommendations on Labeling
The sponsor agreed with nonclinical recommendations for content in labeling of Carcinogenesis, mutagenesis, impairment of fertility, Pregnancy, and Overdosage sections as detailed in Review #01 dated January 7, 2002. Recommended labeling is reproduced below.

The opening paragraphs under the Carcinogenesis, mutagenesis, impairment of fertility and Pregnancy sections should be modified to be consistent as follows:

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.

Pregnancy:
Although animal reproduction studies with CODEPREX™ Pennkinetic (codeine polistirex and chlorpheniramine polistirex) Extended-Release have not been conducted, published data are available for the active ingredients.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings
No preclinical pharmacology or toxicology studies were conducted with Codeprex™ (i.e., codeine/chlorpheniramine extended-release suspension). Codeine and chlorpheniramine are recognized USP monograph drugs. Extensive preclinical pharmacology and toxicology studies have been conducted with the active ingredients of Codeprex™, codeine and chlorpheniramine. Preclinical toxicology studies conducted with the active ingredients, codeine and chlorpheniramine, related to carcinogenicity, genotoxicity, fertility and reproductive performance, teratogenicity, and acute toxicity, were referenced in the preparation of product labeling.

B. Pharmacologic Activity
No preclinical pharmacology or toxicology studies were conducted with Codeprex™ (i.e., codeine/chlorpheniramine extended-release suspension).

However, codeine is a recognized antitussive and chlorpheniramine is a recognized antihistamine.

C. Nonclinical Safety Issues Relevant to Clinical Use
None.

III. Administrative

A. Reviewer signature: _____
Timothy W. Robison, Ph.D.

B. Supervisor signature: Concurrence - _____
C. Joseph Sun, Ph.D.

Non-Concurrence - _____
(see memo attached)

C. cc: list
YuC
SunC
RobisonT

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/s/

Timothy Robison
4/8/04 05:01:02 PM
PHARMACOLOGIST

Joseph Sun
4/9/04 10:44:25 AM
PHARMACOLOGIST
I concur.

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-369
Review number: #03
Sequence number/date/type of submission: #000/ August 18, 2003 /Amendment
Information to sponsor: Yes (X) No ( )
Sponsor and/or agent: Celltech Pharmaceuticals, Inc.
755 Jefferson Road
P.O. Box 31766
Rochester, NY
Manufacturer for drug substance: Same

Reviewer name: Timothy W. Robison, Ph.D.
Division name: Pulmonary and Allergy Drug Products
HFD #: 570
Review completion date: August 28, 2003

Drug:

Trade name: Codeprex™ Extended-Release Suspension
Generic name (list alphabetically): Codeine/Chlorpheniramine Extended-Release Suspension

Drug class: Antitussive/antihistamine

Route of administration: Oral

Qualification of the Drug Substance Impurity, [redacted]

In an amendment dated June 16, 2003, the sponsor proposed to qualify the impurity, [redacted] with a 28-day toxicology study in rats. The study was to be supported by toxicokinetic data. The proposed study was judged to be acceptable by the Division (see review dated June 24, 2003).

In the present amendment, the sponsor reported development of a LC/MS/MS method for toxicokinetic measurement of [redacted]. The lower limit of quantitation was [redacted] ng/mL. However, there was no measurable systemic exposure in a preliminary study with rats that received [redacted] at an oral dose of 2 mg/kg/day (i.e., the proposed high dose of the 28-day toxicology study). The lack of systemic exposure was attributed to poor oral bioavailability and/or rapid clearance by hepatic extraction and metabolism. Following intravenous administration of [redacted] to rats at a dose of 0.2 mg/kg, clearance was measured to be [redacted], which exceeds hepatic blood flow (55.2 mL/min/kg). Further, the T½ was found to be only 15 min, which supports rapid clearance. The sponsor speculated that [redacted]

Given the lack of measurable plasma levels of [redacted] following oral administration of 2 mg/kg/day, the sponsor is seeking FDA concurrence on

Attachment A

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

cc: list:

NDA 21-369, Division File, HFD-570
YuC, HFD-570
ShahVJ, HFD-570
SunC, HFD-570
RobisonT, HFD-570

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/s/

Timothy Robison
8/28/03 03:07:11 PM
PHARMACOLOGIST

Joseph Sun
8/28/03 03:25:37 PM
PHARMACOLOGIST
I concur.

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-369
Review number: #02
Sequence number/date/type of submission: #000/ June 16, 2003 /Amendment
Information to sponsor: Yes (X) No ( )
Sponsor and/or agent: Celltech Pharmaceuticals, Inc.
755 Jefferson Road
P.O. Box 31766
Rochester, NY
Manufacturer for drug substance: Same

Reviewer name: Timothy W. Robison, Ph.D.
Division name: Pulmonary and Allergy Drug Products
HFD #: 570
Review completion date:

Drug:

Trade name: Codeprex™ Extended-Release Suspension
Generic name (list alphabetically): Codeine/Chlorpheniramine Extended-Release Suspension

Drug class: Antitussive/antihistamine

Indication: For the temporary relief of [redacted] cough, and runny nose, sneezing, itching of the nose or throat, and itchy watery eyes, as may occur with the common cold, inhaled irritants, hay fever, or other upper respiratory allergies.

