CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22442Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 22-442
Supporting document/s:	#18 (Resubmission); 21
Applicant's letter date:	Dec. 8, 2010; May 3, 2011
CDER stamp date:	Dec. 8, 2010; May 3, 2011
Product:	REZIRA (Hydrocodone and Pseudoephedrine) Oral Solution
Indication:	Relief of cough and nasal congestion associated with the common cold
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 22-442 are owned by Cypress Pharmaceuticals, Inc. or are data for which NDA 22-442 has obtained a written right of reference.
Any information or data necessary for approval of NDA 22-442 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 22-442.

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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.

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

Under Section 13.1, one minor change was made.

Suggested Labeling sent to the Sponsor:

2 pages of draft labeling has been withheld in full as B(4) 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 22-442
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 22-442 was submitted under the 505(b)(2) process for the combination drug product Hydrocodone and Pseudoephedrine Oral Solution on November 7, 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 monograph 21 CFR 341.20 for pseudoephedrine hydrochloride for safety assessments supporting approval. 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 11, 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-22442	ORIG-1	CYPRESS PHARMACEUTICAL INC	REZIRA-(b)(4)(HYDROCODONE BITARTRATE AND PSEU

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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 22-442
Supporting document/s:	#11
Applicant's letter date:	December 10, 2009
CDER stamp date:	December 11, 2009
Product:	REZIRA Oral Solution (Hydrocodone and Pseudoephedrine Oral Sollution)
Indication:	Relief of cough and nasal congestion associated with the common cold
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

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Any information or data necessary for approval of NDA 22-442 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 22-442.

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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.

(b) (4)

(b) (4)

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22442	ORIG-1	CYPRESS PHARMACEUTICAL INC	REZIRA (b)(4) (HYDROCODONE BITARTRATE AND PSEU

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/s/

GRACE S LEE
05/03/2010

MOLLY E SHEA
05/03/2010

INTEROFFICE MEMO

TO: NDA 22-442
Sequence number/date/type of submission:
#000/November 7, 2008/original NDA

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

DATE: June 22, 2009

NDA 22-442 was submitted under the 505(b)(2) process for the combination drug product Hydrocodone and Pseudoephedrine Oral Solution on November 7, 2008. No nonclinical studies were submitted for review for either the individual monoproducts or the combination drug product. The sponsor (Cypress Pharmaceutical, 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 monograph 21 CFR 341.20 for 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.

Cypress provided a Letter of Authorization from (b) (4), the hydrocodone drug substance manufacturer, allowing the Agency to review the drug master file for hydrocodone (DMF (b) (4) in relation to this NDA. On May 22, 2009, Dr. Marcus S. Delatte of Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) completed the toxicology review of DMF (b) (4) for (b) (4) e and concluded that (b) (4) is not a genotoxic impurity with the concurrence of the Genetic Toxicology Tertiary Review Committee. Therefore, the issue of genotoxic potential for (b) (4) in DMF (b) (4) has been resolved and is not an approvability issue for this NDA.

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 11:44:37 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:	**22-442**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**November 7, 2008**
PRODUCT:	**REZIRA™ Oral Solution (Hydrocodone Bitartrate, and Pseudoephedrine Hydrochloride)**
INTENDED CLINICAL POPULATION:	**Adults** (b) (4) **who need** (b) (4) **relief of cough and** (b) (4) **relief of nasal congestion due to the common cold**
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

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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 REZIRA™ 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 active ingredient, pseudoephedrine, is a recognized OTC monograph drug (21 CFR 341.20) and is generally recognized as safe and effective. 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.

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 22-442
Review number: 001
Sequence number/date/type of submission: 000/November 7, 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) (b) (4)

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

Reviewer name: Jean Q. Wu
Division name: Division of Pulmonary and Allergy Products
HFD #: 570
Review completion date: June 17, 2009

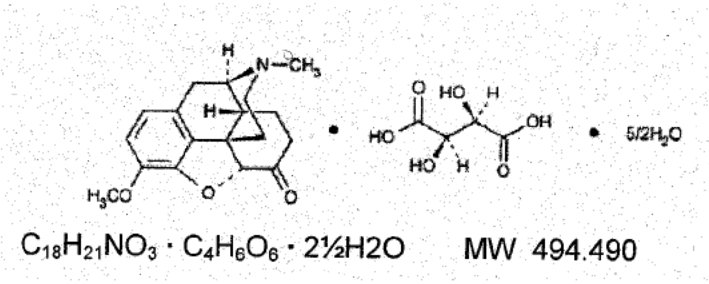
Drug:

