# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**22442Orig1s000**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

**CLINICAL PHARMACOLOGY REVIEW**
**(RESUBMISSION DATED DECEMBER 8, 2010)**

| | |
|---|---|
| NDA: 22-442/SDN 16 | Type of Submission: Resubmission |
| Submission Date(s): | December 8, 2010 |
| Accepted Brand Name | Rezira™ |
| Generic Name | Hydrocodone and Pseudoephedrine Oral Solution |
| Reviewer | Elizabeth Y. Shang, Ph.D., R.Ph |
| Team Leader (Acting) | Suresh Doddapaneni., Ph.D. |
| OCP Division | DCPII |
| OND division | DPARP |
| Sponsor | Cypress Pharmaceuticals |
| Relevant IND(s) | 102,177 |
| Submission Type | 505 (b) (2) |
| Review Priority | Standard |
| Formulation; Strength(s) | Solution; Five milliliters (5 mL) of Rezira™ Oral Solution contains: hydrocodone bitartrate, USP, 5 mg and pseudoephedrine hydrochloride, USP, 60 mg. |
| Proposed Indication | Adults 18 years and older:<br>• Relief of cough and nasal congestion associated with common cold. |
| Proposed Dosing Regimen | Five milliliters (5 mL) orally every 4 to 6 hours as needed, not to exceed 4 doses (20 mL) in 24 hours. |

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# 1 Executive Summary

## 1.1 Recommendation

From the viewpoint of the Office of Clinical Pharmacology, the clinical pharmacology information supporting the approval for NDA 22442 is acceptable. As of May 5, 2011, the clinical pharmacology related labeling language was agreed upon between the Agency and Cypress and as such there are no outstanding labeling issues.

## 1.2 Phase IV Commitments

None

## 1.3 Summary of Clinical Pharmacology Findings

There is no clinical pharmacology data for hydrocodone and pseudoephedrine in Rezira™ Oral Solution per se. Data generated in support of Zutripro™ Oral Solution (NDA 22439) are used in support of this product as well. Because Rezira™ Oral Solution (NDA 22442) and Zutripro™ Oral Solution (NDA 22439) are exactly same formulations except that Zutripro™ consists of one more active ingredient (chlorpheniramine), demonstration of bioequivalence for the hydrocodone and pseudoephedrine components in the bioequivalence study supporting Zutripro™ relative to respective reference products is applicable to this product as well. This approach was discussed in the pre-NDA meeting and the Agency agreed that this approach is acceptable.

The bioequivalence of hydrocodone and pseudoephedrine components relative to respective reference solutions containing hydrocodone bitartrate (hydrocodone bitartrate and homatropine methylbromide syrup manufactured by Hi-Tech Pharmacal Co., Inc,) and single-ingredient pseudoephedrine solution was demonstrated in Study 11058503. The 90% confidence intervals (CIs) for the geometric mean ratios of $C_{max}$ and AUC were included in the 80-125% limits for bioequivalence. The summary of bioequivalence statistics on pharmacokinetic parameters for hydrocodone and pseudoephedrine are provided in Table 1 and Table 2, respectively.

**Table 1 Summary Statistics on Bioequivalence of Hydrocodone Following Single Dose Administration of 5 mL Zutripro™ Oral Solution (Test) and Hydrocodone Bitartrate and Homatropine Methylbromide Syrup Manufactured by Hi-Tech Pharmacal Co., Inc (RLD for Hydrocodone)**

Geometric Means, Ratio of Means, and 90% Confidence Intervals
Based on ANOVA of Ln-Transformed Data
Analyte: Hydrocodone (N = 98)

| Parameter | Test A | Reference B | Ratio | CI* | Intra-Subject %CV |
|---|---|---|---|---|---|
| **AUC0-t** (pg·hr/mL) | 67540.16 | 69723.40 | 0.9687 | 0.9465 - 0.9914 | 9.7130 |
| **AUC0-inf** (pg·hr/mL) | 69747.27 | 72063.25 | 0.9679 | 0.9452 - 0.9911 | 9.9706 |
| **Cmax** (pg/mL) | 10290.79 | 11364.25 | 0.9055 | 0.8795 - 0.9324 | 12.2931 |

* Bioequivalent if confidence intervals are within 0.8000-1.2500 (80.00 to 125.00%) limits.

Source: NDA 22439 (SDN 22) Clinical Study Report, Page 36 of 75

**Table 2 Summary Statistics on Bioequivalence of Pseudoephedrine Following Single Dose Administration of 5 mL Zutripro™ (b) (4) Oral Solution (Test) and Pseudoephedrine Solution (Reference for Pseudoephedrine)**

Geometric Means, Ratio of Means, and 90% Confidence Intervals
Based on ANOVA of Ln-Transformed Data
Analyte: Pseudoephedrine (N = 100)

| Parameter | Test A | Reference C | Ratio | CI* | Intra-Subject %CV |
|---|---|---|---|---|---|
| **AUC0-t** (ng·hr/mL) | 1824.27 | 1813.41 | 1.0060 | 0.9815 - 1.0311 | 10.4633 |
| **AUC0-inf** (ng·hr/mL) | 1943.05 | 1926.70 | 1.0085 | 0.9809 - 1.0368 | 11.7857 |
| **Cmax** (ng/mL) | 207.17 | 204.90 | 1.0111 | 0.9931 - 1.0294 | 7.6000 |

* Bioequivalent if confidence intervals are within 0.8000-1.2500 (80.00 to 125.00%) limits.

Source: NDA 22439 (SDN 22) Clinical Study Report, Page 39 of 75

Division of Scientific Investigations audited this study and concluded that the data be accepted for review.

# 2 Question Based Review

## 2.1 General Attributes of the Drug

### 2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Cypress Pharmaceuticals submitted NDA 22442 originally on November 6, 2008 (SDN 1), along with Zutripro™ Oral Solution (NDA 22439), following the NDA 505 (b) (2) pathway. First resubmission (SDN 9) occurred on December 10, 2009 in response to the Complete Response (CR) Letter of September 9, 2009 for the original NDA. Second resubmission (SDN 16) occurred on December 8, 2010 in response to the CR Letter of June 11, 2010 for the first resubmission.

The accepted trade name for this product is Rezira™. However, the proposed trade name in the original NDA submission was [redacted] (b) (4) Oral Solution. Rezira™ has been used in this review although previous reviews refer to this product as [redacted] (b) (4) Oral Solution.

There is no clinical pharmacology data for hydrocodone and pseudoephedrine obtained with Rezira™ Oral Solution per se. Data generated in support of Zutripro™ Oral Solution (NDA 22439) are used in support of this product as well. Because Rezira™ Oral Solution (NDA 22442) and Zutripro™ Oral Solution (NDA 22439) are exactly same formulations except that Zutripro™ consists of one more active ingredient (chlorpheniramine), demonstration of bioequivalence for the hydrocodone and pseudoephedrine components in the bioequivalence study supporting Zutripro™ relative to respective reference products is applicable to this product as well. This approach was discussed in the pre-NDA meeting and the Agency agreed that this approach is acceptable.

Because the NDA 22442 (Rezira™) relied on clinical pharmacology studies in NDA 22439 (Zutripro™), the detailed regulatory history on NDA 22439 original submission and resubmissions is provided here.

In the original submission, the Sponsor submitted data from a single dose bioequivalence study (S08-0179) between Zutripro™ and Hycodan®, single-ingredient pseudoephedrine and chlorpheniramine solutions to support NDA submission, and the Agency agreed with the plan. The hydrocodone component of the test product, Zutripro™ Oral Solution, was not bioequivalent to to hydrocodone in the reference, Hycodan® syrup, although chlorpheniramine and pseudoephedrine components were bioequivalent to their respective single component solutions. In the CR letter dated September 9, 2009, the Agency provided the Sponsor two options to address the deficiency: a) conduct a single-dose clinical pharmacology study to establish the bioequivalence of Zutripro™ Oral Solution to the reference products; or b) conduct a clinical development program with clinical efficacy and safety studies to support the Sponsor's combination product.

The Sponsor chose Option A and in the resubmission dated December 10, 2009 submitted a new single dose bioequivalence study (SAM-09-1010) to demonstrate that hydrocodone component of Zutripro™ is bioequivalent to the hydrocodone component of the reference hydrocodone bitartrate and homatropine methylbromide syrup manufactured by Hi-Tech Pharmacal Co., Inc. The change of reference in this new bioequivalence study was acceptable due to withdrawal of Hycodan® syrup from the market. However, due to deficiencies both in the conduct of the study and in the methods used at the analytical sites found in the DSI inspection in Study S08-0179 from SDN1 and Study SAM 09-1010 from SND2, a CR Letter was issued on June 11, 2010. In the CR letter, the Agency provided the Sponsor two options to address the deficiency: a) conduct another single-dose clinical pharmacology study to establish the bioequivalence of the proposed hydrocodone 5 mg/chlorpheniramine 4 mg/pseudoephedrine 60 mg/ per 5 ml oral solution to the reference products; or b) conduct a clinical development program with clinical efficacy and safety studies to support Sponsor's combination product.