Route of administration: Oral

Qualification of the Drug Substance Impurity, [redacted]

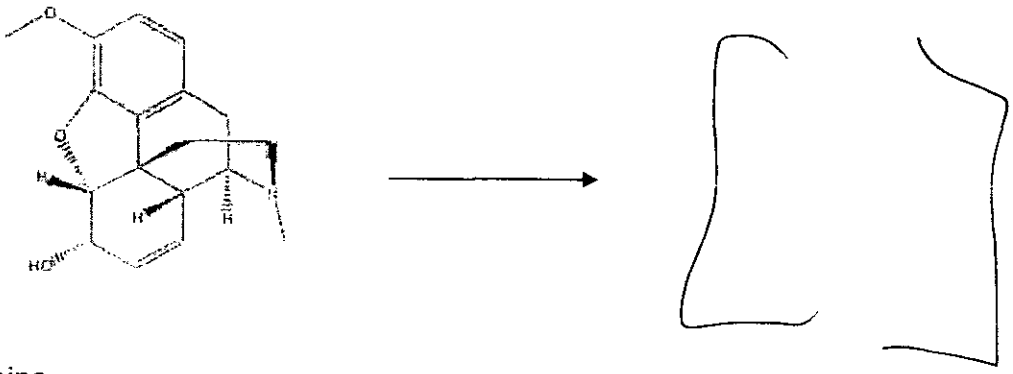
The sponsor has reported the presence of an impurity, [redacted] at [redacted] in the codeine phosphate drug substance. They have proposed to qualify this impurity with a 28-day toxicology study in rats. This compound, [redacted] is apparently readily available for use in this study. Proposed doses are [redacted]

Evaluation:

Codeprex is indicated for short term use (i.e., for codeine containing products, a persistent cough may be a sign of a serious conditions. If cough persists for more than 1 week, tends to recur, or is accompanied by fever, rash, or persistent headache, consult a doctor; CFR 341.74), so the duration of the toxicology study at 28 days appears adequate. The ICH Q3A Guidance indicates that a qualification study can be conducted

in one species, which is most likely to maximize the potential to detect the toxicity of an impurity. The selection of the rat appears acceptable. The objective of this study should be to identify a NOAEL with an acceptable safety margin. Thus, dose selection appears appropriate. For histopathological examination of only the control and high dose groups, there are circumstances when the low and mid dose groups should also be examined, which will be conveyed to the sponsor.

[redacted] does not contain any structural alerts. Thus, no genotoxicity studies are required.



Codeine

Recommendations: The sponsor's proposed qualification scheme for [redacted] appears acceptable. The following comment should be conveyed to the sponsor.

The Division has reviewed the proposed qualification scheme for [redacted] provided in an amendment dated June 16, 2003. We have the following comments regarding the 28-day toxicology study.

If you plan histological evaluation of tissues from only control and high dose treatment groups, you will also need to conduct histopathologic examination of other dose groups under any of the following circumstances: for any macroscopic findings in the low and mid dose groups for a given tissue, you will need to look at that tissue for all of the dose groups; for an increase in the incidence of a finding in the high dose group for a tissue, even if not statistically significant, you will also need to look at the next lower dose group; for an excessive decrease in body weight or survival in the examined dose group, you should examine lower dose groups.

Reviewer signature: _____
Timothy W. Robison, Ph.D.

Supervisor signature: Concurrence - _____
Joseph Sun, Ph.D.

Non-Concurrence - _____
(see memo attached)

cc: list:

NDA 21-369, Division File, HFD-570
YuC, HFD-570
ShahVJ, HFD-570
SunC, HFD-570
RobisonT, HFD-570

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/s/

Timothy Robison
6/23/03 03:46:10 PM
PHARMACOLOGIST
Communication to sponsor regarding design of [redacted]
with rats.

Joseph Sun
6/24/03 10:17:00 AM
PHARMACOLOGIST
I concur.

PHARMACOLOGY/TOXICOLOGY COVER SHEET

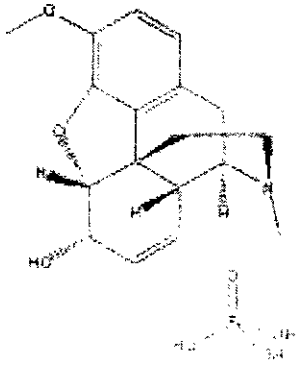
NDA number: 21-369
Review number: #01
Sequence number/date/type of submission: #000 / April 13, 2001 / Initial Submission
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Celltech Pharmaceuticals, Inc.
755 Jefferson Road
P.O. Box 31766
Rochester, NY
Manufacturer for drug substance: Same

Reviewer name: Timothy W. Robison, Ph.D.
Division name: Pulmonary and Allergy Drug Products
HFD #: 570
Review completion date: January 7, 2002

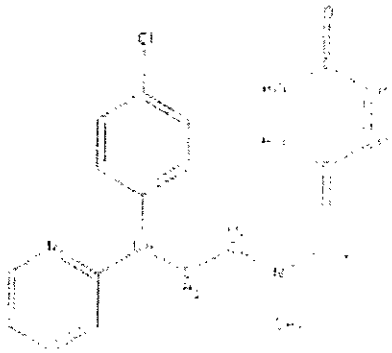
Drug:

Trade name: Codeprex™ Extended-Release Suspension
Generic name (list alphabetically): Codeine/Chlorpheniramine Extended-Release Suspension
Code name:
Chemical name:
Codeine phosphate, (5α,6α)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol, phosphate (1:1) (salt), hemihydrate;
Chlorpheniramine maleate, γ-(4-chlorophenyl)-N,N-dimethyl-2-pyridinepropanamine, (Z)-2-butenedioate
CAS registry number: Codeine Phosphate (41444-62-6); Chlorpheniramine Maleate (113-92-8)
Mole file number:
Molecular formula/molecular weight:
Codeine phosphate $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$ / 406.37
Chlorpheniramine maleate $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ / 390.87

Structure:
Codeine phosphate:



Chlorpheniramine maleate:



Relevant INDs/NDAs/DMFs:

IND 54,892 (Codeine/chlorpheniramine extended-release suspension from Celltech Pharmaceuticals Inc., of Rochester, NY).

NDA 18-928 (Penntuss® Suspension (Controlled release codeine polistirex with chlorpheniramine polistirex) from Fisons Corporation of Rochester, NY).

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Drug Products containing codeine (NDA 8-306 and NDA 12-575)

Drug Products containing chlorpheniramine (NDA 6-921, NDA 7-638, NDA 8-826, NDA 12-152, NDA 13-397, NDA 13-764, NDA 14-968, NDA 17-369, NDA 18-099, NDA 18-556, NDA 18-747, NDA 19-428, NDA 19-746)

DMFs ——————————

Drug class: Antitussive/antihistamine

Indication: For the temporary relief of [redacted] cough, and runny nose, sneezing, itching of the nose or throat, and itchy watery eyes, as may occur with the common cold, inhaled irritants, hay fever, or other upper respiratory allergies.