Trade name: REZIRA™ Oral Solution (Original: REZIRA (b) (4) Oral Solution)
Generic name: Hydrocodone and Pseudoephedrine Oral Solution

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

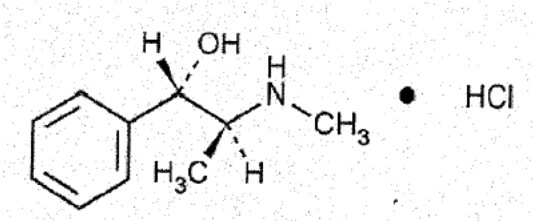
Generic Name: Hydrocodone bitartrate (HC)
Chemical name:
4,5(alpha)-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)
Molecular formula/MW: $C_{18}H_{21}NO_3 .C_4H_6O_6 .2\ ½\ H_2O$/494.5
Drug Class: Narcotic analgesic and antitussive

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



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2½H2O$ MW 494.490

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:



$C_{10}H_{15}NO \cdot HCl$ MW 201.69

Relevant INDs/NDAs/DMFs:
IND 102177 (Hydrocodone, Chlorpheniramine, and Pseudoephedrine Oral Solution)
NDA 22-439 (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
Pseudoephedrine hydrochloride --- nasal decongestant (an alkaloid obtained from Ephedra spp.)

Intended clinical population: adults (b) (4) who need (b) (4) relief of cough and (b) (4) relief of nasal congestion due to the common cold.

Clinical formulation: The product is an oral solution (5 mL) containing 5 mg hydrocodone bitartrate 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 REZIRA (b) (4) Oral Solution						
Component	Reference to Quality Standards	Function	Unit Composition			
			% w/v	mg/mL	mg/15 mL	mg/480 mL
Hydrocodone Bitartrate	USP	Active ingredient				(b) (4)
Pseudoephedrine Hydrochloride	USP	Active ingredient				
Citric Acid, Anhydrous	USP					
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:

(b) (4)

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 and Pseudoephedrine Oral Solution (Rx Only) contains hydrocodone bitartrate 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 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 314.80) is listed in the table below.

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

The recommended dosage of each active ingredient for this NDA is within the dose range 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 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) 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 tertiary review note 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, the (b) (4) as a general impurity, 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.

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/s/

Jean Wu
6/17/2009 10:15:47 AM
PHARMACOLOGIST

Molly Shea
6/17/2009 11:53:30 AM
PHARMACOLOGIST
I concur.

[redacted] EVALUATION MEMORANDUM

TO: NDA 22439, [redacted] AND 22442

FROM: Xiaobin Shen, Ph.D., Reviewer, Branch II, Division I, ONDQA

SUBJECT: Evaluation of [redacted] in DMF [redacted]

DATE: 5/27/2009

CC: Prasad Peri, Ph.D., Pharmaceutical Assessment Lead, Branch II, Division I, ONDQA
Ali, Al Hakim, Ph.D., Branch Chief, Branch II, Division I, ONDQA

Impurity [redacted] present in hydrocodone bitartrate manufactured in DMF [redacted] was identified as a potential structural alert in the review of the NDAs referenced above. A pharmtox consult request was made via email routing for the evaluation of [redacted] as potential structural alert.

At the same time, the evaluation of [redacted] originated from DMF [redacted] took place in the DAARP division. The evaluation results deemed [redacted] as not genotoxic, hence there is no need for Pharmtox in the DPAP division to complete the consult request.

The original consult request and the DAARP evaluation report for [redacted] is attached to this memo to capture the decision making process.