The Sponsor again chose Option A and in the resubmission dated December 8, 2010, data from a new a single dose bioequivalence study (11058503) was submitted demonstrating that each active ingredient in Zutripro™ is bioequivalent to the corresponding components in the respective reference products.

2.1.2 What is the status of pediatric studies and/or any pediatric plan for study?

In the original NDA submission, the Sponsor proposed usage of Zutripro™ [redacted] (b) (4) Waiver for children below 6 years of age is based on the fact that the proposed product contains hydrocodone which is contraindicated for

use in children less than 6 years of age (because of the risk of respiratory depression). The need for conducting pediatric safety and pharmacokinetics study in patients 6 to 17 years (inclusive) was verbally communicated to the Sponsor during the review cycle. The Sponsor submitted their revised pediatric plan proposal to the Agency on May 6, 2010. Sponsor's proposed pediatric plan and Division's assessment were presented to Pediatric Review Committee (PeRC) on May 26, 2010. PeRC agreed with the waiver of studies in children less than 6 years of age and a deferral for patients 6 to 17 years of age, with recommendations to incorporate efficacy assessments and population PK in the proposed safety study. The proposed usage of Zutripro™ as well as Rezira (b) (4) to be prescribed in adults (age 18 years and over) only in the current draft label.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

Adults: Five milliliters (5 mL) orally every 4 to 6 hours as needed, not to exceed 4 doses (20 mL) in 24 hours.

## 2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The Clinical Pharmacology program of NDA 22439 (SDN 22) consisted of a single-dose bioequivalence study (Study 11058503). This study is an open-label, single-dose, randomized, four-period cross-over study under fasting conditions. The objectives of the study were to determine and compare the rate and extent of absorption of hydrocodone, pseudoephedrine, and chlorpheniramine from Zutripro™ Oral Solution to that from homatropine methylbromide/ hydrocodone bitartrate 1.5 mg/5 mg per 5 mL syrup (manufactured by Hi-Tech Pharmacal Co, Inc.), pseudoephedrine solution, and chlorpheniramine solution. Ninety-eight healthy adult subjects completed the study. The study results showed bioequivalence for the hydrocodone, pseudoephedrine, and chlorpheniramine components of the Zutripro™.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Hydrocodone and pseudoephedrine in the plasma samples were measured.

2.2.3 What are the single dose pharmacokinetic parameters?

The arithmetic mean plasma pharmacokinetic parameters for testing product and reference products are summarized in Table 3 and Table 4.

**Table 3 Arithmetic Mean (SD) of Plasma Pharmacokinetic Parameters of Hydrocodone Following Single Dose Administration of 5 mL Zutripro™ Oral Solution (Test) and Hydrocodone Bitartrate and Homatropine Methylbromide Syrup Manufactured by Hi-Tech Pharmacal Co., Inc. (Reference)**

**Summary of Pharmacokinetic Parameters**
**Untransformed Data**
**Analyte: Hydrocodone (N = 98)**

| Pharmacokinetic Parameter | Arithmetic mean ± SD (%CV) | |
|---|---|---|
| | Test A | Reference B |
| **AUC0-t** (pg·hr/mL) | 69401.3314 ± 16433.6643 (23.6792) | 71785.3004 ± 18328.4015 (25.5322) |
| **AUC0-inf** (pg·hr/mL) | 71759.8232 ± 17539.3146 (24.4417) | 74293.9576 ± 19573.8121 (26.3464) |
| **Cmax** (pg/mL) | 10616.4388 ± 2634.2446 (24.8129) | 11829.5000 ± 3598.8372 (30.4226) |
| **Tmax** (hr) | 1.3806 ± 0.5513 (39.9328) | 1.2248 ± 0.4929 (40.2400) |
| **Kel** (1/hr) | 0.1440 ± 0.0229 (15.8926) | 0.1414 ± 0.0204 (14.4431) |
| **T½** (hr) | 4.9246 ± 0.7340 (14.9041) | 5.0060 ± 0.7424 (14.8294) |

Source: NDA 22439 (SDN 22) Clinical Study Report, Page 36 of 75

**Table 4 Arithmetic Mean (SD) of Plasma Pharmacokinetic Parameters of Pseudoephedrine Following Single Dose Administration of 5 mL Zutripro™ Oral Solution (Test) and Pseudoephedrine Solution (Reference)**

**Summary of Pharmacokinetic Parameters**
**Untransformed Data**
**Analyte: Pseudoephedrine (N = 100)**

| Pharmacokinetic Parameter | Arithmetic mean ± SD (%CV) | |
|---|---|---|
| | Test A | Reference C |
| **AUC0-t** (ng·hr/mL) | 1876.1802 ± 474.5503 (25.2934) | 1867.1775 ± 481.3987 (25.7822) |
| **AUC0-inf** (ng·hr/mL) | 2020.8583 ± 652.4217 (32.2844) | 1996.6786 ± 577.1783 (28.9069) |
| **Cmax** (ng/mL) | 211.8165 ± 46.1536 (21.7894) | 209.6139 ± 46.9436 (22.3953) |
| **Tmax** (hr) | 1.7753 ± 0.5580 (31.4325) | 1.6705 ± 0.6321 (37.8374) |
| **Kel** (1/hr) | 0.1309 ± 0.0294 (22.4723) | 0.1312 ± 0.0270 (20.6002) |
| **T½** (hr) | 5.6139 ± 1.5689 (27.9463) | 5.5348 ± 1.3009 (23.5040) |

Source: NDA 22439 (SDN 22) Clinical Study Report, Page 38 of 75

## 2.3 General Biopharmaceutics

2.3.1 What is the relative bioavailability of the formulations (reference and test) based on the pivotal bioequivalence studies? Was the bioequivalence demonstrated between the two formulations?

The bioequivalence of hydrocodone and pseudoephedrine component of Rezira™ has been demonstrated under fasting condition as evident by the observation that the 90% CIs ratios of the

geometric means for $C_{max}$, $AUC_{0-t}$, and $AUC_{0-inf}$ were within the limits for bioequivalence (80-125%) (Table 1 and Table 2).

2.3.2 What is the effect of food on the bioavailability of the drug from the dosage form?

No specific pharmacokinetic studies to determine the effect of food on the disposition of hydrocodone, chlorpheniramine and pseudoephedrine were submitted in this NDA. As a post meeting comment in the minutes of the January 14, 2008 pre-IND meeting ( (b) (4) of this product), the Agency has agreed that no food effect study was needed with the proposed oral solution formulation (b) (4)

## 2.4 Analytical Section

2.4.1 What bioanalytical methods are used to assess concentrations?

The analytical portion of the Cypress Pharmaceuticals, Inc. Protocol No. 11058503 conducted at (b) (4)

2.4.1.1 Hydrocodone

Total plasma concentrations of hydrocodone were measured by a validated method utilizing high performance liquid chromatography-tandem mass spectrometry. The method for the analysis of hydrocodone in human heparin plasma was validated over the range of 100 – 20,000 pg/mL. Summary of plasma hydrocodone bioanalytical validation methods is listed in Table 5. The results of sample analysis on hydrocodone are provided in Table 6.

The results are acceptable as evidenced by QC sample precision and accuracy within ± 15% excluding the quality control values which did not meet the acceptance criteria.