Clinical formulation: Codeine/chlorpheniramine extended-release suspension, an oral suspension product, is an aqueous suspension of coated codeine polistirex and chlorpheniramine maleate. "This product uses an [redacted] resin and Pennikinetic® technology, a patented process for binding of drugs to ion exchange resins and applying a water insoluble semi-permeable membrane coating to impart the extended release properties of the suspension. This system allows for the extended-release delivery of water-soluble active pharmaceutical ingredients in a suspension form. Drug substances used in the manufacture of the codeine/chlorpheniramine extended-release suspension are codeine phosphate and chlorpheniramine maleate, USP." The composition of the Codeine/chlorpheniramine extended-release suspension is shown below.

Ingredients	mg/10 ml
[redacted]	
Dye, D&C Red #33 Certified	
Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF	
Sucrose, NF	
Glycerin, USP	
Propylene Glycol, USP	
Methylparaben, NF	
Propylparaben, NF	
Xanthan Gum, NF	
Citric Acid (Anhydrous), USP	
Edetate Disodium, USP	
Flavor, Artificial Cherry Cream	
Polysorbate 80, NF	
Coated Codeine Polistirex	
Chlorpheniramine Maleate, USP	
Water, Purified, USP	

[redacted]

[1] Based on anhydrous basis

[2] Input quantities vary slightly based on assay of resin bound codeine. The actual amount of coated codeine polistirex is equivalent to 40 mg of [redacted] calculation is based on the following equation:

[redacted]

Route of administration: Oral

Proposed use: The final formulation is an aqueous suspension containing codeine (40 mg/10 mL) and chlorpheniramine maleate (8 mg/10 mL). For adolescents ≥12 years of age and adults, the product is to be administered as a 10 mL (2 teaspoons) dose every 12 hr. For children ages 6 to under 12, the product is to be administered as a 5 mL (1 teaspoon) dose every 12 hr.

Product	Formulation	Dosage Regimen	Total Daily Dose
Codeine/chlorpheniramine Extended Release Suspension	40 mg / 8 mg per 10 mL	Adolescents ≥12 years and adults: 40 mg / 8 mg (2 teaspoons) q 12 hr	80 mg / 16 mg
		Children, ages 6 to under 12: 20 mg / 4 mg (1 teaspoon) q 12 hr	40 mg / 8 mg

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

APPEARS THIS WAY
ON ORIGINAL

Executive Summary

I. Recommendations

A. Recommendation on Approvability
From a preclinical standpoint, the application is approvable.

B. Recommendation for Nonclinical Studies
None

C. Recommendations on Labeling
Recommendations for changes in labeling are described in the Labeling section at the end of this document.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings
No preclinical pharmacology or toxicology studies were conducted with Codeprex™ (i.e., codeine/chlorpheniramine extended-release suspension). Codeine and chlorpheniramine are recognized USP monograph drugs. Extensive preclinical pharmacology and toxicology studies have been conducted with the active ingredients of Codeprex™, codeine and chlorpheniramine. Preclinical toxicology studies conducted with the active ingredients, codeine and chlorpheniramine, related to carcinogenicity, genotoxicity, fertility and reproductive performance, teratogenicity, and acute toxicity, were referenced in the preparation of product labeling

B. Pharmacologic Activity
No preclinical pharmacology or toxicology studies were conducted with Codeprex™ (i.e., codeine/chlorpheniramine extended-release suspension). However, codeine is a recognized antitussive and chlorpheniramine is a recognized antihistamine.

C. Nonclinical Safety Issues Relevant to Clinical Use
None

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:
YuC
HuffR
RobisonT

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions:

Codeprex™ contains codeine and chlorpheniramine maleate in an extended-release suspension. Codeine, an opioid related to morphine, depresses the cough reflex, at least in part by a direct effect on a cough center in the medulla. Chlorpheniramine is a H_1 receptor antagonist that competitively inhibits released histamine from dilating capillaries and causing edema of the respiratory mucosa. For children ≥6 years of age and adults, Codeprex™ is intended to provide sustained relief of symptoms that may occur with the common cold, allergies, or exposure to airborne irritants.

Codeprex™ is indicated for the temporary relief of ———— cough, and runny nose, sneezing, itching of the nose or throat, and itchy watery eyes, as may occur with the common cold, inhaled irritants, hay fever, or other upper respiratory allergies. The drug product is an aqueous suspension containing codeine (40 mg/10 mL) and chlorpheniramine maleate (8 mg/10 mL). Codeprex™ is to be administered as a 10 mL (2 teaspoons) dose twice per day to adolescents >12 years of age and adults. For a 50-kg person (12 years old to adult), the doses of codeine and chlorpheniramine are equivalent to 1.6 and 0.32 mg/kg/day, respectively. On a body surface area basis, using a conversion factor of 37, these doses are equivalent to 59 and 12 mg/m^2/day, respectively. Codeprex™ is to be administered as a 5 mL (1 teaspoon) dose twice per day to children ages 6 to 12. For a 20-kg person (6 to 11 years of age), the doses of codeine and chlorpheniramine are equivalent to 2 and 0.4 mg/kg/day, respectively. On a body surface area basis, using a conversion factor of 25, these doses are equivalent to 50 and 10 mg/m^2/day, respectively. This combination drug product is proposed as a prescription product, in part because codeine is a Schedule III controlled substance.

There are at least two approved drug products, one that is no longer marketed (i.e., Penntuss®) and the other that is currently marketed (i.e., Tussionex®), that are almost identical or similar to Codeprex™ Extended-Release suspension. Both these drug products utilize sodium polystyrene sulfonate ———— as does Codeprex™.

Penntuss® (controlled release codeine polistirex with chlorpheniramine polistirex; NDA 18-928), that is almost identical to Codeprex™, was previously marketed by Fisons Corporation of Rochester, NY. It was withdrawn from the market in 1996 for reasons unrelated to safety or efficacy. Approved dosages of codeine and chlorpheniramine in Penntuss® are similar to those proposed for Codeprex™. Each teaspoonful (5 mL) contained codeine polistirex equivalent to 10 mg codeine base, plus chlorpheniramine polistirex equivalent to 4 mg chlorpheniramine maleate. Adolescents ≥12 years of age and adults received 2 to 3 teaspoonfuls every 12 hr, which was equivalent to codeine and chlorpheniramine maleate doses of 1.2 and 0.48 mg/kg/day, respectively. Children,

6 to 12 years of age, received 1 teaspoonful every 12 hr, which was equivalent to codeine and chlorpheniramine maleate doses of 1 and 0.4 mg/kg/day, respectively.

