

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022439Orig1s000

PHARMACOLOGY REVIEW(S)

INTEROFFICE MEMO

TO: NDA 22-439 [ZUTRIPRO[®] Oral Solution (Hydrocodone, Chlorpheniramine, and Pseudoephedrine Oral Solution)]

FROM: Timothy W. Robison, Ph.D., D.A.B.T.
Pharmacology and Toxicology Team Leader

DATE: May 17, 2011

NDA 22-439 was originally submitted under the 505(b)(2) process for the combination drug product, Hydrocodone, Chlorpheniramine, and Pseudoephedrine Oral Solution on November 6, 2008. Dr. Jean Wu was the nonclinical reviewer for the originally submitted NDA (see Reviews dated May 20, 2009, May 26, 2009, June 17, 2009 and February 22, 2010). See Dr. Molly Topper's secondary review dated June 22, 2009. No nonclinical studies were submitted for review for either the individual monoproducts or the combination drug product. The sponsor (Cypress Pharmaceuticals, Inc.) relied on the previously approved monoproduct NDAs and OTC monograph reviews and labeling for the individual products. Reference is made to NDAs 19-111 and 05-213 for hydrocodone bitartrate and to the OTC monographs 21 CFR 341.12 and 21 CFR 341.20 for chlorpheniramine maleate and pseudoephedrine hydrochloride, respectively, for safety assessments supporting approval of each monoproduct. Additionally, the OTC monograph 21 CFR 341.40 recognizes the combination of any single monograph oral antitussive drug with any single monograph antihistamine and any single monograph nasal decongestant. Due to clinical pharmacology deficiencies, the originally submitted NDA was not approved.

On December 10, 2009, Cypress provided their first NDA resubmission. No new nonclinical information was included in this submission. See Dr. Grace Lee's labeling review dated May 3, 2010 and Dr. Molly Topper's secondary review dated May 11, 2010. Approval was recommended from a PharmTox perspective; however, due to clinical pharmacology deficiencies, the resubmission was not approved.

On December 8, 2010, Cypress provided their second NDA resubmission. See Dr. Grace Lee's labeling review dated May 9, 2011 that recommends minor adjustments to the product labeling. I concur with Dr. Lee's review.

As there are no outstanding pharmacology/toxicology issues for this NDA application, the NDA is recommended for approval from the nonclinical perspective.

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/s/

TIMOTHY W ROBISON
05/17/2011

**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: NDA 22-439

Supporting document/s: #22 (Resubmission); 28

Applicant's letter date: Dec. 8, 2010; May 3, 2011

CDER stamp date: Dec. 8, 2010; May 3, 2011

Product: ZUTRIPRO (Hydrocodone, Chlorpheniramine,
and Pseudoephedrine) Oral Solution

Indication: Relief of cough and nasal congestion associated
with the common cold; Relief of symptoms
including nasal congestion associated with
upper respiratory allergies

Applicant: Cypress Pharmaceuticals, Inc.

Review Division: Pulmonary, Allergy, and Rheumatology
Products

Reviewer: Grace S. Lee, Ph.D.

Supervisor/Team Leader: Timothy W. Robison, Ph.D., D.A.B.T.

Division Director: Badrul Chowdhury, M.D., Ph.D.

Project Manager: Philantha Bowen

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 22-439 are owned by Cypress Pharmaceuticals, Inc. or are data for which NDA 22-439 has obtained a written right of reference.

Any information or data necessary for approval of NDA 22-439 that Cypress Pharmaceuticals 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 22-439.

TABLE OF CONTENTS

1	EXECUTIVE SUMMARY	4
1.1	RECOMMENDATIONS.....	4
11	INTEGRATED SUMMARY AND SAFETY EVALUATION.....	4

1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

From a nonclinical pharmacology and toxicology standpoint, the application is recommended for approval.

1.1.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Several changes are made to the nonclinical sections of the labeling to be consistent with the recent changes to the labeling formatting for nonclinical data, and these changes can be found below.

11 Integrated Summary and Safety Evaluation

Revision of labeling:

The Sponsor submitted revised labeling in their resubmission dated December 8, 2010, based on the FDA recommendations (see PharmTox Labeling Review dated May 3, 2010 by Grace Lee and FDA's Facsimile Correspondences to the Sponsor dated May 5 and 12, 2010). In addition to the previous changes, the Reviewer made further changes according to the recent changes to the labeling formatting regarding nonclinical data as described below, and the Sponsor incorporated these changes in the recently submitted labeling on May 3, 2011, but two changes not in the Sponsor's version of Section 8.1 for chlorpheniramine still need to be incorporated. These changes will be communicated to the Sponsor.

Under Section 10, (b) (4) data were deleted.

Section 13.2 was deleted and the information from this section was incorporated into Section 8.1.

Under Section 13.1, two minor changes were made.

Suggested Labeling sent to the Sponsor:

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

GRACE S LEE
05/09/2011

TIMOTHY W ROBISON
05/09/2011
I concur

INTEROFFICE MEMO

TO: NDA 22-439
Sequence number/date/type of submission:
#011/December 10, 2009/Resubmission

FROM: Molly E. Shea, Ph.D.
Pharmacology/Toxicology Supervisor
Division of Pulmonary, Allergy and Rheumatology Products

DATE: May 11, 2010

NDA 22-439 was submitted under the 505(b)(2) process for the combination drug product Hydrocodone, Chlorpheniramine, and Pseudoephedrine Oral Solution on November 6, 2008. Dr. Jean Wu was the nonclinical reviewer for the originally submitted NDA. No nonclinical studies were submitted for review for either the individual monoproducts or the combination drug product. The sponsor (Cypress Pharmaceuticals, Inc.) relied on the previously approved monoproduct NDAs and OTC monograph reviews and labeling for the individual products. Reference is made to NDAs 19-111 and 05-213 for hydrocodone bitartrate and to the OTC monographs 21 CFR 341.12 and 21 CFR 341.20 for chlorpheniramine maleate and pseudoephedrine hydrochloride, respectively, for safety assessments supporting approval of each monoproduct. Additionally, the OTC monograph 21 CFR 341.40 recognizes the combination of any single monograph oral antitussive drug with any single monograph antihistamine and any single monograph nasal decongestant. Due to clinical pharmacology deficiencies, the originally submitted NDA was not approved.

On December 10, 2009 Cypress resubmitted their NDA. No new nonclinical information was included in this submission. Drs. Grace Lee and Tim Robison reviewed the nonclinical sections of the proposed label and updated Sections 8.1, 8.3, 10.1, 13.1, and 13.2 to include nonclinical information available from the public literature. I concur with these recommended changes.

As there are no outstanding pharmacology/toxicology issues for this NDA application, the NDA is recommended for approval from the nonclinical perspective.

Molly E. Shea, Ph.D.
Pharmacology/Toxicology Supervisor

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22439

ORIG-1

CYPRESS
PHARMACEUTICA
L INC

(b) (4) (HYDROCODONE
BITARTRATE/CHLORPH

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/s/

MOLLY E SHEA
05/11/2010

**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: NDA 22-439
Supporting document/s: #11
Applicant's letter date: December 10, 2009
CDER stamp date: December 11, 2009
Product: Hydrocodone, Chlorpheniramine, and
Pseudoephedrine Oral Solution
Indication: Relief of cough and nasal congestion associated
with the common cold; Relief of symptoms
including nasal congestion associated with
upper respiratory allergies
Applicant: Cypress Pharmaceuticals, Inc.
Review Division: Pulmonary, Allergy, and Rheumatology
Products
Reviewer: Grace S. Lee, Ph.D.
Supervisor/Team Leader: Molly Shea, Ph.D.
Division Director: Badrul Chowdhury, M.D., Ph.D.
Project Manager: Philantha Bowen

Template Version: December 7, 2009

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 22-439 are owned by Cypress Pharmaceuticals, Inc. or are data for which NDA 22-439 has obtained a written right of reference. Any information or data necessary for approval of NDA 22-439 that Cypress Pharmaceuticals, Inc. 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 described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Cypress Pharmaceuticals, Inc. does not own (or from FDA reviews or summaries of

a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-439.