**Table 5 Analytical Method Validation Summary on Hydrocodone**

| | Hydrocodone (pg/mL) |
|---|---|
| **Standard Concentrations** | 100, 200, 500, 1000, 2000, 5000, 10000, 20000 |
| **Linear Range** | 100 – 20,000 |
| **Corelation Coefficient (r)** | ≥ 0.998 |
| Accuracy Across Standard Curve Concentrations (%) | 98.4% - 101.5% |
| **QC Concentrations (pg/mL)** | 300, 3000, 16000 |
| **Intra-Run Precision (%CV) of QC Samples** | |
| 300 | 3.1% |
| 3000 | 1.8% |
| 16000 | 1.3% |
| **Intra-Run Accuracy of QC Samples** | |
| 300 | 97.7% |
| 3000 | 100.6% |
| 16000 | 98.5% |
| **Inter-Run Precision of QC Samples (%CV)** | |
| 300 | 3.1% |
| 3000 | 1.9% |
| 16000 | 2.1% |
| **Inter-Run Accuracy of QC Samples (%CV)** | |
| 300 | 96.7% |
| 3000 | 98.9% |
| 16000 | 96.0% |
| **Recovery (%)** | |
| Analyte | |
| 300 | 97.5% |
| 3000 | 100.7% |
| 16000 | 95.1% |
| Internal standards | 100.1 |
| **Stabilities in Plasma** | |
| Room Temperature | 24 hours; No instability is detected |
| Refrigerated (4°C) | 24 hours; No instability is detected |
| Frozen (-20°C) | 5 days; No instability is detected |
| Frozen (-80°C) | At least 92 days; No instability is detected |
| Freeze-Thaw Stability | 3 cycles; No instability is detected. |
| **Processed Batch Stability** | 24 hours; No instability is detected |
| **Processed Sample Stability** | 25.5 hours; No instability is detected |
| **Dilution Accuracy** (4X High QC, i.e. 64,000 pg/mL) | |
| x5 | 93.5% |
| x10 | 101.2% |

Source: LC-MS/MS-Assay Validation Report VAL-RPT-1261 Rev1

**Table 6 Plasma Assay Parameters for Hydrocodone**

| | Hydrocodone |
|---|---|
| Lower Limit of Quantitation (pg/mL) | 100 |
| Assay Range (pg/mL) | 100 to 20000 pg/mL |
| Linearity (correlation coefficient) | > 0.99 |
| Precision (%CV) | 8.3% at 300 pg/mL; 6.1% at 3000 pg/mL; 5.0% at 16000 pg/mL |
| Accuracy (%Theoretical) | 101.0% at 300 pg/mL; 99.4 at 3000 pg/mL; 94.7% at 16000 pg/mL |

2.4.1.2 Pseudoephedrine

Total plasma concentrations of pseudoephedrine were measured by a validated method utilizing the technique of protein precipitation, followed by high performance liquid chromatography-positive ionization electrospray-tandem mass spectrometry. The method for the analysis of pseudoephedrine in human heparin plasma was validated over the range of 2.00 – 400.00 ng/mL. Summary of plasma hydrocodone bioanalytical validation methods is listed in Table 7. The results of sample analysis on hydrocodone are provided in Table 8.

The results are acceptable as evidenced by QC sample precision and accuracy within ± 15% excluding the quality control values which did not meet the acceptance criteria.

**Table 7 Analytical Method Validation Summary on Pseudoephedrine**

| | Pseudoephedrine (ng/mL) | |
|---|---|---|
| **Standard Concentrations** | 2.00, 4.00, 10.00, 20.00, 40.00, 100.00, 200.00, 400.00 | |
| **Linear Range** | 100 – 20,000 | |
| **Corelation Coefficient (r)** | ≥ 0.9984 | |
| Accuracy Across Standard Curve Concentrations (%) | 97.6% - 104.1% | |
| **QC Concentrations (ng/mL)** | 6.00, 60.00, and 320.00 | |
| **Intra-Run Precision (%CV) of QC Samples** | System K | System N |
| 6.00 | 3.8% | 1.9% |
| 60.00 | 1.3% | 1.3% |
| 320.00 | 1.3% | 1.3% |
| **Intra-Run Accuracy of QC Samples** | System K | System N |
| 6.00 | 99.7% | 96.8% |
| 60.00 | 96.6% | 95.2% |
| 320.00 | 91.0% | 91.5% |
| **Inter-Run Precision of QC Samples (%CV)** | | |
| 6.00 | 5.7% | |
| 60.00 | 2.7% | |
| 320.00 | 3.7% | |
| **Inter-Run Accuracy of QC Samples (%CV)** | | |
| 6.00 | 96.7% | |
| 60.00 | 98.4% | |
| 320.00 | 93.2% | |
| **Recovery (%)** | | |
| Analyte | | |
| 6.00 | 56.7% | |
| 60.00 | 55.4% | |
| 320.00 | 60.0% | |
| Internal standards | 61.5% | |
| **Stabilities in Plasma** | | |
| Room Temperature | 25 hours; No instability is detected | |
| Refrigerated (4°C) | 24 hours; No instability is detected | |
| Frozen (-20°C) | 6 and 10 days; No instability is detected | |
| Frozen (-80°C) | 6 and 35 days; No instability is detected | |
| Freeze-Thaw Stability | 3 cycles; No instability is detected. | |
| **Processed Batch Stability** | 68 hours; No instability is detected | |
| **Processed Sample Stability** | 73 hours; No instability is detected | |
| **Dilution Accuracy** (4X High QC, i.e. 64,000 pg/mL) | | |
| x5 | 93.7% | |
| x10 | 96.6% | |

Source: LC-MS/MS-Assay Validation Report VAL-RPT-1260 Rev 0

**Table 8 Plasma Assay Parameters for Pseudoephedrine**

| | Pseudoephedrine |
|---|---|
| Lower Limit of Quantitation (ng/mL) | 2.00 |
| Assay Range (pg/mL) | 2.00 to 400.00 ng/mL |
| Linearity (correlation coefficient) | > 0.99 |
| Precision (%CV) | 5.3% at 6.00 ng/mL; 6.9% at 60.00 ng/mL; 5.2% at 320.00 ng/mL |
| Accuracy (%Theoretical) | 94.2% at 6.00 ng/mL; 99.4% at 60.00 ng/mL; 94.9% at 320.00 ng/mL |

## 3 Detailed Labeling Recommendations

Following are the labeling changes proposed by this reviewer in section 12.3 of the package insert. Strikethrough text was Cypress proposal while underlined text is Agency's proposal. Cypress proposed text (b) (4) and Agency's proposed change removes that ambiguity. Further, there is no need to mention (b) (4) as that is a review assessment aspect and not a labeling aspect. As of May 5, 2011, the underlined text was agreed upon between the Agency and Cypress and as such there are no outstanding labeling issues.

(b) (4)

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

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/s/

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ELIZABETH Y SHANG
05/12/2011

SURESH DODDAPANENI
05/12/2011

**Addendum to Clinical Pharmacology Review for NDA 22442 on May 3, 2010**

Date: May 24, 2010
NDA: 22442
Drug name: Rezira™ Oral Solution

Because Rezira™ Oral Solution (NDA 22442) and (b) (4) Oral Solution (NDA 22439) are exactly same formulations except that (b) (4) consist of one more active ingredient, the sponsor used the study results from (b) (4) (NDA 22439) to demonstrate bioequivalence of hydrocodone and pseudoephedrine components for Rezira™. The following information reflects update on the bioequivalence (BE) studies SAM-09-1010 and S08-0179 in the clinical pharmacology review for NDA 22439, which was finalized in DARRTs on May 3, 2010.

On January 26, 2010, the Division of Pulmonary and Allergy Products (DPAP) sent a request to the Division of Scientific Investigations (DSI) to audit both the clinical and analytical portions of the following bioequivalence studies:

1. Study #1: S08-00179 "A Relative Bioavailability and Drug-Drug Interaction Study Of Hydrocodone, Pseudoephedrine, and Chlorpheniramine Oral Solution (5 mg/60 mg/4 mg per 5 mL), Pseudoephedrine Oral Solution (60 mg Per 5 mL), Chlorpheniramine Oral Solution (4 mg Per 5 mL) and Hycodan® Syrup (5 mg Hydrocodone Bitartrate/1.5 mg Homatropine Methylbromide Per 5 mL) under Fasted Conditions".
2. Study #2: SAM-09-1010 " A Study to Evaluate the Relative Bioavailability of Hydrocodone Bitartrate in a 5 mg/60 mg/4 mg Hydrocodone Bitartrate/ Pseudoephedrine HCl/ Chlorpheniramine Maleate Oral Solution Compared to Hi-Tech (1.5 mg/5 mg Homatropine Methylbromide/ Hydrocodone Bitartrate) Syrup in Healthy Subjects under Fasted Conditions".

The DSI inspection report was unavailable on May 3, 2010, the primary due date for clinical pharmacology review. Therefore, in the original review, the pharmacokinetic (PK) results of both BE studies were discussed and summarized without DSI inspection results. The PK analyses from Study #1 showed that bioequivalence of chlorpheniramine and pseudoephedrine components in (b) (4) s oral solution formulation to respective single-ingredient chlorpheniramine solution and pseudoephedrine solution. The PK analyses from Study #2 showed that bioequivalence has been established for hydrocodone bitartrate component in (b) (4) oral solution compared to that in 1.5 mg/5 mg homatropine methylbromide/ hydrocodone bitartrate Syrup manufactured by Hi-Tech Pharmacal Co., Inc.

On May 5, 2010, the DSI inspection memorandum on Study SAM-09-1010 was released in DARRTs. Following the inspection, DSI has found the following issues:

1. Failure to adequately document all aspects of study conduct.
2. Stability samples used for processed sample stability validation were not compared against freshly extracted calibrators.