Tussionex® Pennkinetic® (hydrocodone polistirex and chlorpheniramine polistirex) Extended-Release suspension, also marketed by Celltech, is similar to Codeprex™. Each teaspoonful (5 mL) of Tussionex Pennikinetic Extended-Release suspension contains hydrocodone polistirex equivalent to 10 mg of hydrocodone bitartrate and chlorpheniramine polistirex equivalent to 8 mg of chlorpheniramine maleate. The dosage for adults is 1 teaspoonful (5 mL) every 12 hr, which is equivalent to hydrocodone bitartrate and chlorpheniramine maleate doses of 0.4 and 0.32 mg/kg/day, respectively. The dosage for children, 6-12 years of age, is 1/2 teaspoon (2.5 mL) every 12 hr, which is equivalent to hydrocodone bitartrate and chlorpheniramine maleate doses of 0.5 and 0.4 mg/kg/day, respectively.

The Codeprex™ extended-release suspension utilizes the Pennkinetic® System, an ion exchange resin ——— bound with drug (codeine) to form polistirex, ——— The treated bound codeine is then coated with ethylcellulose to provide a semipermeable water insoluble membrane. In the manufacturing process, ——— ———. Following multiple dosing with the Codeprex™ extended release suspension, the C_{max} and T_{max} for codeine were ——— ng/mL and 3 hr, respectively. The C_{max} and T_{max} for chlorpheniramine were ——— ng/mL and 6 hr, respectively. The volume of distribution (V_d) for codeine is 3-6 L/kg, indicating extensive tissue distribution. Plasma protein binding of codeine is ——— Codeine passes the blood brain and placental barriers. Small amounts of codeine and its metabolites are transferred to human breast milk. The V_d of chlorpheniramine is 3.2 L/kg in adults and children, indicating extensive tissue distribution. Chlorpheniramine is known to distribute into the central nervous system. Chlorpheniramine and its metabolites appear to cross the placental barrier and are excreted in human breast milk. Codeine is primarily conjugated with glucuronic acid to form codeine-6-glucuronide. Codeine is metabolized by O-demethylation, through cytochrome P450 2D6, to form morphine (10% of the administered dose) or N-demethylation, through cytochrome P450 3A4, to form norcodeine. Morphine and norcodeine are conjugated with glucuronic acid to form glucuronide conjugates. Chlorpheniramine undergoes demethylation, through cytochrome P450 2D6, to form mono- and didesmethyl derivatives. Codeine and its metabolites are excreted in the urine (90% of administered dose), primarily in inactive forms. The half-life of codeine is 3 hr. Chlorpheniramine and its metabolites are primarily excreted in urine, with large individual variation. Half-lives of chlorpheniramine in children and adults are 5-16 hr and 2-43 hr, respectively.

No preclinical pharmacology or toxicology studies were conducted with Codeprex™ (i.e., codeine/chlorpheniramine extended-release suspension). Codeine and chlorpheniramine maleate are recognized USP monograph drugs. The sponsor referenced OTC and USP Monographs as follows: (1.) Final Monograph for OTC Antitussive Drug Products (52 FR 30055, August 12, 1987); (2.) Final Monograph for OTC Antihistamine Drug Products (57 FR 58374, December 9, 1992); (3.) Tentative

Final Monograph for Combination Products (53 FR 30561, August 12, 1988); (4.) Codeine Phosphate (USP 24 Monograph), and (5.) Chlorpheniramine maleate (USP 24 Monograph).

The antitussive monograph defines codeine ingredients as free codeine base, codeine sulfate, and codeine phosphate. However, the Codeprex™ formulation contains codeine polistirex (i.e., sodium polystyrene sulfonate). Codeine polistirex is found in other drug products (i.e., Penntuss® and Tussionex®). Polistirex, a cation exchange resin, has a low bioavailability. Further, it has been extensively evaluated in preclinical toxicology studies (see Review of NDA 18-928 dated May 10, 1985), including a life-long dietary study in rats, with no findings of significant adverse effects.

Extensive preclinical pharmacology and toxicology studies have been conducted with the active ingredients of Codeprex™, codeine and chlorpheniramine. The scientific literature was searched for preclinical toxicology studies conducted with codeine and chlorpheniramine related to carcinogenicity, genotoxicity, fertility and reproductive performance, teratogenicity, and acute toxicity. Summaries of these studies are provided below.

The National Toxicology Program (NTP) has conducted carcinogenicity and genotoxicity studies with codeine and chlorpheniramine as described below.

NTP studies with codeine were reported in "Toxicology and Carcinogenesis Studies of Codeine (CAS No. 76-57-3) in F344 Rats and B6C3F1 Mice (Feed Studies), Technical Report No. TR-455 (August 1996)." In a 2-year study in F344/N rats, codeine showed no evidence of tumorigenicity at dietary doses of 15, 30, and 70 mg/kg/day in males and 15, 40, and 80 mg/kg/day in females. In a 2-year study in B6C3F1 mice, codeine showed no evidence of tumorigenicity at dietary doses of 100, 200, and 400 mg/kg/day in males and females. Codeine was not mutagenic with four strains of *Salmonella typhimurium* in the presence or absence of metabolic activation. Codeine was negative in the Chinese hamster ovary (CHO) cell chromosomal aberration assay in the presence or absence of metabolic activation. In the CHO cell sister chromatid exchange assay, codeine induced dose-related increases in exchanges in the presence or absence of metabolic activation, although, only at concentration levels that caused cell cycle delay.