TABLE OF CONTENTS

1	EXECUTIVE SUMMARY	5
1.1	RECOMMENDATIONS.....	5
11	INTEGRATED SUMMARY AND SAFETY EVALUATION.....	5

Table of Tables

Table 1: Dose Multiples and Parameters 11

1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

From a nonclinical pharmacology and toxicology standpoint, the application is recommended for approval.

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

Changes were made to the nonclinical sections of the proposed labeling to conform to 21 CFR Part 201 (April 2009) and the Draft Guidance for Industry “Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements” (January 2006). The changes included addition of nonclinical findings and rearrangement of the text accordingly. The recommended labeling, changes to the proposed labeling, and rationale and clarification for these proposed changes can be found in the Labeling Review below.

11 Integrated Summary and Safety Evaluation

Evaluation of labeling:

Changes were made to the nonclinical sections of the proposed labeling to conform to 21 CFR Part 201 (April 2009) and the Draft Guidance for Industry “Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements” (January 2006). The changes included addition of nonclinical findings as described below and rearrangement of the text accordingly.

Under Sections 8.1 (b) (4), teratogenic effects of hydrocodone in hamsters (Am J Obstet Gynecol 123:705-13, 1975) and results of the reproductive toxicology studies using codeine, an opiate related to hydrocodone, in rats, rabbits and mice (which were stated in the Codeprex label) were added.

Under Section 8.3, excretion of hydrocodone (Breastfeed Med. 2:10-14, 2007) and pseudoephedrine (Br J Clin Pharmacol, 18(6):901-6 1984; Br J Clin Pharmacol, 56(1):18-24, 2003) into human milk were added.

Under Section 13.1, carcinogenicity studies using codeine, an opiate related to hydrocodone, in rats and mice (which were stated in the Codeprex label) were added. In addition, carcinogenicity studies using ephedrine sulfate, a structurally related drug with pharmacological properties similar to pseudoephedrine, in rats and mice (which were stated in the Allegra-D label) were added.

(b) (4)

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22439	ORIG-1	CYPRESS PHARMACEUTICA L INC	(b) (4) (HYDROCODONE BITARTRATE/CHLORPH

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/s/

GRACE S LEE
05/03/2010

MOLLY E SHEA
05/03/2010

**PHARMACOLOGY/TOXICOLOGY REVIEW
FOR CHEMISTRY CONSULTATION REQUEST**

NDA number: 22-439 SN011

Request date:/Type of Request: December 17, 2009/General

Requested by: ONDQA/DPA1/Branch II

Information to sponsor: Yes () No (X)

Sponsor and/or agent: Cypress Pharmaceuticals, Inc.

Reviewer name: Jean Q. Wu, MD, PhD

Division name: Division of Pulmonary and Allergy Products

HFD #: 570

Review completion date: February 22, 2010

Drug:

NDA 22-439

Trade name: (b) (4) Oral Solution

Active Drug: Hydrocodone Bitartrate, Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride

Relevant INDs/NDAs/DMFs: IND 102177 (Hydrocodone, Chlorpheniramine and Pseudoephedrine Oral Solution), (b) (4) (b) (4) NDA 21-369 (Codeprex™), DMF (b) (4) (chlorpheniramine maleate)

Drug class: Hydrocodone --- antitussive and opioid analgesic
Chlorpheniramine maleate--- antihistamine (H₁ receptor antagonist)
Pseudoephedrine hydrochloride --- nasal decongestant

Intended clinical population: Adults (b) (4)
(b) (4)

Clinical formulation:

NDA 22-439: The product is an oral solution, which contains hydrocodone bitartrate (HC) 5 mg, chlorpheniramine maleate (CPM) 4 mg and pseudoephedrine (PSE) hydrochloride 60 mg per 5 mL.

Route of administration: Oral

Intended Dosage:

For adults (b) (4):
(b) (4) (5 mL: 5 mg HC/4 mg CPM/60 mg PSE) every 4-6 hours, NTE 4 doses (20 mL) in 24 hours

(b) (4)

Consultation requested:

This chemistry consult was requested by the review chemist, Xiaobin Shen, PhD, for the safety evaluation of one identified impurity, (b) (4) ((b) (4) structure shown below) of chlorpheniramine maleate manufactured (DMF (u) (4)) at the latest specification level of (b) (4). A Bacterial Reverse Mutation assay (b) (4) was submitted to DMF (u) (4) in response to the Agency's request on May 28, 2009 (refer to Dr. Jean Wu's Consultation Review dated May 20, 2009 and May 26, 2009) to support the proposed specification.

(b) (4)

APPEARS THIS WAY ON
ORIGINAL

Review

Study title: Mutagenicity Study of (b) (4) with the Bacterial Reverse Mutation Assay

Key study findings:

The test article, (b) (4) is not considered to have mutagenic potential under the test conditions of this study.

Study no.: 13971

Volume #, and page #: Volume B5.1 (page # not indicated except narrative page 1-10)

Conducting laboratory and location: (b) (4)

Date of study initiation: October 13, 2009

GLP compliance: The compliance statement indicated the study was conducted in compliance with the OECD Principles of GLP 1997.

QA report: yes (X) no ()

Drug, lot #, and % purity: (b) (4) Lot# 1404009 13308179, purity: (b) (4)

MethodsStrains/species/cell line:

Salmonella typhimurium bacteria TA98, TA100, TA1535 and TA1537; *Escherichia coli* WP2 *uvrA*;

Doses used in definitive study:

Two main tests were conducted using the pre-incubation method.

The following six doses were selected for all strains both with and without metabolic activation in both main tests: 156, 313, 625, 1250, 2500 and 5000 µg per plate.

Basis of dose selection:

The test article (b) (4) was dissolved at 50 mg/mL DMSO. The test article was dissolved and diluted in DMSO to the desired concentrations. The dose selection was based on the preliminary test using 7 dose levels (1.2, 4.9, 20, 78, 313, 1250 and 5000 µg per plate). In the preliminary test, the growth inhibition by the test article (ranging 17-84%) was observed at 5000 µg per plate in all strains with metabolite activation and in all strains except TA1535 without metabolite activation. No precipitation was observed on any plates.

Negative controls: vehicle control, DMSO (dimethyl sulfoxide)

Positive controls: The following positive controls were used in the study.