3. For validation batch HCMl130a, chromatograms with the original integration before the manual change were not maintained, and justification for the manual reintegration was not documented.
4. Failure to establish objective criteria to consistently calculate mean internal standard (IS) response. For example, for analytical batch HydroG66, mean IS response was calculated based on the IS response of the calibration standards, whereas in batch HydroG85A, mean IS response was calculated from the IS response of the QCs. The justification for how mean IS response was calculated was also not documented.

DSI has made the following conclusions related to the analytical portion of Study SAM-09-1010:

1. The bioequivalence data for Study SAM-09-1010 submitted in the NDA are questionable due to the absence of source documentation at (b) (4) the experiments conducted as part of pre-study method validations cannot be assured.
2. To assure accuracy of bioequivalence data in study SAM-09-1010, the sponsor should provide new stability data (including frozen Long-term, freeze-thaw, refrigerated, room-temperature and processed stability) to support integrity of the BE data generated in the study. The data needs to be generated while maintaining complete source documentation for all the stability experiments.

On May 24, 2010, the DSI inspection memorandum on Study S08-0179 was released in DARRTs. Following the inspection, DSI has found the following issues:

1. Records for the extraction of subject samples in numerous studies were falsified.

   The falsification is part of the Agency's investigation of a complaint received by the Agency in June of 2009, in which an ex-employee of (b) (4) alleged misconduct in a number of bioanalytical studies. The falsification was pervasive for extractions conducted on weekends and holidays over the time period of April 2005 to June 2009 and affected numerous studies for multiple sponsors. Affected data for Study S08-0179 include Runs (b) (4) for Hydrocodone/ Chlorpheniramine and Runs (b) (4) for Pseudoephedrine.

   The complaint also alleged that laboratory staff altered the outcome of analytical runs (i.e., runs were "fixed") through "prep" runs injected prior to the actual subject sample batch. Unexplained discrepancies between the initial system equilibration result ("prep" run) and the actual run result in four runs from three studies. Specifically, "prep" run calibration standards had no drug or internal standard peak present yet the actual subject sample run had these peaks. As the (b) (4) investigation to date could not explain this discrepancy.

2. Validation documentation was incomplete in that extraction times for some validation runs were not recorded and the storage location of stability samples to demonstrate freeze/thaw and long term stability was not documented.

Following the above inspection, the DSI recommends the followings for Study S08-0179:

1. Study S08-0179 should not be accepted for review at this time due to record falsification and incomplete investigation of complaint allegations by (b) (4)
2. Due to lack of source documentation, free/thaw (F/T) and long term stability (LTS) determinations cannot be assured. Appropriate F/T and LTS data to demonstrate analyte stability under the same conditions as the subject samples (hydrocodone/ chlorpheniramine/pseudoephedrine in combination) are needed.

Based upon the two DSI inspection results on the two pivotal BE studies in NDA 22439, it is in this reviewer's opinion that unquestionable bioequivalence data is necessary to claim bioequivalence between the (b) (4) oral solution (test product) and respective reference products.

***Conclusions***

In conclusion, the results of the bioequivalence studies from S08-0179 and SAM-09-1010 are *not* accepted based on the DSI audit outcome from clinical pharmacology perspective. The Agency will ask the sponsor in the CR letter to address the deficiencies.

The following conclusions from DSI inspection memorandums should be convey to the sponsor:

Study S08-0179

a. Study S08-0179 is not accepted for review at this time due to record falsification and incomplete investigation of complaint allegations by (b) (4)
b. Due to lack of source documentation, free/thaw (F/T) and long term stability (LTS) determinations cannot be assured. Appropriate F/T and LTS data to demonstrate analyte stability under the same conditions as the subject samples (hydrocodone/ chlorpheniramine/pseudoephedrine in combination) are needed.

Study SAM-09-1010

a. Due to the absence of source documentation at (b) (4) the experiments conducted as part of pre-study method validations cannot be assured. Hence the bioequivalence data for study SAM-09-1010 submitted in the NDA are questionable.
b. To assure accuracy of bioequivalence data in study SAM-09-1010, the sponsor should provide new stability data (including frozen Long-term, freeze-thaw, refrigerated, room-temperature and processed stability) to support integrity of the BE data generated in the study. The data needs to be generated while maintaining complete source documentation for all the stability experiments.

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

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/s/

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ELIZABETH Y SHANG
05/25/2010

YUN XU
05/25/2010

# CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| NDA: 22-442 Submission 0009 | Submission Date(s): December 10, 2009 |
| Proposed Brand Name | Rezira™ |
| Generic Name | Hydrocodone and Pseudoephedrine Oral Solution |
| Reviewer | Elizabeth Y. Shang, Ph.D., R.Ph |
| Team Leader (Acting) | Yun Xu, M.D., Ph.D. |
| OCP Division | DCPII |
| OND division | DPARP |
| Sponsor | Cypress Pharmaceuticals |
| Relevant IND(s) | 102,177 |
| Submission Type | 505 (b) (2) |
| Review Priority | Standard |
| Formulation; Strength(s) | Solution; Five milliliters (5 mL) of Rezira™ Oral Solution contains: hydrocodone bitartrate, USP, 5 mg and pseudoephedrine hydrochloride, USP, 60 mg. |
| Proposed Indication | (b) (4) relief of cough; for the (b) (4) relief of nasal congestion due to the common cold. |
| Proposed Dosing Regimen | Adults:<br>• Five milliliters (5 mL) orally every 4 to 6 hours as needed, not to exceed 4 doses (20 mL) in 24 hours. |

## Table of Contents

# 1 Executive Summary

This is a 505 (b) (2) NDA for an oral solution containing hydrocodone bitartrate and pseudoephedrine hydrochloride (5 mg and 60 mg per 5 mL, respectively). The proposed proprietary name for this product is Rezira™ Oral Solution. Hydrocodone bitartrate is approved for the symptomatic relief of cough in Hycodan (NDA 05213), and pseudoephedrine HCl is an accepted nasal decongestant in the OTC Monograph (21 CFR §341.20). Hydrocodone bitartrate and homatropine methylbromide syrup manufactured by Hi-Tech Pharmacal Co., Inc. was approved by the Agency as a 505 (j) (2) ANDA (40613) referencing Hycodan syrup (NDA 05231) without any efficacy and safety clinical trials conducted. Hycodan marketing has been discontinued and hydrocodone bitartrate and homatropine methylbromide syrup manufactured by Hi-Tech Pharmacal Co is currently listed as a reference listed drug (RLD) in the Orange Book.

The proposed indication for Rezira™ Oral Solution is (b) (4) relief of cough; and the (b) (4) relief of nasal congestion due to the common cold.

## 1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology-2 (OCP/DCP-2) has reviewed the Clinical Pharmacology information supporting the approval for NDA 22439 Submission 0000 submitted on November 6, 2008 and Submission 0009 submitted on December 10, 2009. At the time of this review due (May 3, 2010), DSI inspection results are not available until its due date of May 14, 2010. OCP finds the submission for approval is acceptable contingent on satisfactory DSI inspection results. Recommendation and labeling comments should be conveyed to the sponsor as appropriate.

## 1.2 Phase IV Commitments

None

## 1.3 Summary of Clinical Pharmacology Findings

The clinical pharmacology results on hydrocodone and pseudoephedrine for ReziraTM oral solution was generated from (b) (4) oral solution bioequivalence study (NDA 22439). For detailed regulatory history, see Section 2.1.1

The bioequivalence of pseudoephedrine components in R (b) (4) oral solution formulation to respective single-ingredient pseudoephedrine solution was demonstrated in Study S08-0179 in the sponsor's first NDA submission (0000). The 90% confidence intervals (CIs) for the geometric mean ratios of $C_{max}$ and AUC were included in the 80-125% limits for bioequivalence. The systemic exposure pharmacokinetic parameters were similar between (b) (4) formulation (combination product) and single-ingredient products pseudoephedrine. The summary of bioequivalence statistics on pharmacokinetic parameters for pseudoephedrine are provided in Table 1.

**Table 1 Summary Statistics on Bioequivalence of Pseudoephedrine Following Single Dose Administration of 5 mL Rezira™ (b) (4) Oral Solution (Test) and Pseudoephedrine Solution (Reference for Pseudoephedrine).**

| | Geometric Mean | | |
|---|---|---|---|
| | (b) (4) | | |
| $AUC_{0-inf}$ (ng×hr/mL) | | | |
| $AUC_{0-t}$ (ng×hr/mL) | | | |
| $C_{max}$ (ng/mL) | | | |

The bioequivalence of hydrocodone component in (b) (4) to hydrocodone bitartrate and homatropine methylbromide syrup manufactured by Hi-Tech Pharmacal Co., Inc. (RLD) was demonstrated in Study SAM-09-1010 in the sponsor's NDA resubmission (0009). The 90% CIs ratios of the geometric means for $C_{max}$, AUC were within the limits for bioequivalence (80-125%) for hydrocodone. The systemic exposure pharmacokinetic parameters were similar between (b) (4) (b) (4) formulation (combination product) and the RLD. The summary of bioequivalence statistics on pharmacokinetic parameters for hydrocodone is provided in Table 2.

