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RESEARCH**

APPLICATION NUMBER:
204307Orig1s000

PHARMACOLOGY REVIEW(S)

INTEROFFICE MEMO

TO: NDA 204-307
Original Submission
Hydrocodone bitartrate/Chlorpheniramine maleate Oral Solution
(Proprietary Name to be determined)

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

DATE: August 2, 2012

NDA 204-307 was submitted under the 505(b)(2) process for the combination drug product Hydrocodone and Chlorpheniramine Oral Solution on April 24, 2012. Dr. Carol Rivera-Lopez 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 their previously approved NDA 22-439 for the triple combination product Hydrocodone, Chlorpheniramine and Pseudoephedrine Oral Solution approved on June 8, 2011. NDA 22-439 referenced the individual monoproducts, 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 for chlorpheniramine maleate, 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.

Dr. Carol Rivera-Lopez reviewed the nonclinical sections (8.1, 8.3, 10.1, 13.1, and 13.2) of the proposed label for this NDA (NDA 204-307) and concluded that no changes to the proposed labeling are needed as these sections are appropriate for the proposed doses of each monoproduct and the label for hydrocodone and chlorpheniramine is identical to the previously approved label for NDA 22439. I concur with Dr Rivera-Lopez's conclusions.

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

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/s/

MOLLY E SHEA

08/02/2012

I concur.

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 204-307
Supporting document/s: SDN 0
Applicant's letter date: April 23, 2012
CDER stamp date: April 24, 2012
Product: Hydrocodone bitartrate and chlorpheniramine
maleate oral solution
Indication: Relief of cough associated with common cold
and relief of symptoms associated with upper
respiratory allergies.
Applicant: Cypress Pharmaceutical, Inc.
Review Division: Division of Pulmonary, Allergy, and
Rheumatology Products (DPARP)
Reviewer: Carol M. Rivera-Lopez, Ph.D.
Supervisor/Team Leader: Molly E. Shea, Ph.D.
Division Director: Badrul A. Chowdhury, M.D., Ph.D.
Project Manager: Leila Hann

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 204-307 are owned by Cypress Pharmaceutical, Inc. or are data for which Cypress Pharmaceutical, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 204-307 that Cypress Pharmaceutical, 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 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 204-307.

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1 Executive Summary

1.1 Introduction

This review evaluates nonclinical information to support safety of hydrocodone bitartrate and chlorpheniramine maleate. Cypress Pharmaceutical, Inc. submitted a 505(b)(2) New Drug Application (NDA) on April 23, 2012 for hydrocodone bitartrate and chlorpheniramine maleate (5 mg and 4 mg per 5 mL, respectively) oral solution. The proposed indication is relief of cough associated with common cold and symptoms associated with upper respiratory allergies. The proposed product is identical to the approved Zutripro[®] Oral Solution (Cypress NDA 22-439 approved on June 8, 2011), except for the absence of pseudoephedrine hydrochloride. Cypress had also submitted NDA 22-442 for Rezira[®] Oral Solution (hydrocodone bitartrate and pseudoephedrine hydrochloride, 5 mg and 4 mg per 5 mL, respectively), which is similar to Zutripro[®], except for the absence of chlorpheniramine maleate.

Hydrocodone is a semisynthetic narcotic antitussive and analgesic with multiple actions qualitatively similar to those of codeine. The precise mechanism of action of hydrocodone is not known; however, hydrocodone is believed to act directly on the cough center. Chlorpheniramine is an antihistamine (H₁ receptor antagonist) that also possesses anticholinergic and sedative activity. It prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa.

Hydrocodone bitartrate has been used clinically for over 50 years, demonstrating an acceptable safety profile in humans. It has been marketed as Hycodan[®] (Endo Pharmaceuticals, Inc. NDA 005213 approved on March 23, 1943). Regarding chlorpheniramine maleate, it was developed in line with the OTC monograph under 21CFR 341.12. In addition, Cypress conducted a single-dose, randomized, 4-period, 4-treatment, crossover study under fasting conditions to determine the relative bioavailability of hydrocodone, pseudoephedrine, and chlorpheniramine in Zutripro[®] Oral Solution. The results pertaining to hydrocodone and chlorpheniramine are applicable to this NDA and will be used to support approvability of this product.

1.2 Brief Discussion of Nonclinical Findings

No nonclinical pharmacology or toxicology studies were conducted with the proposed hydrocodone bitartrate and chlorpheniramine maleate oral solution. The toxicology profiles of hydrocodone bitartrate and chlorpheniramine maleate, the active ingredients, are well characterized. The nonclinical safety of hydrocodone bitartrate is supported by the reference drug Zutripro[®] Oral Solution (NDA 22-439 approved on June 8, 2011), which in turn references the Hycodan[®] Syrup (NDA 005213 approved on March 23, 1943). The nonclinical safety of chlorpheniramine maleate is demonstrated by the OTC monograph under 21CFR 341.12.