Strain	Without S9 (μ g/plate)	With S9 (μ g/plate)
TA100	AF-2 (0.01)	B[a]P (5.0)
TA1535	NaN ₃ (0.5)	2AA (2.0)
WP2 <i>uvrA</i>	AF-2 (0.01)	2AA (10.0)
TA98	AF-2 (0.1)	B[a]P (5.0)
TA1537	ICR-191 (1.0)	B[a]P (5.0)
AF-2	2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide (^{(b) (4)}) Special grade of JIS; Purity more than 95%; Lot No. WKK3086)	
NaN ₃	Sodium azide (^{(b) (4)}) Special grade of JIS; Purity more than 95%; Lot No. ALL2016)	
ICR-191	2-Methoxy-6-chloro-9-[3-(2-chloroethyl)aminopropylamino]acridine·2HCl (^{(b) (4)}) Purity more than 95%; Lot No. 492624)	
2AA	2-Aminoanthracene (^{(b) (4)}) Special grade of JIS; Purity more than 95%; Lot No. ASM1101)	
B[a]P	Benzo[a]pyrene (^{(b) (4)}) Purity more than 95% (GC); Lot No. HQAXE)	

Incubation and sampling times: Vehicle control, positive controls and each dose of the test article were plated with culture of tester strains on selective agar in the presence and absence of S9. All plates were incubated for approximately 48 hours at approximately 37 °C.

Results

Study validity: Vehicle control, positive controls and each dose of the test article were tested in triplicate. The number of revertant colonies was counted with a colony counter (Colony Analyzer CA-11, System Science Co. Ltd).

The following criteria were used for evaluation and were considered reasonable.

In the main tests, if the number of revertant colonies on the test plate increased significantly in comparison with that on the control plates (based on twice as many as that of the negative control), and dose-response and reproducibility were also observed, the test substance was to be judged positive.

The revertant colonies of the positive controls showed an increase of more than twice that of the negative controls. The negative controls were within limit of controls (mean +/- 3SD) in background data.

In the main tests, doses up to 5000 μ g per plate were tested in all strains. The growth inhibition by the test article in all strains (ranging 6-71%) was observed at highest dose 5000 μ g per plate.

In the sterility test on the test solution and the S9 mix, no growth of bacteria was observed.

Taken together all of the data, the reviewer considered that the study was valid.

Study outcome: In the two main tests, neither an increase in the number of revertant colonies (more than twice as many as that of the negative control) nor a dose-related response was observed at any doses in any strains with or without metabolic activation.

Based on the results, the test article, [REDACTED]^{(b) (4)} is not considered to have mutagenic potential under the test conditions of this study.

Summary

(b) (4) was identified as an impurity in one of the drug substances, chlorpheniramine maleate (DMF (b) (4)). Based on the review of the submitted bacterial reverse mutation assay, (b) (4) was not considered to have mutagenic potential and should be regulated as a non-genotoxic impurity according to ICH Q3A. For the proposed maximum dose of Chlorpheniramine Maleate (16 mg per day) in the current drug product, the daily intake for (b) (4) would be (b) (4) in drug substance, which is within the qualification threshold per ICH Q3A. Therefore, the proposed specification (b) (4) in drug substance is considered acceptable.

Recommendation:

(b) (4) was not considered to have mutagenic potential and should be regulated as a non-genotoxic impurity according to ICH Q3A.

The proposed specification (b) (4) in drug substance is considered acceptable.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

Appendix 1: Request for Consultation

Appendix 1

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO (Division/Office): PharmTox Review Team (Dr. Jean Wu)			FROM: Xiaobin Shen, Ph.D. CMC Reviewer, DPAP in ONDQA/DPA1/Branch 2	
DATE: Dec. 17, 2009	NDA: 22439	TYPE OF DOCUMENT: NDA	DATE OF DOCUMENT 10-Dec-2009	
NAME OF DRUG (b) (4)	PRIORITY CONSIDERATION: S	CLASSIFICATION OF DRUG: 3	DESIRED COMPLETION DATE: Jan. 31, 2010	
NAME OF FIRM: Cypress Pharmaceuticals, Inc.				
REASON FOR REQUEST: (b) (4) of chlorpheniramine maleate manufactured based on DMF (b) (4) is a potential structural alert. The agency requested the holder to complete genotoxicity study. The study results have been submitted to DMF (b) (4) vol. B5.1. Please evaluate if the study results support the specification of (b) (4) level in the drug substance.				
COMMENTS/SPECIAL INSTRUCTIONS: Additional information that may help your review — <div style="background-color: #cccccc; height: 150px; width: 100%; margin-top: 10px;">(b) (4)</div>				
The previous pharmtox review performed by Dr. Jean Wu is embedded below. I currently have DMF (b) (4) vol. B5.1, please let me know when you need it. Thanks! Xiaobin.				

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
(b) (4)	ORIG-1	(b) (4)	CHLORPHENIRAMINE MALEATE USP
NDA-22439	ORIG-1	CYPRESS PHARMACEUTICA L INC	(b) (4) (HYDROCODONE BITARTRATE/CHLORPH

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/s/

JEAN Q WU
02/22/2010

MOLLY E SHEA
02/22/2010
I concur.

INTEROFFICE MEMO

TO: NDA 22-439
Sequence number/date/type of submission:
#000/November 6, 2008/original NDA

FROM: Molly E. Shea, Ph.D.
Acting Pharmacology/Toxicology Supervisor
Division of Pulmonary and Allergy Products

DATE: June 22, 2009

NDA 22-439 was submitted under the 505(b)(2) process for the combination drug product Hydrocodone, Chlorpheniramine, and Pseudoephedrine Oral Solution on November 6, 2008. No nonclinical studies were submitted for review for either the individual monoproducts or the combination drug product. The sponsor (Cypress Pharmaceuticals, Inc.) has relied on the previously approved monoproduct NDAs and OTC monograph reviews and labeling for the individual products. Reference is made to NDAs 19-111 and 05-213 for hydrocodone bitartrate and to the OTC monographs 21 CFR 341.12 and 21 CFR 341.20 for chlorpheniramine maleate and pseudoephedrine hydrochloride, respectively, for safety assessments supporting approval of each monoproduct. Additionally, the OTC monograph 21 CFR 341.40 recognizes the combination of any single monograph oral antitussive drug with any single monograph antihistamine and any single monograph nasal decongestant. As the primary reviewer Dr. Jean Wu noted, hydrocodone is not an OTC monograph antitussive; however, a hydrocodone combination product containing monograph active ingredients has been accepted based on the precedent NDA 19-111 (Tussionex). For this submission, there were no labeling negotiations.

Dr. Xiabon Shen, the chemistry reviewer for this NDA, requested a pharmacology/toxicology consultation for the safety evaluation of an impurity that contains a structural alert for genetic toxicity, (b)(4) of the chlorpheniramine maleate (DMF (b)(4)). The sponsor proposed a specification of (b)(4). At this specification, the potential daily exposure to (b)(4) is (b)(4). Dr. Jean Wu provided a toxicological evaluation of this Impurity in her reviews dated May 19 and May 26, 2009. Dr. Wu recommended that the sponsor reduce the level of (b)(4) to not more than (b)(4) day or conduct a bacterial reverse mutation assay to qualify the proposed specification. Dr. Shen relayed this recommendation to the DMF holder. In an e-mail dated June 19, 2009 sent to Dr. Wu, Dr. Shen summarized the DMF holder's response to the recommendation and declared that the DMF is considered adequate based on submitted data that showed the level of (b)(4) observed in 13 lots of chlorpheniramine maleate is not more than (b)(4) and that the potential daily exposure to (b)(4) is (b)(4). Therefore, the toxicological concern regarding (b)(4) has been resolved for DMF (b)(4).

As there are no outstanding pharmacology/toxicology issues for this NDA application, the NDA may be approved pending labeling negotiations.