**Table 2 Summary Statistics on Bioequivalence of Hydrocodone Following Single Dose Administration of 5 mL (b) (4) Oral Solution (Test) and Hydrocodone Bitartrate and Homatropine Methylbromide Syrup Manufactured by Hi-Tech Pharmacal Co., Inc (RLD for Hydrocodone).**

| | Geometric Mean | | |
|---|---|---|---|
| | (b) (4) | | |
| $AUC_{0-inf}$ (pg×hr/mL) | | | |
| $AUC_{0-t}$ (pg×hr/mL) | | | |
| $C_{max}$ (pg/mL) | | | |

## 2 Question Based Review

### 2.1 General Attributes of the Drug

#### 2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Rezira™ Oral Solution (NDA 22442) was submitted along with (b) (4) Oral Solution (NDA 22439) by Cypress Pharmaceuticals on November 6, 2008 following NDA 505 (b) (2). A resubmission (Submission 0009) occurred on December 10, 2009 in response to the Complete Response Letter.

The proposed trade name in NDA submission 0009 is Rezira™ Oral Solution, which is changed from (b) (4) proposed in the original NDA submission 0000.

Five milliliter (5 mL) of Rezira™ Oral Solution contains hydrocodone bitartrate, USP, 5 mg and pseudoephedrine hydrochloride, USP, 60 mg. In addition to hydrocodone and pseudoephedrine, 5 mL of (b) (4) Oral Solution contains chlorpheniramine maleate, USP, 4 mg.

Because Rezira™ Oral Solution (NDA 22442) and (b) (4) Oral Solution (NDA 22439) are exactly same formulations except that (b) (4) consist of one more active ingredient, the sponsor used the study results from (b) (4) (NDA 22439) to demonstrate bioequivalence of hydrocodone and pseudoephedrine components for Rezira™. As discussed in the pre-NDA meeting minutes, the Agency agreed this approach is acceptable.

In the original submission (0000) of NDA 22439, the sponsor used a single dose bioequivalent study (S08-0179) between (b) (4) and Hycodan®, single-ingredient pseudoephedrine and chlorpheniramine solutions to support NDA submission, and the Agency agreed with the plan. The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP-2) reviewed the submission and found it unacceptable. The hydrocodone component of the test product, (b) (4) Oral Solution, was not bioequivalent to RLD, Hycodan® syrup, although chlorpheniramine and pseudoephedrine components of (b) (4) had demonstrated bioequivalence to their respective single component solutions. A Complete Response (CR) Letter was issued on September 09, 2009. In the CR letter, the Agency provided the sponsor two options to address the deficiency: a) Conduct a single-dose clinical pharmacology study to establish the bioequivalence of the proposed (b) (4) oral solution to the reference products; or b) Conduct a clinical development program with clinical efficacy and safety studies to support the sponsor's combination product. The sponsor had chosen Option A and resubmitted a single dose bioequivalence study (SAM-09-1010) on December 10, 2009 (Submission 0009) to demonstrate that hydrocodone component of (b) (4) is bioequivalent to the RLD of hydrocodone component of hydrocodone bitartrate and homatropine methylbromide syrup manufactured by Hi-Tech Pharmacal Co., Inc. The change of RLD in Submission 0009 is acceptable due to withdrawal of Hycodan® syrup from the market.

2.1.2 What is the status of pediatric studies and/or any pediatric plan for study?

In the NDA submission, the sponsor proposed usage of Rezira™ Oral Solution in (b) (4) (b) (4) based upon labeling from Hycodan and Monographs on nasal decongestant drug products. However, safety and effectiveness of Rezira™ Oral Solution in (b) (4) have not been established. A proposed Post Marketing Requirement on conducting pediatric safety and pharmacokinetics study was verbally communicated to the sponsor by the medical team on April 29, 2010. Sponsor has been asked to submit the pediatric plan proposal to the Agency on May 7, 2010. (b) (4)

2.1.3 What are the proposed dosage(s) and route(s) of administration?

Adults: Five milliliters (5 mL) orally every 4 to 6 hours as needed, not to exceed 4 doses (20 mL) in 24 hours.

## 2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The Clinical Pharmacology package submitted for NDA 22439 consisted of two single-dose bioequivalent studies in two submissions. First submission (0000) contained Study S08-0179. It was an open-label, single-dose, randomized, four period cross-over study under fasting conditions. The objectives of the study were to determine and compare the rate and extent of absorption of hydrocodone, pseudoephedrine, and chlorpheniramine from R (b) (4) 4) Oral Solution to that from Hycodan Syrup (RLD for hydrocodone), pseudoephedrine solution, and chlorpheniramine solution. Twenty-five healthy adult subjects completed the study. The study results showed bioequivalence on pseudoephedrine and chlorpheniramine component of the (b) (4) but failed to demonstrate bioequivalence to hydrocodone component of RLD.

Study SAM-09-1010 was then submitted in Submission 0009. It was an open-label, single-dose, randomized, two-period, two-treatment, two-sequence crossover study under fasting conditions. Each period was separated by a minimum of 7-day washout. One hundred forty seven subjects completed the study. The objective of this study was to demonstrate the bioequivalence of hydrocodone component in (b) (4) to homatropine methylbromide/ hydrocodone bitartrate 1.5 mg/5 mg per 5 mL syrup (RLD, manufactured by Hi-Tech Pharmacal Co, Inc.) in healthy adult subjects.

No clinical study to determine safety and efficacy of the product was carried out in this NDA. The sponsor is relying for safety and efficacy on Agency's DESI review finding for Hycodan syrup, NDA 05213 and OTC Monographs for pseudoephedrine and chlorpheniramine.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Hydrocodone, chlorpheniramine, and pseudoephedrine in the plasma samples were measured in NDA 22439.

2.2.3 What are the single dose pharmacokinetic parameters?

Single dose pharmacokinetic parameters for hydrocodone in healthy volunteers under fasting conditions were presented in Table 3. Single dose pharmacokinetic parameters for pseudoephedrine are listed in Appendix 4.2.

## 2.3 General Biopharmaceutics

2.3.1 What is the relative bioavailability of the formulations (reference and test) based on the pivotal bioequivalence studies? Was the bioequivalence demonstrated between the two formulations?

Results of Study S08-0179 in Submission 0000 have been extensively reviewed in Clinical Pharmacology Review by Dr. Sheetal Agarwal on July 20, 2009. For details, see Appendix 4.2. It has been concluded that the components of pseudoephedrine and chlorpheniramine in (b) (4) oral solution are bioequivalent under fasting condition as evident that the 90% CIs for the ratios of the geometric means for $C_{max}$, $AUC_{0-t}$, and $AUC_{0-inf}$ were within the limits for bioequivalence (80-125%).

Results from Study SAM-09-1010 in Submission 0009 of the NDA are discussed below. The bioequivalence of hydrocodone component in (b) (4) has been demonstrated under fasting condition as evident by the observation that the 90% CIs ratios of the geometric means for $C_{max}$, $AUC_{0-t}$, and $AUC_{0-inf}$ were within the limits for bioequivalence (80-125%) for hydrocodone

(Table 4). Ratio of Test over Reference on hydrocodone parameters of $C_{max}$, $AUC_{0-t}$, and $AUC_{0-inf}$ are similar to that from Study S08-0179.

The arithmetic mean plasma pharmacokinetic parameters for the two formulations are summarized in Table 3.