NTP studies with chlorpheniramine maleate were reported in "Toxicology and Carcinogenesis Studies of Chlorpheniramine Maleate (CAS No. 113-92-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies), Technical Report No. TR-317 (September 1986)." In a 2-year study in F344/N rats, chlorpheniramine maleate showed no evidence of tumorigenicity when administered 5 days/week at oral doses of 15 and 30 mg/kg/day in males and 30 and 60 mg/kg/day in females. In a 2-year study in B6C3F1 mice, chlorpheniramine maleate showed no evidence of tumorigenicity when administered 5 days/week at oral doses of 25 or 50 mg/kg/day to males. However, incidences of thyroid gland follicular cell cysts and thyroid gland follicular cell hyperplasia were increased in a dose-related manner for female mice that received chlorpheniramine maleate 5 days/week at oral doses of 100 or 200 mg/kg/day. The incidences of thyroid gland follicular cell adenomas were increased in female mice at

100 and 200 mg/kg/day, although, there was not a dose-response relationship. This finding was considered toxicologically important, because thyroid gland neoplasms are uncommon in mice and are often preceded by hyperplasia of the follicular epithelium. In an overall analysis of the mouse carcinogenicity study, NTP judged that there was no evidence of tumorigenicity with chlorpheniramine maleate in males and females, despite the findings in female mice. Chlorpheniramine maleate was not mutagenic with *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 in the presence or absence of metabolic activation. Chlorpheniramine was negative in the L5178Y mouse lymphoma forward mutation assay at the TK locus in the presence or absence of metabolic activation. In the Chinese hamster ovary (CHO) cell sister chromatid exchange assay, chlorpheniramine maleate induced a weak but reproducible increase in exchanges in the absence of exogenous metabolic activation. In the CHO cell chromosomal aberration assay, chromosomal aberrations were induced at the highest dose tested, in the presence of metabolic activation. A negative micronucleus test for chlorpheniramine was mentioned; however, no details were provided.

Reproductive toxicology studies with codeine (several drug products) and chlorpheniramine maleate (Ornade® Spansule® Capsules; NDA 12-152) have been conducted in rats and rabbits and described in the labeling for current and discontinued drug products. Labeling for codeine, with regard to teratology, stated, "A study in rats and rabbits reported no teratogenic effect of codeine administered during the period of organogenesis in doses ranging from 5 to 120 mg/kg. In the rat, doses at the 120 mg/kg level, in the toxic range for adult animals, were associated with an increase in embryo resorption at the time of implantation. In another study, a single 100 mg/kg dose of codeine administered to pregnant mice reportedly resulted in delayed ossification in the offspring." Labeling for chlorpheniramine maleate, with regard to fertility and reproductive performance, stated, "In an early study in rats with chlorpheniramine maleate a reduction in fertility was observed in female rats at doses approximately 67 times the human dose. More recent studies in rabbits and rats, using more appropriate methodology and doses up to approximately 50 and 85 times the human dose, showed no reduction in fertility." Labeling for chlorpheniramine maleate, with regard to teratology, stated, "Studies with chlorpheniramine maleate in rabbits and rats at doses up to 50 times and 85 times the human dose, respectively, revealed no evidence of harm to the fetus." Labeling for chlorpheniramine maleate, with regard to nonteratogenic effects, stated, "Studies of chlorpheniramine maleate in rats showed a decrease in the postnatal survival rate of offspring of animals dosed with 33 and 67 times the human dose." The human dose of chlorpheniramine was 12 mg q 12 hr or 24 mg/day (equivalent to 0.48 mg/kg/day for 50 kg person).

The above mentioned teratology studies with codeine in rats and rabbits as well as additional studies in pregnant hamsters and mice are described below.

Mated female rats received codeine at oral doses of 0, 10, 35, or 120 mg/kg/day from days 6 to 15 of gestation (Arzneimittelforschung 18: 188-194, 1968). Maternal toxicity (i.e., reduced body weight gain and lethargy) was evident at 120 mg/kg/day. Reduced fetal body weight and increased resorptions were evident at 120 mg/kg/day. Codeine was not teratogenic in rats at oral doses ≤120 mg/kg/day.

Pregnant rabbits received codeine at oral doses of 0, 5, 12.5, or 30 mg/kg/day from days 6 to 18 of gestation (Arzneimittelforschung 18: 188-194, 1968). No maternal toxicity or fetal effects were evident with doses ≤30 mg/kg/day. Dosing appeared to be inadequate in this study, although, the high dose was approximately one-third of the LD_{50}. Codeine was not teratogenic in rabbits at oral doses ≤30 mg/kg/day.

Mated female Syrian hamsters received codeine at oral doses of 0, 10, 50, or 150 mg/kg BID (total doses of 0, 20, 100, or 300 mg/kg/day, respectively) from days 5 to 13 of gestation (Fundamental and Applied Toxicology 16: 401-413, 1991). The NOAEL was 10 mg/kg BID (i.e., 20 mg/kg/day). Maternal toxicity was evident at doses of 50 and 150 mg/kg BID. Body weight gains from days 5 to 13 for hamsters at 50 and 150 mg/kg BID were reduced to 80.8 and 14.1% of the control, respectively. Lethargy was evident for 1 female at 150 mg/kg BID during three days of treatment. Resorptions (% per litter) were increased to 38% at 150 mg/kg BID as compared to 11% for the control. Fetal body weights at 50 and 150 mg/kg BID were reduced to 91.7 and 74.5% of the control (2.10 g), respectively. An external malformation, meningocephalocele (i.e., cranial defect), was observed at 150 mg/kg BID for 5 fetuses (3%) in 3 litters (19%) as compared to no similar finding in the concurrent control, although, these occurrences were not statistically significant. The historical background incidence for this external malformation is not known; however, it should be noted that this finding occurred in presence of maternal toxicity. Incidence of incomplete ossification, a skeletal variation, at 50 and 150 mg/kg BID was increased to 3 (1%) and 9 (5%) fetuses, respectively, as compared to the 1 (0.5%) fetus in the control group, although, these occurrences were not statistically significant.

Central nervous system malformations have been reported in hamsters (i.e., cranioschisis; American Journal of Obstetrics and Gynecology 123: 705-713, 1975) and in several strains of mice (i.e., cerebral ventricular dilatation or spinal cord kinking; Developmental Growth Differences 22: 61-78, 1980) following single subcutaneous injections of codeine phosphate on gestation days 8 or 9, respectively. However, these effects were observed only at high doses of codeine (i.e., 73-360 mg/kg in hamsters and 110-120 mg/kg in mice) and there were apparently no considerations of other endpoints such as maternal toxicity, fetal body weight, and resorptions.