Molly E. Shea, Ph.D.
Acting Pharmacology/Toxicology Supervisor

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/s/

Molly Shea
6/22/2009 09:49:31 AM
PHARMACOLOGIST



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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22-439
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: November 6, 2008
PRODUCT: (b) (4) Oral Solution
(Hydrocodone Bitartrate, Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride)
INTENDED CLINICAL POPULATION: Adults (b) (4)
(b) (4)

SPONSOR: Cypress Pharmaceutical, Inc.
DOCUMENTS REVIEWED: Module 1, Vol. 1, Module 2, Vol. 1.1
REVIEW DIVISION: Division of Pulmonary and Allergy Products
PHARM/TOX REVIEWER: Jean Q. Wu, M.D., Ph.D.
PHARM/TOX SUPERVISOR (Acting): Molly Shea, Ph.D.
DIVISION DIRECTOR: Badrul Chowdhury, M.D., Ph.D.
PROJECT MANAGER: Philantha Bowen

Date of review submission to Division File System (DFS): June 17, 2009

TABLE OF CONTENTS

EXECUTIVE SUMMARY	3
2.6 PHARMACOLOGY/TOXICOLOGY REVIEW	5
2.6.1 INTRODUCTION AND DRUG HISTORY.....	5
2.6.2 PHARMACOLOGY.....	10
2.6.2.1 Brief summary	10
2.6.2.2 Primary pharmacodynamics	10
2.6.2.3 Secondary pharmacodynamics	10
2.6.2.4 Safety pharmacology	10
2.6.2.5 Pharmacodynamic drug interactions.....	10
2.6.3 PHARMACOLOGY TABULATED SUMMARY.....	10
2.6.4 PHARMACOKINETICS/TOXICOKINETICS	10
2.6.4.1 Brief summary	10
2.6.4.2 Methods of Analysis:.....	10
2.6.4.3 Absorption	10
2.6.4.4 Distribution.....	10
2.6.4.5 Metabolism	10
2.6.4.6 Excretion.....	10
2.6.4.7 Pharmacokinetic drug interactions.....	10
2.6.4.8 Other Pharmacokinetic Studies.....	10
2.6.4.9 Discussion and Conclusions	11
2.6.4.10 Tables and figures to include comparative TK summary	11
2.6.6 TOXICOLOGY.....	11
2.6.6.1 Overall toxicology summary	11
2.6.6.2 Single-dose toxicity	11
2.6.6.3 Repeat-dose toxicity	11
2.6.6.4 Genetic toxicology.....	11
2.6.6.5 Carcinogenicity.....	11
2.6.6.6 Reproductive and developmental toxicology.....	11
2.6.6.7 Local tolerance	11
2.6.6.8 Special toxicology studies	11
2.6.6.9 Discussion and Conclusions	11
2.6.6.10 Tables and Figures	11
2.6.7 TOXICOLOGY TABULATED SUMMARY	11
OVERALL CONCLUSIONS AND RECOMMENDATIONS.....	12

EXECUTIVE SUMMARY

I. Recommendations

- A. Recommendation on approvability: Approval
- B. Recommendation for nonclinical studies: None
- C. Recommendations on labeling: Labeling review will be completed at a later time when a labeling negotiation is needed.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

No preclinical pharmacology or toxicology studies were conducted with (b) (4) Oral Solution. The active ingredient, hydrocodone bitartrate, was approved as an antitussive in a sustained release resin suspension in 1987 (NDA 19-111, Tussionex) and in Hycodan Tablet and Syrup in 1943 (NDA 05-213). It was not included in the OTC monograph process and is available on a prescription only basis. It is generally recognized as safe and effective. Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the recommended human dose. The other two active ingredients, chlorpheniramine and pseudoephedrine, are recognized OTC monograph drugs (21 CFR 341.12 and 21 CFR 341.20). They are generally recognized as safe and effective. In studies with chlorpheniramine in which mice were dosed throughout pregnancy, an oral dose of 20 mg/kg/day was embryolethal, and postnatal survival was decreased when dosing was continued after parturition. Embryo lethality was also observed when male and female rats were dosed with 10 mg/kg/day prior to mating. 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 to 50 mg/kg/day. In animal studies, pseudoephedrine reduced average weight, length, and rate of skeletal ossification in the animal fetus (USP Convention. USPDI – Drug Information for the Health Care Professional. 16th edition Volume I, Rockville, MD: U.S. Pharmaceutical Convention, Inc. 1996 (Plus updates), pg. 2508.).

B. Pharmacologic activity

Hydrocodone bitartrate is a recognized antitussive, with efficacy established in DESI Notice #5213, dated June 1, 1982. It is also a controlled prescription opioid. The precise mechanism of action of hydrocodone and other opiates is not known. However, it is believed to act directly on the cough center.

Chlorpheniramine is an antihistamine drug that also possesses anticholinergic and sedative activity. As an H₁ receptor antagonist, it antagonizes many of the

pharmacologic actions of histamine. It prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa (Mosby's Drug Consult™ 2006).

Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. It has the potential for excitatory side effects (Mosby's Drug Consult™ 2005). Pseudoephedrine is recognized as an effective agent for the relief of nasal congestion due to allergic rhinitis, the common cold, hay fever, or other upper respiratory allergies, and nasal congestion associated with sinusitis (21 CFR 341.80).

C. Nonclinical safety issues relevant to clinical use: None.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: NDA 22-439

Review number: 001

Sequence number/date/type of submission: 000/November 6, 2008/Original
SN 006/April 8, 2009/Nonclinical Section 2.4

Information to sponsor: Yes () No (X)

Sponsor and/or agent:

Cypress Pharmaceutical, Inc.
135 Industrial Blvd.
Madison, MS 39110

Manufacturer for drug substance:

Hydrocodone Bitartrate (DMF (b) (4)):

Chlorpheniramine Maleate (DMF (b) (4)):

Pseudoephedrine Hydrochloride (DMF (b) (4)):

Reviewer name: Jean Q. Wu

Division name: Division of Pulmonary and Allergy Products

HFD #: 570

Review completion date: June 17, 2009

Drug:

Trade name: (b) (4) Oral Solution (Original: (b) (4) Oral Solution)

Generic name: Hydrocodone, Chlorpheniramine and Pseudoephedrine Oral Solution

Three active pharmaceutical ingredients (API) in the following list:

Generic Name: Hydrocodone bitartrate (HC)

Chemical name:

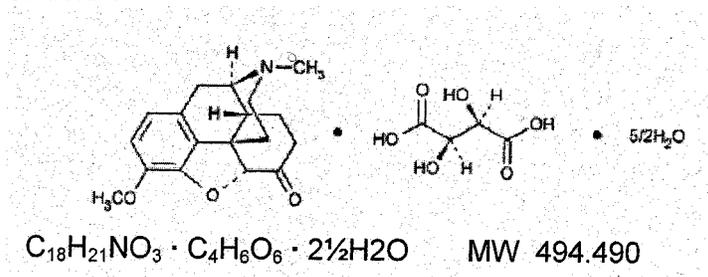
4,5(alpha)-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)

Molecular formula/MW: $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2 \frac{1}{2} H_2O/494.5$

Drug Class: Narcotic analgesic and antitussive

Related: NDA 19-111 (Tussionex® Suspension), NDA 5-213 (Hycodan® Tablets and Syrup), NDA 19-410 (Hycomine Syrup), DMF (b) (4)

Structure:



Generic Name: Chlorpheniramine Maleate (CPM)