1.3 Recommendations

1.3.1 Approvability

From the nonclinical pharmacology/toxicology perspective, NDA 204-307 is recommended for approval.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

The labeling submitted by Cypress mirrors the approved labeling for NDA 22-439 (Zutripro[®] Oral Solution), except for the absence of information on pseudoephedrine hydrochloride. The following nonclinical sections were reviewed to verify that the language mirrors the June 8, 2011 approved labeling for Zutripro[®] Oral Solution. No changes are suggested.

(b) (4)

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

2 Drug Information

2.1 Drug

CAS Registry Number:

Hydrocodone bitartrate: 34195-34-1

Chlorpheniramine maleate: 113-92-8

Generic Name: hydrocodone bitartrate and chlorpheniramine maleate

Code Name: Not Applicable

Chemical Name:

Hydrocodone bitartrate: morphinan-6-one, 4,5-epoxy-3-methoxy-17-methyl-, (5 α)-, [*R*-(*R*^{*},*R*^{*})]-2,3-dihydroxybutanedioate (1:1), hydrate (2:5)

Chlorpheniramine maleate: 2-pyridinepropanamine, γ -(4-chlorophenyl)-*N,N*-dimethyl-, (Z)-2-butenedioate (1:1)

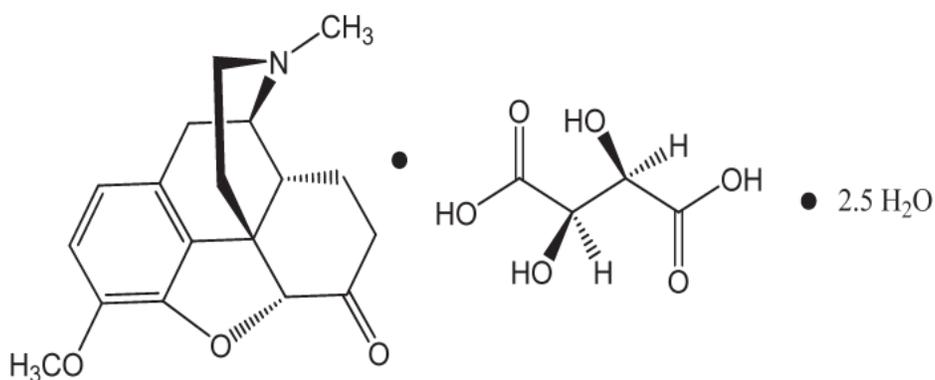
Molecular Formula/Molecular Weight:

Hydrocodone bitartrate: $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2.5H_2O$ / 494.5

Chlorpheniramine maleate: $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ / 390.86

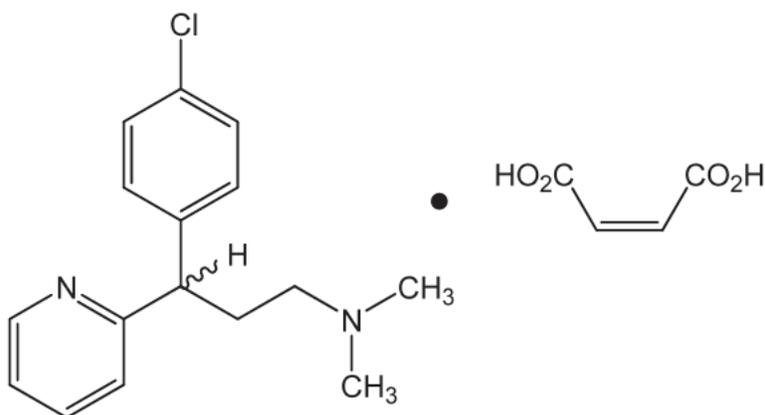
Structure or Biochemical Description¹:

Figure 1: Hydrocodone bitartrate



Hydrocodone Bitartrate
 $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2.5 H_2O$
 Molecular weight = 494.5

Figure 2: Chlorpheniramine maleate



Chlorpheniramine Maleate
 $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$
 Molecular weight = 390.86

¹ Taken from applicant's submission

Pharmacologic Class:

Hydrocodone bitartrate: narcotic antitussive and analgesic

Chlorpheniramine maleate: antihistamine

2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 102,177: hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine oral solution (Cypress Pharmaceuticals, Inc.)
- NDA 22-439: Zutripro[®] Oral Solution (Cypress Pharmaceuticals, Inc.; approved on June 8, 2011)
- NDA 22-442: Rezira[®] Oral Solution (Cypress Pharmaceuticals, Inc.; approved on June 8, 2011)

2.3 Drug Formulation

The proposed drug product (oral solution) is a clear, colorless to light yellow liquid with a grape odor and free from precipitation. Each milliliter of the solution contains 1.0 mg of hydrocodone bitartrate and 0.8 mg of chlorpheniramine maleate as the active ingredients. The composition of the drug product is presented below in Table 1.

Table 1: Unit Composition of Hydrocodone Bitartrate and Chlorpheniramine Maleate Oral Solution.

| Component | Reference to Quality Standards | Function | Unit Composition | | | |
|---------------------------|--------------------------------|-------------------|------------------|-------|---------|-----------|
| | | | % w/v | mg/mL | mg/5 mL | mg/480 mL |
| Hydrocodone Bitartrate | USP | Active ingredient | 0.10 | 1.0 | 5.0 | 480 |
| Chlorpheniramine Maleate | USP | Active ingredient | 0.08 | 0.8 | 4.0 | 384 |
| Citric Acid, Anhydrous | USP | (b) (4) | | | | |
| Sodium Citrate (b) (4) | 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. | | | | | | |

2.4 Comments on Novel Excipients

There are no novel excipients in the drug product or excipient levels above the levels in currently approved oral products.