**Table 3 Arithmetic Mean (SD) of Plasma Pharmacokinetic Parameters of Hydrocodone Following Single Dose Administration of 5 mL (b) (4) Oral Solution (Test) and Hydrocodone Bitartrate and Homatropine Methylbromide Syrup Manufactured by Hi-Tech Pharmacal Co., Inc. (Reference) †**

| Parameters | Test Product | Reference Product |
|---|---|---|
| N | (b) (4) | |
| $C_{max}$ (pg/mL) | | |
| $AUC_{0-inf}$ (hr×pg/mL) | | |
| $AUC_{0-t}$ (hr×pg/mL) | | |
| $T_{max}$ (hr)†† | | |
| $T_{1/2}$ (hr) | | |

† Analysis performed by reviewer
†† Median [range]

**Table 4 Pharmacokinetics Parameters and Bioequivalence Statistics of Hydrocodone Following Single Dose Administration of 5 mL (b) (4) Oral Solution (Test) and Hydrocodone Bitartrate and Homatropine Methylbromide Syrup Manufactured by Hi-Tech Pharmacal Co., Inc. (Reference)**

| PK Parameter | Statistics | Test | Ref | Test-to-Ref Ratio (90% CI)[1] |
|---|---|---|---|---|
| AUC(0-t) [pg.hr/ml] | N | (b) (4) | | |
| | Mean ± SD | | | |
| | CV% | | | |
| | Median | | | |
| | Min, Max | | | |
| | GeoLSM[1] | | | |
| AUC(0-inf) [pg.hr/ml] | N | | | |
| | Mean ± SD | | | |
| | CV% | | | |
| | Median | | | |
| | Min, Max | | | |
| | GeoLSM[1] | | | |
| Cmax [pg/ml] | N | | | |
| | Mean ± SD | | | |
| | CV% | | | |
| | Median | | | |
| | Min, Max | | | |
| | GeoLSM[1] | | | |

[1]GeoLSMs and 90% CI for ratio of GeoLSMs calculated from ANOVA model on log-transformed data with terms of treatment, period, sequence and subject within sequence, and expoentiated back to the original scale.

2.3.2 What is the effect of food on the bioavailability of the drug from the dosage form?

No specific pharmacokinetic studies to determine the effect of food on the disposition of hydrocodone, chlorpheniramine and pseudoephedrine were conducted in this NDA package. As a post meeting comment on January 14, 2008 to the pre-IND meeting on an (b) (4) the Agency has agreed that no food effect study was needed with the proposed oral solution formulation (b) (4) (b) (4)
This has also been discussed internally within the Office of Clinical Pharmacology and same agreement has been reached.

## 2.4 Analytical Section

2.4.1 What bioanalytical methods are used to assess concentrations?

For the analytical portion of the Cypress Pharmaceuticals, Inc. Protocol No. S08-0179, please see Clinical Pharmacology Review by Dr. Sheetal Agarwal on July 20, 2009 (Appendix 4.2).

The analytical portion of the Cypress Pharmaceuticals, Inc. Protocol No. SAM-09-1010 was on hydrocodone only. It was analyzed a (b) (4) (b) (4)

(b) (4)

**Table 5 Analytical Method Validation Summary on Hydrocodone**

(b) (4)

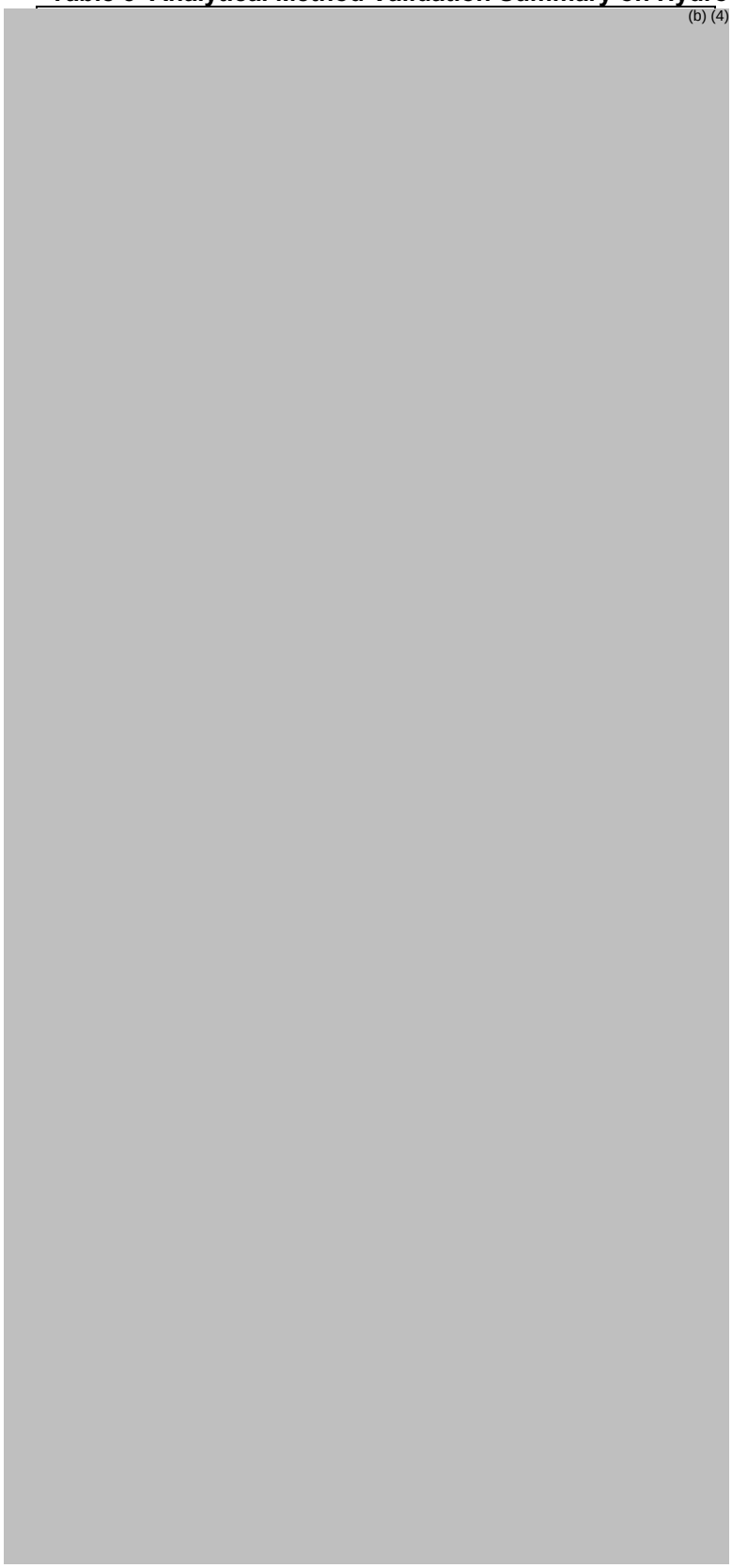


**Table 6 Plasma Assay Parameters for Hydrocodone**

| | Hydrocodone |
|---|---|
| Lower Limit of Quantitation (pg/mL) | (b) (4) |
| Assay Range (pg/mL) | |
| Linearity (correlation coefficient) | |
| Precision (%CV)† | |
| Accuracy (%Theoretical)† | |

† Included quality control values which did not meet the acceptance criteria.

## 3 Detailed Labeling Recommendations



11 pages of draft labeling have been withheld in full as B(4) CCI/TS immediately following this page

# 4 Appendix

## 4.1 Cover Sheet and OCPB Filing/Review Form

| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION | | Clinical Pharmacology<br>Tracking/Action Sheet for Formal/Informal Consults | |
|---|---|---|---|
| From: **Sandra Suarez-Sharp** | | **To: DOCUMENT ROOM (LOG-IN and LOG-OUT)**<br>**Please log-in this consult and review action for the specified IND/NDA submission** | |
| **DATE OF SUBMISSION:**<br>November 7, 2008 | **NDA No.:** 22-442<br>**Serial No.:** | BLA No. | **DATE OF REVIEW:**<br>December 4, 2008 |
| **NAME OF DRUG:**<br>REZIRA™ (b)<br>(Hydrocodone Bitartrate and Pseudoephedrine Hydrochloride) Oral Solution | **PRIORITY CONSIDERATION:**<br>**S or P** | | **Date of informal/Formal Consult**:<br>November 12, 2008 |

**NAME OF THE SPONSOR**: Cypress Pharmaceutical, Inc.

**TYPE OF SUBMISSION**

**CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE**

| | | |
|---|---|---|
| ☐ PRE-IND | ☐ DISSOLUTION/IN-VITRO RELEASE | ☐ FINAL PRINTED LABELING |
| ☐ ANIMAL to HUMAN SCALING | ☐ BIOAVAILABILITY STUDIES | ☐ LABELING REVISION |
| ☐ IN-VITRO METABOLISM | ☐ IN-VIVO WAIVER REQUEST | ☐ CORRESPONDENCE |
| ☐ SAFETY PROTOCOL | ☐ SUPAC RELATED | ☐ DRUG ADVERTISING |
| ☐ PHASE II PROTOCOL | ☐ CMC RELATED | ☐ ADVERSE REACTION REPORT |
| ☐ PHASE III PROTOCOL | ☐ PROGRESS REPORT | ☐ ANNUAL REPORTS |
| ☐ DOSING REGIMEN CONSULT | ☐ SCIENTIFIC INVESTIGATIONS | ☐ FAX SUBMISSION |
| ☐ PK/PD- POP PK ISSUES | ☐ MEETING PACKAGE | ☒ OTHER *(SPECIFY BELOW):* *NDA Filing Review* |
| ☐ PHASE IV RELATED | | |