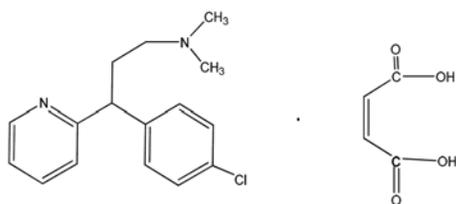
Chemical name: 2-[p-chloro-(alpha)-[2-(dimethylamino)ethyl]benzyl]pyridine maleate (1:1)

Molecular formula/MW: $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4/390.86$

Drug Class: Antihistamine

Related: NDA 21-441 (Advil Allergy Sinus, combination of chlorpheniramine maleate and pseudoephedrine HCl), NDA 19-111 (Tussionex® Suspension, combination of hydrocodone polistirex and chlorpheniramine polistirex), NDA 21-369 (Codeprex™, combination of chlorpheniramine and codeine), DMF (b) (4)

Structure:



Generic Name: Pseudoephedrine HCl

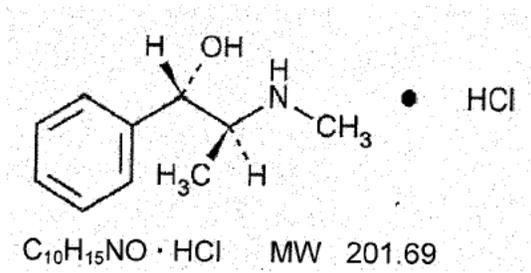
Chemical name: Benzenmethanol,-[1-(methylamino)ethyl]-,[S-(R*, R*)]-, hydrochloride

Molecular formula/MW: $C_{10}H_{15}NO \cdot HCl/201.7$

Drug Class: Nasal decongestant

Related: NDA 21-585 (Mucinex® D, guaifenesin with pseudoephedrine HCl), DMF (b) (4)

Structure:

**Relevant INDs/NDAs/DMFs:**

IND 102177 (Hydrocodone, Chlorpheniramine, and Pseudoephedrine Oral Solution)

Other relevant INDs/NDAs/DMFs are listed above with each relevant active ingredient.

Drug class:

Hydrocodone bitartrate --- narcotic analgesic and antitussive

Chlorpheniramine maleate --- antihistamine

Pseudoephedrine hydrochloride --- nasal decongestant (an alkaloid obtained from Ephedra spp.)

Intended clinical population: adults

(b) (4)

(b) (4)

Clinical formulation: The product is an oral solution (5 mL) containing 5 mg hydrocodone bitartrate, 4 mg chlorpheniramine maleate and 60 mg pseudoephedrine HCl per 5 mL. The composition and function of each component is shown below (excerpted from Module 2, Vol. 1. Section 2.3. P.1. page 5).

Table 2.3.P-1. Unit Composition of (b) (4) Oral Solution		Unit Composition		
Component	Reference to Quality Standards	Function	(b) (4)	
			% w/v	mg/480 mL
Hydrocodone Bitartrate	USP	Active ingredient	(b) (4) 1.0	480
Chlorpheniramine Maleate	USP	Active ingredient	0.8	384
Pseudoephedrine Hydrochloride	USP	Active ingredient	12.0	5760
Citric Acid, Anhydrous	USP	(b) (4)	(b) (4)	
Sodium Citrate	USP			
Sodium Saccharin	USP			
Methylparaben	NF			
Propylparaben	NF			
Sucrose	NF			
Glycerin (b) (4)	USP			
Propylene Glycol	USP			
Grape Flavor (b) (4)	In-house			
Water, Purified	USP			

NF = National Formulary.

Route of administration: Oral

Proposed use:

Recommended dose for adults (b) (4) :
 (b) (4) (5 mL) every 4-6 hours, NTE 4 doses in 24 hours

(b) (4)

Proposed dose/Age Group		Adult (b) (4)	(b) (4)
Hydrocodone	q 4-6 hr.	5 mg	(b) (4)
	NTE in 24 hr.	20 mg	
Pseudoephedrine	q 4-6 hr.	60 mg	
	NTE in 24 hr.	240 mg	
Chlorpheniramine	q 4-6 hr.	4 mg	
	NTE in 24 hr.	16 mg	

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: The sponsor intended to obtain approval through a 505(b)(2) application.

Studies reviewed within this submission: None

Studies not reviewed within this submission: None

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Not applicable (N/A)

2.6.2.2 Primary pharmacodynamics

N/A

2.6.2.3 Secondary pharmacodynamics

N/A

2.6.2.4 Safety pharmacology

N/A

2.6.2.5 Pharmacodynamic drug interactions

N/A

2.6.3 PHARMACOLOGY TABULATED SUMMARY

N/A

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

N/A

2.6.4.2 Methods of Analysis:

N/A

2.6.4.3 Absorption

N/A

2.6.4.4 Distribution

N/A

2.6.4.5 Metabolism

N/A

2.6.4.6 Excretion

N/A

2.6.4.7 Pharmacokinetic drug interactions

N/A

2.6.4.8 Other Pharmacokinetic Studies

N/A

2.6.4.9 Discussion and Conclusions

N/A

2.6.4.10 Tables and figures to include comparative TK summary

N/A

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

N/A

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

N/A

2.6.6.2 Single-dose toxicity

N/A

2.6.6.3 Repeat-dose toxicity

N/A

2.6.6.4 Genetic toxicology

N/A

2.6.6.5 Carcinogenicity

N/A

2.6.6.6 Reproductive and developmental toxicology

N/A

2.6.6.7 Local tolerance

N/A

2.6.6.8 Special toxicology studies

N/A

2.6.6.9 Discussion and Conclusions

N/A

2.6.6.10 Tables and Figures

N/A

2.6.7 TOXICOLOGY TABULATED SUMMARY

N/A

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusion:

Hydrocodone, Chlorpheniramine and Pseudoephedrine Oral Solution (Rx Only) contains hydrocodone bitartrate, chlorpheniramine maleate and pseudoephedrine hydrochloride in a 5-mL oral solution. This combination drug product is proposed as a prescription product. The application is submitted under the 505(b)(2) process. No preclinical pharmacology and toxicology studies were conducted with Hydrocodone, Chlorpheniramine and Pseudoephedrine Oral Solution. Each active ingredient is widely used in the US and is generally recognized as safe and effective.

Hydrocodone is a semisynthetic narcotic antitussive and analgesic with multiple actions qualitatively similar to those of codeine. The precise mechanism of action of hydrocodone and other opiates is not known; however, hydrocodone is believed to act directly on the cough center. Hydrocodone bitartrate is a recognized antitussive, with efficacy established in Drug Efficacy Study Implementation (DESI) Notice 5213, dated June 1, 1982. Hydrocodone bitartrate is not included in any OTC monograph and is available on a prescription (Rx only) basis. Currently, there are several approved formulations containing hydrocodone including Hycodan® (NDA 05-213, 1943) and Tussionex® (NDA 19-111, 1987). Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the recommended human dose (Label of Tussionex® Extended Release Suspension, Rev. 01/2008 1E). The maximum human dose of hydrocodone in Tussionex® is 10 mg q12h, equivalent to 20 mg hydrocodone per day. In excessive doses, hydrocodone, like other opium derivatives, will depress respiration. Hydrocodone can produce miosis, euphoria, and physical and psychological dependence. The approved dose in Hycodan® is shown in the table below.

Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. It has the potential for excitatory side effects (Mosby's Drug Consult™ 2005). Pseudoephedrine is recognized as an effective agent for the relief of nasal congestion due to allergic rhinitis, the common cold, hay fever, or other upper respiratory allergies, and nasal congestion associated with sinusitis (21 CFR 341.80). In animal studies, pseudoephedrine reduced average weight, length, and rate of skeletal ossification in the animal fetus (USP Convention. USPDI – Drug Information for the Health Care Professional. 16th edition Volume I, Rockville, MD: U.S. Pharmaceutical Convention, Inc. 1996 (Plus updates), pg. 2508.). The monograph recommended dose (21 CFR 341.80) is listed in the table below.

Chlorpheniramine is an antihistamine drug (H₁ receptor antagonist) that also possesses anticholinergic and sedative activity. It prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa (Mosby's Drug Consult™ 2006). The monograph recommended dose (21 CFR 341.72) is listed in the table below.

Chlorpheniramine combined with antitussive agents were approved in Tussionex® (Chlorpheniramine with Hydrocodone) and Codeprex™ Pennkinetic® Extended-Release Suspension (Chlorpheniramine and Codeine). Codeprex™ was approved on June 21, 2004 and withdrawn by the sponsor on February 21, 2007 (without a specified safety reason). The maximum human dose of chlorpheniramine in Codeprex™ was 8 mg q12 h, equivalent to 16 mg per day (Label of Codeprex™ 6/2004). According to the Label of Codeprex™ (6/2004), chlorpheniramine with oral doses up to approximately 20 and 25 times the maximum recommended daily dose for adults on a mg/m² basis produced no adverse developmental effects in pregnant rats and rabbits, respectively. However, when mice were dosed throughout pregnancy, an oral 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 10 mg/kg/day (approximately 5 times the maximum recommended daily dose for adults on a mg/m² basis) prior to mating. In rats and rabbits, oral doses of chlorpheniramine maleate up to approximately 20 to 25 times the human dose on a mg/m² basis, respectively, did not impair fertility.

The National Toxicology Program (NTP) studies with chlorpheniramine maleate were reported in Technical Report No. TR-317 (September 1986) entitled with “Toxicology and Carcinogenesis Studies of Chlorpheniramine Maleate (CAS No. 113-92-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies).” The report concluded that there was no evidence of carcinogenicity for F344/N rats or B6C3F1 mice of either sex administered chlorpheniramine maleate in deionized water, 5 days per week for 2 years at oral doses up to 30-60 mg/kg or 25- 50 mg/kg/day. However, due to high mortality in high dose female rats and high dose male mice, the sensitivity of these groups to detect a carcinogenic response was reduced. In the introduction section, this report also summarized that chlorpheniramine maleate was not mutagenic in bacteria (*salmonella typhimurium*) in the presence or absence of metabolic activation, and was negative in the L5178Y mouse lymphoma forward mutation assay at the TK locus. Chlorpheniramine induced a weak but reproducible increase in sister-chromatid exchanges in the absence of metabolic activation which was not observed in the presence of metabolic activation. In the CHO cells, an increase in chromosomal aberration was not observed in the absence of metabolic activation but was present in the presence of metabolic activation at the highest dose which was toxic or nearly toxic (no details provided).

Oral LD₅₀ values for chlorpheniramine maleate were 130, 306, and 198 mg/kg in mice, rats, and guinea pigs, respectively (NTP Chemical Repository, Catalog ID No. 000676).

Doses recommended in Monographs/approved products		Adults and children 12 years of age and over	Children 6 to12 years of age
Hydrocodone (in Hycodan®)	q 4-6 hr.	5 mg	2.5 mg
	NTE in 24 hr.	30 mg	15 mg
Pseudoephedrine	q 4-6 hr.	60 mg	30 mg
	NTE in 24 hr.	240 mg	120 mg
Chlorpheniramine	q 4-6 hr.	4 mg	2 mg
	NTE in 24 hr.	24 mg	12 mg

The recommended dosage of each active ingredient for this NDA is within the dose ranges recommended in OTC monographs and the approved products. The OTC monograph 21 CFR 341.40 recognizes the combination of any single monograph oral antitussive drug (such as codeine phosphate) with any single monograph antihistamine and any single monograph nasal decongestant. Although hydrocodone is not an OTC monograph antitussive, hydrocodone combination product containing monograph active ingredients has been accepted based on the precedent (Tussionex®, NDA 19-111).

(b) (4) was identified as an impurity in the drug substance, chlorpheniramine maleate (DMF (b) (4)). Chlorpheniramine maleate from the same manufacturer (DMF (b) (4)) was one of the active drug components in Codeprex™. However, (b) (4) was not addressed as a structural alert for genotoxicity in the review process of Codeprex™. A consultation for genotoxic potential of (b) (4) was requested by the chemist reviewer in this NDA and was responded in the Pharmacology/Toxicology Review dated May 20, 2009 and its addendum dated May 26, 2009. The sponsor was requested to reduce the level of (b) (4) to NMT (b) (4)/day, or conduct a bacterial reverse mutation assay to qualify the proposed specification (see details in the Pharmacology/Toxicology Review and Addendum for this consultation, and the Chemistry Review for this NDA).

(b) (4) as an impurity in hydrocodone bitartrate manufactured in DMF (b) (4), was identified as a potential structural alert by the chemist. An evaluation of (b) (4) originated from DMF (b) (4) was completed by Dr. Marcus S. Delatte of Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) dated May 22, 2009 and concluded with a note of tertiary review that (b) (4) was considered as a non-genotoxic impurity and should be regulated as a general impurity per ICH Q3A guidance. In this NDA, the specification of (b) (4) is not provided by the sponsor. However, according to the chemist, (b) (4) is not required to be reported since it is present in the historical lots at levels (b) (4) much lower than the reporting threshold (0.05%) set in ICH Q3A guidance (see details in the Chemistry Review for this NDA).

Unresolved toxicology issues (if any): None

Recommendations: From a preclinical perspective, approval is recommended for the application pending a labeling review.

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

/s/

Jean Wu
6/17/2009 12:03:12 PM
PHARMACOLOGIST

Molly Shea
6/17/2009 12:24:25 PM
PHARMACOLOGIST
I concur.

**PHARMACOLOGY/TOXICOLOGY REVIEW
FOR CHEMISTRY CONSULTATION REQUEST
ADDENDUM 1**

NDA number: 22-439 (b) (4)
Request date:/Type of Request: August 8, 2007/Safety-General
Requested by: ONDQA/DPA1/Branch II
Information to sponsor: Yes (X) No ()
Sponsor and/or agent: Cypress Pharmaceuticals, Inc.

Reviewer name: Jean Q. Wu, MD, PhD
Division name: Division of Pulmonary and Allergy Products
HFD #: 570
Review completion date: May 26, 2009

Drug:
NDA 22-439
Trade name: (b) (4) Oral Solution
Active Drug: Hydrocodone Bitartrate, Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride

(b) (4)

Relevant INDs/NDAs/DMFs: IND 102177 (Hydrocodone, Chlorpheniramine and Pseudoephedrine Oral Solution), (b) (4)
(b) (4) NDA 21-369 (Codeprex™), DMF (b) (4) (chlorpheniramine maleate)

Drug class: Hydrocodone --- antitussive and opioid analgesic
Chlorpheniramine maleate--- antihistamine (H₁ receptor antagonist)
Pseudoephedrine hydrochloride --- nasal decongestant
(b) (4)

Intended clinical population: (b) (4) Adults (b) (4)
(b) (4)

Clinical formulation:
NDA 22-439: The product is an oral solution, which contains hydrocodone bitartrate (HC) 5 mg, chlorpheniramine maleate (CPM) 4 mg and pseudoephedrine (PSE) hydrochloride 60 mg per 5 mL.