Mated female CD1 mice received codeine at oral doses of 0, 37.5, 75, 150, or 300 mg/kg BID (total doses of 0, 75, 150, 300, or 600 mg/kg/day, respectively) from days 6 to 15 of gestation (Fundamental and Applied Toxicology 16: 401-413, 1991). The NOAEL was 75 mg/kg BID (i.e., 150 mg/kg/day). Maternal toxicity was evident at 150 and 300 mg/kg BID. Incidences of mortality at 150 and 300 mg/kg BID were 2 and 20%, respectively, as compared to 0% for the control. Maternal body weight gains at 150 and 300 mg/kg BID during the treatment period were reduced to 82.8 and 62.9% of the control, respectively. Resorptions (% per litter) at 37.5 and 300 mg/kg BID were increased to 16 and 20%, respectively, as compared to 8% for the control. The number of litters with 100% resorptions at 37.5, 75, 150, and 300 mg/kg BID were 2, 0, 1, and 4, respectively, as compared to 0 for the concurrent control. The treatment relationship of resorptions appears to be unclear given that there is no concordance with dose. Fetal body weights at 150 and 300 mg/kg BID were reduced to 87.3 and 74.6% of the control

(0.985 g), respectively. There were no findings of treatment-related external, visceral, or skeletal malformations or variations in mice at doses ≤300 mg/kg BID.

The source(s) of rat and rabbit teratology studies with chlorpheniramine maleate that are noted in Ornade® Spansule® Capsules (NDA 12-152) labeling is not known. Other reproductive toxicology studies with chlorpheniramine maleate in rats and mice are described below.

Under NDA 12-152, the report of a 60-day pre-feeding reproductive toxicology study with chlorpheniramine maleate in rats was provided to the Agency in 1965. This study was conducted by Schering Corporation of Bloomfield, NJ. Chlorpheniramine maleate was administered to albino rats at doses of 10 and 20 mg/kg/day. The study was conducted in two parts. Part A consisted of control and 20 mg/kg groups. Part B consisted of control and 10 mg/kg. Part B was started when it became evident that number of offspring at 20 mg/kg was reduced as compared to the control. Chlorpheniramine maleate was mixed in the diet and given to male and female rats for 8 weeks prior to mating. It was not clear if treatment continued during the mating and gestation periods. Male and female rats were allowed to mate over a 5-day period. Female rats were allowed to deliver their offspring and nurse them for 12 (Part A) or 21 (Part B) days, followed by sacrifice of surviving pups. Ten days after the last litter was sacrificed, rats were again mated. There were no treatment-related deaths of parental (F_0) animals. Body weight gains over the 8-week treatment period for male and female rats at 20 mg/kg were 89.6 and 86.8% of the control, respectively. Numbers of live offspring at 10 and 20 mg/kg were reduced as compared to corresponding controls (see table below). Numbers of dead fetuses at birth were increased at 10 and 20 mg/kg as compared to controls. Survival and growth of pups from days 1-12 or 1-21 was comparable between control and treatment groups. Following the completion of the second pregnancy, the sponsor reported that nidation (i.e., implantation) sites per dam in the 20 mg/kg group were reduced as compared to the control. Although this study is unconventional in design (i.e., two mating periods for female rats) and it is unclear whether treatment continued during gestation, embyrolethality is evident in this study and should be reported in labeling.

Litter data following first mating period for rats that received chlorpheniramine maleate in the diet at doses of 0, 10, or 20 mg/kg/day for 8 weeks prior to mating.

Parameter	Part A		Part B	
	Control	20 mg/kg	Control	10 mg/kg
Number of female rats	20	20	20	20
% Pregnant	100% (20/20)	80% (16/20)	85% (17/20)	95% (19/20)
Live fetuses/dam	12.05 (241/20)	7 (112/16)	11.4 (193/17)	8.5 (153/18)
Dead fetus	0.4 (8/20)	1.3 (21/16)	0.2 (3/17)	0.6 (10/18)
Fetal BW, g	5.9	5.5	6.8	6.1

In another reproductive toxicology study, pregnant Swiss-Webster mice received chlorpheniramine maleate by the oral route in drinking water at approximate doses of 18-20, 80-100, and 142-200 mg/kg/day for approximately 44 days after day 0 of gestation (Arzneimittelforschung 18: 188-194, 1968). It should be noted that drug treatment was not confined to the period of organogenesis. During pregnancy, the weight of females was controlled. When the delivery or abortion occurred, weight, sex, and external characteristics of the fetus or newborn were recorded. After parturition, dams continued to drink the antihistamine solution, and pups began to drink it after weaning. Body weight gain of pups was monitored for 44 days after birth. At the end of this period, animals were sacrificed and submitted to pathological examination. At the high dose, all dams aborted at approximately midterm. All fetuses at the high dose were either aborted or resorbed. At the low and mid doses, numbers of newborns delivered per litter were reduced to 88.4 and 73.9% of controls (6.9 pups/litter), respectively. Percentages of female pups at the low and mid doses were reduced to 39.8 and 35.2%, respectively, as compared to 47.6-48.2% for controls. Number of stillbirths and mortality up to 60 hr and 60 hr-40 days after birth was increased for pups in the low and mid dose groups. Survival at day 44 for pups in low and mid dose groups was reduced to 23.3 and 18.0%, respectively as compared to 81.1-86.8% for controls. Approximately 10-20% of offspring were observed to have gas inside the peritoneal cavity under pressure. The abdominal wall had a thin, transparent consistency. Pathological examination revealed the absence of perforation in the diaphragm and the small and large intestines. The offspring with this condition were stillbirths or died within 6 hr after birth. Body weight gains for pups in the low and mid dose groups were reduced as compared to the control. Developmental delays for pups in the low and mid groups were evident (i.e., a vaginal aperture was not evident in females until day 58 as compared to days 33-35 for controls). The low, mid, and high doses were 4.5, 20, and 35 times the human dose (i.e., 12 mg/m^2/day). The sponsor has incorporated this study into the labeling for teratology; however, drug treatment in this study extended before and after the period of organogenesis, and there was no examination of fetuses. Thus, labeling needs to be reworded to accurately convey results.