## REVIEW ACTION

| | | |
|---|---|---|
| ☐ NAI (No action indicated)<br>☐ E-mail comments to:<br>☐Medical ☐Chemist ☐Pharm-Tox ☐Micro ☐ Pharmacometrics ☐Others (Check as appropriate and attach e-mail) | ☐ Oral communication with<br>Name: [ ]<br>☐ Comments communicated in meeting/Telecon. see meeting minutes dated:<br>[ ] | ☒ Formal Review/Memo (attached)<br>☐See comments below<br>☐See submission cover letter<br>☐ OTHER *(SPECIFY BELOW)*:<br>[Please see attached memo] |

**REVIEW COMMENT(S)**

☒ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

## COMMENTS/SPECIAL INSTRUCTIONS:

### 1. Summary

This NDA filing review is for REZIRA™ (b) Oral Solution. REZIRA™ (b) Oral Solution is a

combination product containing Hydrocodone Bitartrate (HC) 5 mg and Pseudoephedrine Hydrochloride (PSE) 60 mg per 5 mL. The sponsor is seeking approval of REZIRA™ (b) for the (b) (4) relief of cough and for the (b) (4) relief of nasal congestion due to the common cold. (b) (4). The proposed dosing regimen is 5 mL every 4-6 h, as needed, NTE 4 doses (20 mL) in 24 h in adults (b) (4) (b) (4) HC is approved for the symptomatic relief of cough in Hycodan (NDA 05-213) and PSE is an accepted nasal decongestant in the OTC Monograph (21 CFR §341.20).

The sponsor is filing the NDA for REZIRA™ (b) through 505(b)(2) pathway, relying on the Agency's findings in DESI review for HC and OTC Monograph for PSE to support the safety and efficacy of their combination drug product. There are no clinical pharmacology studies conducted with REZIRA™ (b). Reference is made to the pre-IND meeting for IND (b) (4) with Cypress Pharmaceuticals on 01/14/2008 where the DPAP agreed to extrapolate the results from a BE/BA and drug-drug interaction (DDI) study to be conducted for Hydrocodone Bitartrate, Chlorpheniramine maleate, and Pseudoephedrine Hydrochloride Oral Solution. During the pre-IND meeting for IND (b) (4) the DPAP stated the following:

*"The waiver of BE requirements for your proposed oral solution products cannot be granted (b) (4) (b) (4) Therefore, you need to conduct in vivo BE studies for the following proposed products using the appropriate reference for each active ingredient. These studies may also provide information for potential drug-drug interaction among the components:*

- (b) (4)
- (b) (4)
- *Hydrocodone, Chlorpheniramine, and Pseudoephedrine Oral Solution.*

*The waiver of BE requirements for the following proposed oral solution products may be granted based on the results of the above mentioned BE studies provided no major changes in the formulation (inactive ingredients) has occurred:*

- *Hydrocodone and Pseudoephedrine Oral Solution*
- (b) (4)

It is noted that the formulation for REZIRA™ (b) is very similar to that for (b) (4) (Hydrocodone Bitartrate, Chlorpheniramine maleate, and Pseudoephedrine Hydrochloride Oral Solution). The only difference between both formulations is the presence of CPM in the three-ingredient formulation (b) (4) (see appendix under drug product). (b) (4) was submitted to the FDA on November 6, 2008 and is also under review for filing.

It should be noted that the results of any BE/BA and DDI study perform with the 3 ingredient product (Hydrocodone, Chlorpheniramine, and Pseudoephedrine Oral Solution) may be extrapolated to the 2 ingredient product (b) (4) if there is no DDI among the 3 components. However, in the presence of a DDI in the 3-ingredient combination product, declaration of bioequivalence between the proposed two combination product and the references

may not hold true.

In support of NDA 22-439 for [redacted] (three-ingredient combination product)[1] the sponsor included the results of one clinical pharmacology study (Study S08-0179) entitled "A Relative Bioavailability and Drug-Drug Interaction Study of Hydrocodone, Pseudoephedrine, and Chlorpheniramine Oral Solution (5 mg/60 mg/4 mg per 5 mL), Pseudoephedrine Oral Solution (60 mg per 5 mL), Chlorpheniramine Oral Solution (4 mg per 5 mL) and Hycodan® Syrup (5 mg Hydrocodone Bitartrate/1.5 mg Homatropine Methylbromide per 5 mL) Under Fasted Conditions" This study is a randomized, four-period crossover, open-label, single dose study conducted in 28 healthy adult volunteers. Following an overnight fast of at least 10 hours, subjects received a single oral dose of the following treatments with a washout period of 14 days between treatments:

A. 5 mL (5 mg/4 mg/60 mg per 5 mL oral solution) of the test product, hydrocodone bitartrate/chlorpheniramine maleate/pseudoephedrine HCl oral solution or
B. 5 mL (60 mg per 5 mL oral solution) of pseudoephedrine HCl oral solution; or
C. 5 mL (4 mg per 5 mL oral solution) of chlorpheniramine maleate oral solution; or
D. 5 mL (5 mg/1.5 mg per 5 mL oral solution) of Hycodan® oral solution.

Dr. Suarez stated in the review for NDA 22-439 that preliminary assessment of the data indicates that [redacted] is equally bioavailable to Hycodan solution in terms of AUC. However, the 90% CI of the ratio of geometric Cmax means was (78.9-93.8) which is outside of the goal post for BE. [redacted] was bioequivalent to the reference products CPM solution and PSE solution, indicating that HC and CPM do not affect the systemic exposure of PSE when the 3 components are coadminstered. The data also indicated that HC and PSE do not affect the systemic exposure of CPM when the 3 components are coadministered. She stated that the PK study as designed would not determine the effect of PSE and CPM on the systemic exposure of HC. A comparison of the test product vs. Hycodan does not address for the potential effect of CPM and PSE on the PK of HC due to the possibility of a confounded formulation effect. Therefore, the sponsor needs to provide information on the potential effect of PSE and CPM on the PK of HC.

It is noted that information on the potential for food effect on the PK of REZIRA™ [redacted] was not included in the present submission. Reference is made to the pre-IND meeting with the sponsor where the DPAP recommended the assessment of food effect [redacted]

**1.1 Recommendation**

The Division of Clinical Pharmacology 2 (DCP2) has reviewed NDA 22-442 submitted on November 7, 2008 for filing purposes. The NDA is filable from a clinical pharmacology perspective. The following comments should be conveyed to the sponsor as part of the 74-day letter.

**Comments:**

- The results of the BE/BA and drug-drug interaction (DDI) study performed with the 3 ingredient product ([redacted] may be extrapolated to the 2 ingredient product

[1] Clinical Pharmacology filing review for NDA 21-439 by Dr. Sandra Suarez. The filing for NDA 21-439 is happening at the same time as the filing for NDA 21-422.

(REZIRA™ (b) ) if there is no DDI among the 3 components. However, in the presence of a DDI in the 3-ingredient combination product, declaration of bioequivalence between the proposed two combination product and the references may not hold true. The PK study (S08-0179) included under NDA 21-439 would not determine the effect of pseudoephedrine (PSE) and chlorpheniramine (CPM) on the systemic exposure of Hydrocodone (HC). A comparison of (b) (4) vs. Hycodan (TRT A vs. D) does not address for the potential effect of CPM or PSE on the PK of HC due to the possibility of a confounded formulation effect. Therefore, you are requested to provide information on the potential effect of PSE and CPM on the PK of HC. You may rely on published information or conduct an additional PK study.

- It is noted that information on the potential of food effect on the PK of REZIRA™ (b) was not included in the present submission. Reference is made to the pre-IND meeting for IND (b) (4) (01/14/2008) with the sponsor where the DPAP recommended the assessment of food effect (b) (4) Therefore, you are requested to provide information on the effect of food on the BA of REZIRA™ (b) You may choose to submit food effect information based on published literature, (b) (4) or conduct and additional food effect study.

| | |
|---|---|
| **SIGNATURE OF REVIEWER:**<br>Sandra Suarez-Sharp, Ph.D.<br>_____<br>**SIGNATURE OF TEAM LEADER (acting):**<br>Wei Qiu, Ph.D. _____ | Date _____<br><br>Date _____ |
| **CC.: HFD # [ ]; TL: [ ]; DD: [ ]** | **Project Manager:**_____<br>**Date** _____ |

**Background**

The sponsor is filing the NDA for REZIRA™ (b) through 505(b)(2) pathway, relying on the Agency's findings in DESI review for HC and OTC Monograph for PSE to support the safety and efficacy of their two-ingredient combination product. There are no clinical pharmacology studies conducted with REZIRA™-D. Reference is made to the pre-IND meeting for IND (b) (4) with Cypress Pharmaceuticals on 01/14/2008 where the DPAP agreed to extrapolate the results obtained from a BE/BA and DDI study to be conducted for Hydrocodone Bitartrate, Chlorpheniramine maleate, and Pseudoephedrine Hydrochloride Oral Solution. Thus, the sponsor is also relying on the results of study S08-01479 submitted under NDA 21-439 for the three-ingredient combination product to support the approval of REZIRA™ (b)

HC is approved for the symptomatic relief of cough in Hycodan (NDA 05-213) and PSE is an accepted nasal decongestant in the OTC Monograph (21 CFR §341.20).