(b) (4)

Intended Dosage:

NDA 22-439

For adults (b) (4):

(b) (4) (5 mL: 5 mg HC/4 mg CPM/60 mg PSE) every 4-6 hours, NTE 4 doses (20 mL) in 24 hours

(b) (4)

(b) (4)

Consultation requested:

This chemistry consult was requested by the review chemists, Xiaobin Shen, PhD (NDA 22-439) and Sheldon Markofsky, PhD (b) (4) for the safety evaluation of one identified impurity, (b) (4) ((b) (4) structure shown below) of chlorpheniramine maleate manufactured (DMF (b) (4)) at the latest specification level of (b) (4) in drug substance. The chemist identified (b) (4) as a potential structural alert for genotoxicity. As clarified with the chemist (Xiaobin Shen) in the Email of May 18, 2009, (b) (4) its specification in drug product is not applicable.

(b) (4)

Notes for Evaluation

As indicated in the original Consultation Review (finalized on May 20, 2009), the threshold of toxicological concern for genotoxic impurities in a marketed product has been identified as (b) (4)/day (draft FDA Guidance for Industry, Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches, December 2008). For the proposed maximum dose of Chlorpheniramine Maleate (16 mg per day) in the current drug products ((b) (4) NDA 22-439 (b) (4)), the daily intake for (b) (4) would be (b) (4) in drug

substance, and was not considered acceptable. Based on an updated discussion regarding *in vitro* assays required to qualify the potential genotoxic impurities, Dr. David Jacobson-Kram, Associate Director of Pharmacology Toxicology (OND CDER), indicated that one bacterial reverse mutation assay would be sufficient in the Pharmacology and Toxicology Coordinating Committee (PTCC) monthly meeting on May 21, 2009 (conveyed by Dr. Molly Shea who attended the PTCC meeting). In the email followed on May 22, 2009, Dr. David Jacobson-Kram confirmed that a bacterial reverse mutation assay only was considered sufficient to qualify the identified impurity in this case. Therefore, the sponsor should be requested to reduce the level of (b) (4) to NMT (b) (4)/day, or conduct a bacterial reverse mutation assay to qualify the proposed specification. A computational toxicology service for genotoxicity endpoints evaluation of this impurity is being requested for additional information.

Recommendation:

(b) (4) is identified as a potential structural alert for genotoxicity. The sponsor should be requested to reduce the level of (b) (4) to NMT (b) (4)/day, or conduct a bacterial reverse mutation assay to qualify the proposed specification.

Convey the following information to the sponsor.

Draft letter to the sponsor:

(b) (4) in one of the drug substances, Chlorpheniramine Maleate, is identified as a potential structural alert for genotoxicity. Reduce the level of (b) (4) NMT (b) (4) day, or conduct a bacterial reverse mutation assay to qualify the proposed specification.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS**Appendix 1: Request for Consultation**

Appendix 1

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION	
TO (Division/Office): PharmTox Review Team (Dr. Jean Wu/Dr. Molly Shea)		FROM: Sheldon Markofsky, Ph.D. and Xiaobin Shen, Ph.D. CMC Reviewers, DPAP in ONDQA/DPA1/Branch 2	
DATE: Apr. 14, 2009	NDA: 22-439 (b) (4)	TYPE OF DOCUMENT: NDA	DATE OF DOCUMENT 6-Nov-2008 to 17-Nov-2008
NAME OF DRUG (b) (4)	PRIORITY CONSIDERATION: S	CLASSIFICATION OF DRUG: 3	DESIRED COMPLETION DATE: May 30, 2009
NAME OF FIRM: Cypress Pharmaceuticals, Inc.			
REASON FOR REQUEST: (b) (4) of chlorpheniramine maleate manufactured based DMF (b) (4) is a potential structural alert. Please evaluate if it is genotoxic and determine the maximum allowable level in the drug substance.			
COMMENTS/SPECIAL INSTRUCTIONS: Additional information that may help you research — (b) (4)			
The latest specification (received by CDER on 09/26/2008) in DMF (b) (4) is (b) (4); The level of (b) (4) reported in three representative lots (relevant DMF pages were received by CDER on 05/19/2005) are all (b) (4).			
Xiaobin.			

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

/s/

Jean Wu
5/26/2009 02:11:40 PM
PHARMACOLOGIST

Molly Shea
5/26/2009 02:36:08 PM
PHARMACOLOGIST
I concur with the addendum.



FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology Products
10903 New Hampshire Avenue, Silver Spring, MD 20993

PHARMACOLOGY TOXICOLOGY REVIEW

Date: May 21, 2009

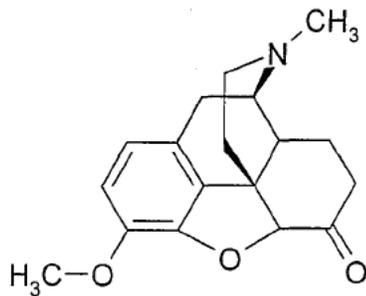
To: [Redacted] (b) (4)

From: Marcus S. Delatte, Ph.D.
Pharmacology/Toxicology Reviewer, DAARP
(HFD-170)

Through: R. Daniel Mellon, Ph.D.
Supervisory Pharmacologist, DAARP (HFD-170)

Subject: Amendments dated April 17, 2009 for: [Redacted] (b) (4)

Background: The DMF holder [Redacted] (b) (4) that provides this drug substance has identified [Redacted] (b) (4) impurity in hydrocodone drug substance. [Redacted] (b) (4)



Hydrocodone

The DMF holder conducted two genetic toxicity studies for the impurity (b) (4) which were reviewed previously.

1. (b) (4) Bacterial Reverse Mutation Assay (Study Report № AA85YF.503.BTL).
2. (b) (4) In Vitro Mammalian Chromosome Aberration Test (Study Report № AA85YF.341.BTL).

Following review of the above studies, the in vitro chromosome aberrations assay was deemed inadequate; therefore a deficiency letter was sent to the DMF holder.

Excerpt from Deficiency Letter dated March 13, 2009:

The submitted in vitro chromosome aberration assay (Study number AA85YF.341.BTL) did not adequately characterized the cytogenetic potential of (b) (4), a potential drug substance impurity (b) (4). Therefore, you should either repeat the in vitro study (b) (4) or conduct an in vivo genetic toxicology study in order to complete the genetic toxicology safety qualification for (b) (4).

In their submission dated April 17, 2009, the DMF holder addresses the nonclinical pharmacology toxicology deficiency, specifically the safety qualification for (b) (4).

Sponsor's response (summarized): As noted in the submission, on January 29, 2004 (b) (4) met with the Agency and agreed to evaluate (b) (4) using in vitro genetic toxicity assays (e.g., Ames test and chromosomal aberration test). The doses used in these studies were selected based on established regulatory guidelines and (b) (4) standard operating procedures. In both assays, (b) (4) was reported to be nonmutagenic at the doses selected; however, scoring in the chromosomal aberration test was precluded (b) (4).

(b) (4)

Primary Reviewer Conclusion: The Reviewer does not concur with (b) (4) suggestion, (b) (4)

(b) (4) This is supported by evidence (b) (4)

Therefore, in order to complete the genetic toxicology safety qualification for (b) (4)

[REDACTED] (b) (4) should either repeat the in vitro study [REDACTED] (b) (4) or conduct an in vivo genetic toxicology study.