In the NTP Chemical Repository for codeine phosphate (Catalog ID Number: 001551), the acute toxicity of this compound by the oral route has been reported for mice, rats, and guinea pigs. Oral LD_{50} values for codeine phosphate in mice, rats, and guinea pigs were 237, 266, and 654 mg/kg, respectively. The oral LD_{Lo} for codeine phosphate in rabbits was 100 mg/kg. Oral LD_{50} values for codeine base in mice and rats were 250 and 427 mg/kg, respectively (NTP Chemical Repository, Catalog ID number 001769).

In the NTP Chemical Repository for chlorpheniramine maleate (Catalog ID Number: 000676), the acute toxicity of this compound by the oral route has been reported for mice, rats, and guinea pigs. Oral LD_{50} values for chlorpheniramine maleate in mice, rats, and guinea pigs were 130, 306, and 198 mg/kg, respectively.

In the pharmacology review of IND 54,892 dated January 20, 1998, the sponsor was reminded that the safety of inactive ingredients, impurities, extractables, and leachables, present in the drug product, should be evaluated.

Codeprex™ Extended-Release suspension contains the following excipients: D & C red dye #33, microcrystalline cellulose/sodium carboxymethylcellulose, sucrose, glycerin, propylene glycol, methylparaben, propylparaben, xanthan gum, citric acid, disodium edetate, artificial cherry cream [redacted] flavor, polysorbate 80, polyethylene glycol 3350, ethyl cellulose, vegetable oil [redacted], sodium hydroxide, sodium polystyrene sulfonate ([redacted] , and purified water.

Sodium citric acid (184.1033), glycerin (182.1320), methylparaben (184.1490), propylparaben (184.1670 or 184.1571), propylene glycol (184.1666), sodium hydroxide (184.1763), purified water, and sucrose (184.1854) have all been classified as "generally recognized as safe" (GRAS) under CFR 21. The following excipients have been used in several oral drug products: microcrystalline cellulose (up to 505.0 mg or 2.0%), microcrystalline sodium carboxymethylcellulose (up to 79.53 mg or 1.3125%), polyethylene glycol 3350 (up to 10 mg), xanthan gum (up to 1.6%), ethyl cellulose (up to 225.0 mg), polysorbate 80 (up to 418.37 mg), vegetable oil (up to 2.55 mg), disodium edetate (up to 4.0 mg or 0.1%), and D & C Red Dye #33 (up to 0.15 mg or 0.002%). [redacted] is used in the approved drug product Tussionex®.

A possible degradant of codeine in the Codeprex™ Extended-Release suspension is [redacted] The sponsor has stated that according to the codeine monograph (USP 24), "individual impurities may be present as long as no one impurity is present at >2% of the amount of codeine and no other impurity with an Rf > codeine is present at >1% of the amount of codeine. This suggests that [redacted] levels of [redacted] may be present in products that conform to the USP monograph." Celltech has proposed a finished product specification for [redacted] in the codeine/chlorpheniramine extended-release suspension of [redacted] over the shelf life. In the chemistry review of IND 54,892 dated March 18, 1998, the sponsor was given several comments regarding drug substances and drug product that needed to be addressed in an NDA submission. With regard to the drug substances (i.e., codeine polistirex and chlorpheniramine maleate), the impurity limits proposed in the acceptance specifications for codeine phosphate and chlorpheniramine maleate (NMT [redacted]) were not acceptable. An individual impurity/degradation product ≥0.1% should be identified, qualified, and individually controlled for both, codeine phosphate and chlorpheniramine maleate. With regard to the drug product (i.e., codeine polistirex and chlorpheniramine maleate extended-release suspension), an impurity /degradation profile specific to each of the parent compounds, codeine and chlorpheniramine maleate, in the drug product should be established. An individual impurity/degradation product ≥0.2% needs to be identified and ≥0.5% needs to be qualified. At the time of this review, there were no known issues related to qualification of impurities, degradants, extractables, or leachables.

General Toxicology Issues: No preclinical pharmacology or toxicology studies were conducted with Codeprex™ (i.e., codeine/chlorpheniramine extended-release suspension). Codeine and chlorpheniramine are recognized USP monograph drugs. Extensive preclinical pharmacology and toxicology studies have been conducted with the active ingredients of Codeprex™, codeine and chlorpheniramine. Preclinical

toxicology studies conducted with the active ingredients, codeine and chlorpheniramine, related to carcinogenicity, genotoxicity, fertility and reproductive performance, teratogenicity, and acute toxicity, were referenced in the preparation of product labeling.

Recommendations: From a preclinical standpoint, the application is approvable.

Labeling with basis for findings:

1. Carcinogenesis, Mutagenesis, Impairment of Fertility:

Evaluation: The text should be revised to incorporate carcinogenicity and genotoxicity studies conducted with codeine and chlorpheniramine by the NTP. Results from sister chromatid exchange assays conducted with codeine and chlorpheniramine have not been conveyed in the labeling, because results with this assay have not been found to correlate reliably with any human health consequences (e.g., cancer induction). Further, there are questions about what is measured in this assay and the validity of the assay (i.e., high background levels of activity in controls). Doses of chlorpheniramine maleate used in fertility studies with rats and rabbits have not been found in the literature and are not definitively stated in other product labels. Therefore, labeling for chlorpheniramine maleate was referenced from Ornade® Spanule® capsules (NDA 12-152) and doses used in the animal studies were inferred based on assumptions that dose comparisons in said labeling were on a mg/kg basis since NDA 12-152 labeling is from the 1980's. In NDA 12-152, the clinical dose was 24 mg/day and it is assumed that a human body weight of 50 kg was used for calculations. Adult doses of codeine and chlorpheniramine used for calculations for the current labeling were 59 and 12 mg/m^2/day, respectively.

Proposed Labeling:

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/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 15 times the maximum recommended dose for adults and children 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.