Xiaobin Shen, Ph.D.
Reviewer, Branch II, Division I, ONDQA

-DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**REQUEST FOR CONSULTATION**
TO *(Division/Office)*: **PharmTox Review Team (Dr. Virgil Whitehurst)**		FROM: **Xiaobin Shen, Ph.D.** **CMC Reviewer, DPAP in ONDQA/DPA1/Branch 2**	
DATE: **Mar. 12, 2008**	NDA: **22439, (b) (4) and 22442**	TYPE OF DOCUMENT: NDA	DATE OF DOCUMENT 6-Nov-2008 to 18-Nov-2008
NAME OF DRUG **REZIRA, (b) (4) and (b) (4)**	PRIORITY CONSIDERATION: S	CLASSIFICATION OF DRUG: 3	DESIRED COMPLETION DATE May 30, 2009
NAME OF FIRM: **Cypress Pharmaceuticals, Inc.**			
REASON FOR REQUEST: Evaluation of The safety of the levels of (b) (4) impurity exists in the drug substance hydrocodone bitartrate used in the three NDAs at up to (b) (4)			
COMMENTS/SPECIAL INSTRUCTIONS: See below. All three NDAs are in EDR. The relevant pages are shown attached. Thanks! Xiaobin.			

5 pages has been withheld in full as B(4) CCI/ TS immediately following this page

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

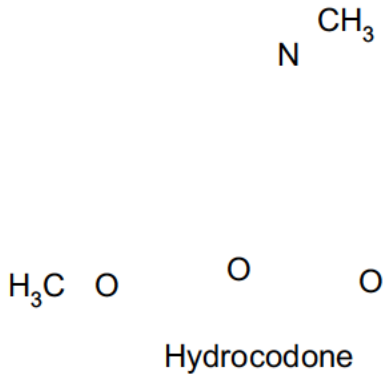
To: DMF (b) (4) (Hydrocodone, (b) (4)
DMF (b) (4) (Hydrocodone, (b) (4)
DMF (b) (4) (Hydrocodone, (b) (4)

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:
DMF (b) (4) hydrocodone bitartrate (SDN 235),
DMF (b) (4) for hydrocodone alkaloid (SDN 15), and
DMF (b) (4) for hydrocodone polistirex (SDN 12).

Background: The DMF holder ((b) (4) (b) (4) that provides this drug substance has identified (b) (4) as a process impurity in hydrocodone drug substance. (b) (4) contains (b) (4) which is a structural alert for mutagenicity. The chemical structures for hydrocodone and (b) (4) are depicted in the diagram below with the (b) (4)



Hydrocodone

(b) (4)

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, due to the presence of (b) (4) Therefore, you should either repeat the in vitro study using a cell line that does not result in confounding (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 by (b) (4) at doses that produced (b) (4) cytotoxicity. (b) (4) explained that (b) (4) is known to cause apoptosis, which is characterized by blebbing, cell shrinkage and chromatin condensation; and suggested that the chromosomal condensation is not specific to the cell line used. Based on this information, (b) (4) suggested that this phenomenon would likely occur across cell lines and asked that the Agency agree that further testing is not needed.

Primary Reviewer Conclusion: The Reviewer does not concur with (b) (4) suggestion, based on the lack of experimental evidence demonstrating that (b) (4) produces chromosomal condensation in multiple cell lines at cytotoxic concentrations. This is supported by evidence that (b) (4) reportedly produces various effects such as (b) (4) which has not been observed across cell lines at cytotoxic concentrations (Hitosugi N, et al., 2003; Kawase M, et al., 2002; Takeuchi R, et al., 2005a). (b) (4) Findings that the effects of (b) (4) are not necessarily observed across cell lines support the Agency's suggestion that (b) (4) use another cell line if the chromosomal aberration test is repeated. Therefore, in order to complete the genetic toxicology safety qualification for (b) (4)

(b) (4) should either repeat the in vitro study using a cell line that does not result in confounding (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), the excessive chromosomal condensation 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 (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

(b) (4)

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: (b) (4)

It appears that (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
MF (b) (4)	(b) (4)	HYDROCODONE BITARTRATE-MFGR (b) (4) (b) (4) (b) (4) (b) (4)
MF (b) (4)	(b) (4)	
MF (b) (4)	(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 (b) (4) and (b) (4) was submitted on April 20th and recieved on April 22.

RICHARD D MELLON
05/22/2009

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

/s/

Xiaobin Shen
5/27/2009 01:15:53 PM
PHARMACIST

Ali Al-Hakim
5/27/2009 01:20:39 PM
CHEMIST