NOTE REGARDING TERTIARY REVIEW AND FINAL CONCLUSION: Following further discussion of this case with Dr. David Jacobson-Kram, Associate Director of Pharmacology Toxicology (OND CDER), [REDACTED] (b) (4) has been deemed evidence of toxicity and therefore, the highest concentrations tested in the already completed assay are deemed to be the maximum feasible concentrations. As such, Dr. Jacobson-Kram deems these studies valid (see Attachment 1). Therefore, the Agency considers [REDACTED] (b) (4) to have been adequately tested and deemed negative in a minimal genetic toxicology screen. In terms of genotoxic potential, this impurity can be considered as a non-genotoxic impurity and regulated as per ICH Q3A.

Reference List



Attachment 1:

Mellon, Dan

From: Jacobson-Kram, David
Sent: Thursday, May 21, 2009 11:53 AM
To: Mellon, Dan
Cc: Brown, Paul C
Subject: RE: Request tertiary input re [REDACTED] (b) (4)

It appears that [REDACTED] (b) (4) is precluding evaluation of metaphases at the ICH specified level of toxicity. However, some toxicity is present at lower concentrations and the material does not appear to be clastogenic. My recommendation is to accept the study as is and consider the highest scorable dose at the maximal feasible concentration.

David Jacobson-Kram, Ph.D., D.A.B.T.
Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-0175
Fax: 301-796-9856
email: david.jacobsonkram@fda.hhs.gov

Linked Applications

Sponsor Name

Drug Name / Subject

(b) (4)

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/s/

MARCUS S DELATTE

05/22/2009

Via phone conversation with Art Shaw, MSD verified that the Quality Response to DMFs [REDACTED] was submitted on April 20th and recieved on April 22.

(b) (4)

RICHARD D MELLON

05/22/2009

**PHARMACOLOGY/TOXICOLOGY REVIEW
FOR CHEMISTRY CONSULTATION REQUEST**

NDA number: 22-439 (b) (4)

Request date:/Type of Request: August 8, 2007/Safety-General

Requested by: ONDQA/DPA1/Branch II

Information to sponsor: Yes (X) No ()

Sponsor and/or agent: Cypress Pharmaceuticals, Inc.

Reviewer name: Jean Q. Wu, MD, PhD

Division name: Division of Pulmonary and Allergy Products

HFD #: 570

Review completion date: May 20, 2009

Drug:

NDA 22-439

Trade name: (b) (4) Oral Solution

Active Drug: Hydrocodone Bitartrate, Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride

(b) (4)

Relevant INDs/NDAs/DMFs: IND 102177 (Hydrocodone, Chlorpheniramine and Pseudoephedrine Oral Solution), (b) (4)

(b) (4) NDA 21-369 (Codeprex™), DMF (b) (4) (chlorpheniramine maleate)

Drug class: Hydrocodone --- antitussive and opioid analgesic
Chlorpheniramine maleate--- antihistamine (H₁ receptor antagonist)
Pseudoephedrine hydrochloride --- nasal decongestant

(b) (4)

Intended clinical population: (b) (4) Adults (b) (4)

(b) (4)

Clinical formulation:

NDA 22-439: The product is an oral solution, which contains hydrocodone bitartrate (HC) 5 mg, chlorpheniramine maleate (CPM) 4 mg and pseudoephedrine (PSE) hydrochloride 60 mg per 5 mL.

(b) (4)

Intended Dosage:

NDA 22-439

For adults (b) (4):

(b) (4) (5 mL: 5 mg HC/4 mg CPM/60 mg PSE) every 4-6 hours, NTE 4 doses (20 mL) in 24 hours

(b) (4)

(b) (4)

Consultation requested:

This chemistry consult was requested by the review chemists, Xiaobin Shen, PhD (NDA 22-439) and Sheldon Markofsky, PhD (b) (4) for the safety evaluation of one identified impurity, (b) (4) ((b) (4) structure shown below) of chlorpheniramine maleate manufactured (DMF (b) (4)) at the latest specification level of (b) (4) in drug substance. The chemist identified (b) (4) as a potential structural alert for genotoxicity. As clarified with the chemist (Xiaobin Shen) in the Email of May 18, 2009, (b) (4) its specification in drug product is not applicable.

(b) (4)

Evaluation

(b) (4) was identified as an impurity in one of the drug substances, chlorpheniramine maleate (DMF (b) (4)). Chlorpheniramine maleate from the same manufacturer (DMF (b) (4)) was one of the active drug components in the product Codeprex™ Pennkinetic® Extended-Release Suspension which was approved on June 21, 2004 and withdrawn by the sponsor on February 21, 2007 (without a specified safety reason). However (b) (4) was not addressed as a structural alert for genotoxicity in Codeprex™. It is not known if other chlorpheniramine DMFs have the same impurity (Email communication with Dr. Xiaobin Shen of April 9, 2009). The threshold of toxicological concern for genotoxic

impurities in a marketed product has been identified as (b) (4) day (draft FDA Guidance for Industry, Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches, December 2008). For the proposed maximum dose of Chlorpheniramine Maleate (16 mg per day) in the current drug product (b) (4) NDA 22-439 (b) (4) the daily intake for (b) (4) would be (b) (4) in drug substance, and was not considered acceptable. The sponsor should be requested to reduce the level of (b) (4) to NMT (b) (4) day, or conduct a bacterial reverse mutation assay and a chromosomal aberration assay to qualify the proposed specification.

Recommendation:

(b) (4) is identified as a potential structural alert for genotoxicity. The sponsor should be requested to reduce the level of (b) (4) to NMT (b) (4) day, or conduct a bacterial reverse mutation assay and a chromosomal aberration assay to qualify the proposed specification.

Convey the following information to the sponsor.

Draft letter to the sponsor:

(b) (4) in one of the drug substances, Chlorpheniramine Maleate, is identified as a potential structural alert for genotoxicity. Reduce the level of (b) (4) to NMT (b) (4)/day, or conduct a bacterial reverse mutation assay and a chromosomal aberration assay to qualify the proposed specification.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

Appendix 1: Request for Consultation

Appendix 1

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION	
TO (Division/Office): PharmTox Review Team (Dr. Jean Wu/Dr. Molly Shea)		FROM: Sheldon Markofsky, Ph.D. and Xiaobin Shen, Ph.D. CMC Reviewers, DPAP in ONDQA/DPA1/Branch 2	
DATE: Apr. 14, 2009	NDA: 22-439 (b) (4)	TYPE OF DOCUMENT: NDA	DATE OF DOCUMENT 6-Nov-2008 to 17-Nov-2008
NAME OF DRUG (b) (4)	PRIORITY CONSIDERATION: S	CLASSIFICATION OF DRUG: 3	DESIRED COMPLETION DATE: May 30, 2009
NAME OF FIRM: Cypress Pharmaceuticals, Inc.			
REASON FOR REQUEST: (b) (4) of chlorpheniramine maleate manufactured based DMF (b) (4) is a potential structural alert. Please evaluate if it is genotoxic and determine the maximum allowable level in the drug substance.			
COMMENTS/SPECIAL INSTRUCTIONS: Additional information that may help you research — (b) (4)			
The latest specification (received by CDER on 09/26/2008) in DMF (b) (4) is (b) (4); The level of (b) (4) reported in three representative lots (relevant DMF pages were received by CDER on 05/19/2005) are (b) (4).			
Xiaobin.			

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/s/

Jean Wu
5/20/2009 04:16:54 PM
PHARMACOLOGIST

Molly Shea
5/20/2009 06:02:55 PM
PHARMACOLOGIST
I concur.