In rats and rabbits, oral doses of chlorpheniramine maleate up to approximately 20 and 25 times the human dose on a mg/m^2 basis, respectively, did not impair fertility.

2. Pregnancy: Teratogenic Effects:

Evaluation: Data from published teratology studies with codeine and chlorpheniramine maleate in animals along with comparisons to human doses need to be accurately incorporated into the labeling. The sponsor incorporated a reproductive toxicology study in which pregnant Swiss-Webster mice received chlorpheniramine maleate by the oral route in drinking water at approximate doses of 18-20, 80-100, and 142-200 mg/kg/day for approximately 44 days after day 0 of gestation (Arzneimittelforschung 18: 188-194, 1968). Drug treatment in this study extended before and after the period of organogenesis, and there was no examination of fetuses, limiting the endpoints that can be assessed. However, chlorpheniramine clearly had an embryocidal effect in the study that should be conveyed in labeling. A 60-day pre-feeding reproductive toxicology study with chlorpheniramine maleate in rats that was submitted to NDA 12-152 in 1965 has also been incorporated into labeling. Doses of chlorpheniramine maleate used in teratology studies with rats and rabbits have not been found in the literature and are not definitively stated in other product labels. Therefore, labeling for chlorpheniramine maleate was referenced from Ornade® Spanule® capsules (NDA 12-152) and doses used in the animal studies were inferred based on assumptions that dose comparisons in said labeling were on a mg/kg basis since NDA 12-152 labeling is from the 1980's. In NDA 12-152, the clinical dose was 24 mg/day and it is assumed that a human body weight of 50 kg was used for calculations. Adult doses of codeine and chlorpheniramine used for calculations for the current labeling were 59 and 12 mg/m^2/day, respectively.

Proposed Version:

Pregnancy Category C

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/m^2 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/m^2 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/m^2 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/m^2 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/m^2 basis).

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.

There are no adequate and well-controlled studies in pregnant women. Codeprex™ ——————— should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

3. OVERDOSAGE:

Evaluation: Only labeling concerning preclinical information was addressed in this review. Labeling concerning clinical information is not reiterated below so as to facilitate viewing of preclinical changes. Information for the acute toxicity of codeine phosphate in animals was considered to be unnecessary given the identification of lethal doses in adults and toxic doses in children, which appeared to raise greater safety concerns. NTP Chemical Repository information for the acute toxicity of chlorpheniramine should be incorporated into the text, as indicated below.

Proposed Labeling:

Oral lethal doses of chlorpheniramine maleate were 130, 306 and 198 mg/kg in mice, rats and guinea pigs, respectively (approximately 35, 170 and 150 times, respectively, the maximum recommended daily dose for adults and children on a mg/m^2 basis).

APPEARS THIS WAY
ON ORIGINAL

Drug: **Codeine**

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m²
Pediatric	[redacted]		[redacted]	40	18	2.2222	25	55.56
Adult	>12		[redacted]	80	50	1.6000	37	59.20

	route	mg/kg/d	conv. factor	mg/m²	Dose Ratio Adults	Dose Ratio Children	Rounded Dose Ratio Adults	Rounded Dose Ratio Children
Carcinogenicity:								
mouse	[redacted]	100	3	1200	20.27	21.60	20	20
rat	[redacted]	70	6	420	7.09	7.56	7	8
hamster	[redacted]		4	0	---	---	---	---
rat	[redacted]		6	0	---	---	---	---
rat	[redacted]		6	0	---	---	---	---
Reproduction and Fertility:								
mouse	[redacted]		3	0	---	N/A	---	N/A
rat	[redacted]		6	0	---	N/A	---	N/A
rat	[redacted]		6	0	---	N/A	---	N/A
rat	[redacted]		6	0	---	N/A	---	N/A
Teratogenicity:								
mouse	[redacted]	600	3	1800	30.41	N/A	30	N/A
rat	[redacted]	120	6	720	12.16	N/A	10	N/A
rabbit	[redacted]	360	12	360	6.08	N/A	6	N/A
hamster	[redacted]	300	4	1200	20.27	N/A	20	N/A
mouse	[redacted]		3	0	---	N/A	---	N/A
Overdosage:								
mouse	[redacted]	237	3	711	12.01	12.80	10	15
mouse	[redacted]		3	0	---	---	---	---
g. pig	[redacted]	654	8	5232	88.38	94.18	90	95
rat	[redacted]	266	6	1596	26.96	28.73	25	30

Drug: **Chlorpheniramine**

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m²
Pediatric	[redacted]			8	18	0.4444	25	11.11
Adult	>12	[redacted]		16	50	0.3200	37	11.84

	route	mg/kg/d	conv. factor	mg/m²	Dose Ratio Adults	Dose Ratio Children	Rounded Dose Ratio Adults	Rounded Dose Ratio Children
Carcinogenicity:								
mouse	[redacted]		3	150	12.67	13.50	15	15
rat	[redacted]		6	180	15.20	16.20	15	15
hamster	[redacted]		4	0	---	---	---	---
rat	[redacted]		6	0	---	---	---	---
rat	[redacted]		6	0	---	---	---	---
Reproduction and Fertility:								
mouse	[redacted]		3	0	---	N/A	---	N/A
rat	[redacted]		6	0	---	N/A	---	N/A
rat	[redacted]		6	0	---	N/A	---	N/A
rat	[redacted]		6	0	---	N/A	---	N/A
Teratogenicity:								
mouse	[redacted]		3	0	---	N/A	---	N/A
rat	[redacted]		6	0	---	N/A	---	N/A
rabbit	[redacted]		12	0	---	N/A	---	N/A
rabbit	[redacted]		12	0	---	N/A	---	N/A
mouse	[redacted]		3	0	---	N/A	---	N/A
Overdosage:								
mouse	oral	130	3	390	32.94	35.10	35	35
mouse	[redacted]		3	0	---	---	---	---
G. pig	oral	198	8	1584	133.78	142.56	130	140
rat	oral	306	6	1836	155.07	165.24	160	170

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/s/

Timothy Robison
1/7/02 03:07:32 PM
PHARMACOLOGIST

Robin Huff
1/7/02 04:01:14 PM
PHARMACOLOGIST
I concur.