2.5 Comments on Impurities/Degradants of Concern

Impurities and/or degradants of concern are addressed in a review to NDA 22-439 (CMC consult review under NDA 22-439 dated February 22, 2010). Refer to this review for complete details.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed oral solution is a combination product containing an antitussive (hydrocodone bitartrate) and an antihistamine (chlorpheniramine maleate) indicated for relief of cough associated with common cold and relief of symptoms associated with upper respiratory allergies. It is not indicated for pediatric patients under 18 years of age. The dosing regimen is 5 mL every 4 to 6 hours as needed, not to exceed 4 doses (20 mL) in 24 hours.

2.7 Regulatory Background

Cypress Pharmaceuticals submitted a request for advice on November 8, 2011 to IND 102,177. The Division responded in writing via facsimile on March 7, 2012. This NDA was submitted on April 23, 2012 and stamped as received on April 24, 2012.

11 Integrated Summary and Safety Evaluation

Cypress Pharmaceutical, Inc. submitted a 505(b)(2) NDA on April 23, 2012 for hydrocodone bitartrate and chlorpheniramine maleate (5 mg and 4 mg per 5 mL, respectively) oral solution. The proposed indication is relief of cough associated with common cold and symptoms associated with upper respiratory allergies. The proposed drug product is identical to the approved Zutripro[®] Oral Solution (NDA 22-439 approved on June 8, 2011), except for the absence of pseudoephedrine hydrochloride.

Hydrocodone, a narcotic antitussive and analgesic, has been used clinically for more than 50 years and has an acceptable safety profile in humans. It has been marketed as Hycodan[®] (NDA 005213 approved on March 23, 1943). The precise mechanism of action of hydrocodone is not known, but it is believed to act directly on the cough center. Chlorpheniramine, an antihistamine, was developed in line with the OTC monograph under 21CFR 341.12. Chlorpheniramine prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa.

No nonclinical pharmacology or toxicology studies were conducted with the proposed oral solution. The nonclinical safety of hydrocodone bitartrate is supported by the reference drug Zutripro[®] Oral Solution (Cypress NDA 22-439 approved on June 8, 2011), which in turns references the Hycodan[®] Syrup (Endo Pharmaceuticals NDA 005213 approved on March 23, 1943). The nonclinical safety of chlorpheniramine maleate is demonstrated by the OTC monograph under 21CFR 341.12. 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. Although hydrocodone is not an OTC monograph antitussive, hydrocodone combination products containing monograph active ingredients have been accepted based on the prior regulatory precedent of approving Tussionex[®] (the combination of hydrocodone and chlorpheniramine; NDA 19-111), for which approval can be based on establishment of bioequivalence only.

There are no outstanding pharmacology/toxicology issues for this NDA application, and from a nonclinical perspective, approval is recommended for this application.

The nonclinical sections of the proposed labeling mirror the approved labeling for Zutripro[®] Oral Solution (June 8, 2011), except for the absence of information on pseudoephedrine hydrochloride. See above under Section 1.3.3 "Labeling".

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/s/

CAROL M RIVERA-LOPEZ
08/01/2012

MOLLY E SHEA
08/01/2012
I concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 204307

**Applicant: Cypress
Pharmaceutical, Inc.**

Stamp Date: 4/24/2012

**Drug Name: Hydrocodone
bitartrate/chlorpheniramine
maleate oral solution**

NDA/BLA Type: Standard

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

| | Content Parameter | Yes | No | Comment |
|---|--|-----|----|---|
| 1 | Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin? | | | Not applicable. A pharmacology/toxicology section was not included in the submission. |
| 2 | Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin? | | | Not applicable. Refer to comment under #1. |
| 3 | Is the pharmacology/toxicology section legible so that substantive review can begin? | | | Not applicable. Refer to comment under #1. |
| 4 | Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)? | | | Not applicable as no toxicology studies were requested or submitted. |
| 5 | If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA). | | | Not applicable. Refer to comment under #4. |
| 6 | Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route? | | | Not applicable. Refer to comment under #4. |
| 7 | Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations? | | | Not applicable. Refer to comment under #4. |

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

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

| | Content Parameter | Yes | No | Comment |
|----|---|------------|-----------|---|
| 8 | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? | | | Not applicable. Refer to comment under #4. |
| 9 | Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57? | X | | |
| 10 | Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.) | X | | |
| 11 | Has the applicant addressed any abuse potential issues in the submission? | X | | From the nonclinical perspective, abuse potential has been addressed. |
| 12 | If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted? | | | Not applicable. |

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

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

No comments.

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

No issues from the nonclinical perspective.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

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

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/s/

CAROL M RIVERA-LOPEZ
06/12/2012

MOLLY E SHEA
06/12/2012
I concur.