HC is an analgesic opioid and antitussive. The precise mechanism of action of HC and other opioids is not known. It is believed to relate to the existence of opioid receptors in the central nervous system. HC and related compounds are used for the symptomatic relief of non-productive cough associated with upper and lower respiratory tract congestion. HC's binding to plasma protein ranges between 19% and 45%. The mean peak serum concentration (Cmax) of HC is 23.6 ± 5.2 ng/mL when administered as an oral dose of 10 mg. Maximum serum levels are reached in 1.3 ± 0.3 hours and the elimination half-life (t1/2) was determined to be 3.8 ± 0.3 hours. HC exhibits a complex pattern of metabolism, including O- demethylation, N-demethylation, and 6-keto reduction to the corresponding 6-α- and 6-ß-hydroxy metabolites. Hydromorphone, a potent opioid, is formed from the O-demethylation of HC and contributes to the total analgesic effect of HC.

PSE is a sympathomimetic amine that acts as an α-adrenergic agonist. It is indicated for use as a nasal decongestant. The Tmax for PSE following 60 mg or 120 mg doses is from 1.4 to 2 hours. Administration of a single large dose of 180 mg PSE increases Tmax to 3 hours. The reported t1/2 is 4-8 hours for pseudoephedrine.

HC and PSE are not currently approved in combination in the USA as a new drug, but each is offered in approved products separately. In the USA, HC is marketed as Hycodan® syrup and is a prescription product, PSE is marketed as Advil Allergy Sinus, respectively, and is a over-the-counter (OTC) product.

**Drug Product**

REZIRA (b) (4) (hydrocodone bitartrate and pseudoephedrine hydrochloride) Oral Solution is a clear, colorless to light yellow liquid with a grape odor. Each milliliter of the solution contains (b) (4) of HC and (b) (4) of PSE as the active ingredients. The components and composition for REZIRA (b) (4) are shown in Table 1.

It is noted that the formulation for REZIRA (b) (4) is very similar to that for REZIRA-CC (see Table 2) . The only difference between both formulations is the presence of CPM in the three-ingredient formulation and a slight change in water content to make up for the absence of CPM.

**Table 1. Unit Composition of REZIRA (b) (4) Oral Solution**

| Component | Reference to Quality Standards | Function | Unit Composition | | | |
|---|---|---|---|---|---|---|
| | | | % w/v | mg/mL | (b) (4) | mg/480 mL |
| Hydrocodone Bitartrate | USP | Active ingredient | (b) (4) | | | |

| | | |
|---|---|---|
| Pseudoephedrine Hydrochloride | USP | (b) (4) |
| 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.

**Table 2. Unit Composition of (b) (4) Oral Solution**

| Component | Reference to Quality Standards | Function | Unit Composition | | | |
|---|---|---|---|---|---|---|
| | | | % w/v | mg/mL | (b) (4) | mg/480 mL |
| Hydrocodone Bitartrate | USP | | | | | (b) (4) |
| Chlorpheniramine Maleate | USP | | | | | |
| Pseudoephedrine Hydrochloride | USP | | | | | |
| 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 | (b) (4) (b) (4) |

NF National Formulary.

**Clinical Pharmacology Study Included Under NDA 21-439 Submission for** (b) (4) (b) (4)

**Study (S08-0179):** "A Relative Bioavailability and Drug-Drug Interaction Study of Hydrocodone, Pseudoephedrine, and Chlorpheniramine Oral Solution (5 mg/60 mg/4 mg per 5 mL), Pseudoephedrine Oral Solution (60 mg per 5 mL), Chlorpheniramine Oral Solution (4 mg per 5 mL) and Hycodan® Syrup (5 mg Hydrocodone Bitartrate/1.5 mg Homatropine Methylbromide per 5 mL) Under Fasted Conditions"

**STUDY OBJECTIVES**

The objectives of this study were:

1) To determine and compare the rate and extent of absorption of hydrocodone from the following products under fasted conditions:
   a) Hydrocodone, Pseudoephedrine, and Chlorpheniramine Oral Solution (5 mg / 60 mg / 4 mg per 5 mL)
   b) Hycodan® Syrup (5 mg hydrocodone bitartrate / 1.5 mg homatropine methylbromide per 5 mL)
2) To evaluate the drug-drug interaction of pseudoephedrine with hydrocodone and clorpheniramine from the following products under fasted conditions:
   a) Hydrocodone, Pseudoephedrine, and Chlorpheniramine Oral Solution (5 mg / 60 mg /4 mg per 5 mL)
   b) Pseudoephedrine Oral Solution (60 mg per 5 mL)
3) To evaluate the drug-drug interaction of chlorpheniramine with pseudoephedrine and hydrocodone from the following products under fasted conditions:
   a) Hydrocodone, Pseudoephedrine, and Chlorpheniramine Oral Solution (5 mg / 60 mg /4 mg per 5 mL)
   b) Chlorpheniramine Oral Solution (4 mg per 5 mL)

**Overall Study Design and Plan**

This study is a randomized, four-period crossover, open-label, single dose study conducted in 28 healthy adult volunteers (male and female). Following an overnight fast of at least 10 hours, subjects received a single oral dose of the following treatments with a washout period of 14 days between treatments:

A. 5 mL (5 mg/4 mg/60 mg per 5 mL oral solution) of the test product, hydrocodone bitartrate/chlorpheniramine maleate/pseudoephedrine HCl oral solution; or
B. 5 mL (60 mg per 5 mL oral solution) of pseudoephedrine HCl oral solution; or
C. 5 mL (4 mg per 5 mL oral solution) of chlorpheniramine maleate oral solution; or
D. 5 mL (5 mg/1.5 mg per 5 mL oral solution) of Hycodan® oral solution.

**Blood Sampling**

Serial blood samples for PK determination of HC, PSE and CPM were collected at pre-dose and up to 96 hours. For treatments A and C blood samples were to be collected within 90 minutes prior to dosing (0 hour) and after dose administration at study hours

0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96. For treatments B and D blood samples were to be collected within 90 minutes prior to dosing (0 hour) and after dose administration at study hours 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, and 24.

**Analytical Methodology**


**Data Analysis**


**Prior and Concomitant Medication**

Subjects were not to be allowed to use prescription medications during the 14 days preceding the study and throughout the study with the exception of contraceptive

medication . Subjects were not to be allowed to use non-prescription medications during the 7 days preceding the study and throughout the study.

**Results**

Figure 1-3 show the concentration-time profile following administration of the treatments. A summary of the mean PK parameters for HC, PSE and CPM following administration of the treatments is shown in Table 1. The results of the statistical analysis for the comparison of interest are summarized in Table 2. A preliminary assessment of the data indicates that REZIRA™ (b) is equally bioavailable to Hycodan solution in terms of AUC. However, the 90% CI of the ratio of geometric Cmax means was outside of the goal post for BE ((b) (4)). REZIRA™ (b) was bioequivalent to the reference products CPM solution and PSE solution, indicating that HC and CPM do not affect the systemic exposure of PSE when the 3 components are coadminstered. The data also indicate that HC and PSE do not affect the systemic exposure of CPM when the 3 components are coadministered. The PK study, however, was not designed to determine the effect of PSE and CPM on the systemic exposure of HC. A comparison of the test product vs. Hycodan does not address for the potential effect of CPM or PSE on the PK of HC due to the possibility of a confounded formulation effect.

It is noted that information on the potential of food effect on the PK of REZIRA™ (b) was not included in the present submission. Reference is made to the pre-IND meeting with the sponsor where the DPAP recommended the assessment of food effect (b) (4)

(b) (4)

PLASMA HYDROCODONE NG/ML

**Figure 1.** Mean plasma concentration-time profile for HC following single dose administration 5 mL (5 mg/4 mg/60 mg per 5 mL oral solution) of HC /CPM/PSE oral solution (Test) and 5 mL (5 mg/1.5 mg per 5 mL oral solution) of Hycodan® oral solution (Reference).


**Figure 2.** Mean plasma concentration time profile for PSE following single dose administration of 5 mL of Test and 5 mL (60 mg per 5 mL oral solution) of PSE HCl oral solution (Reference).

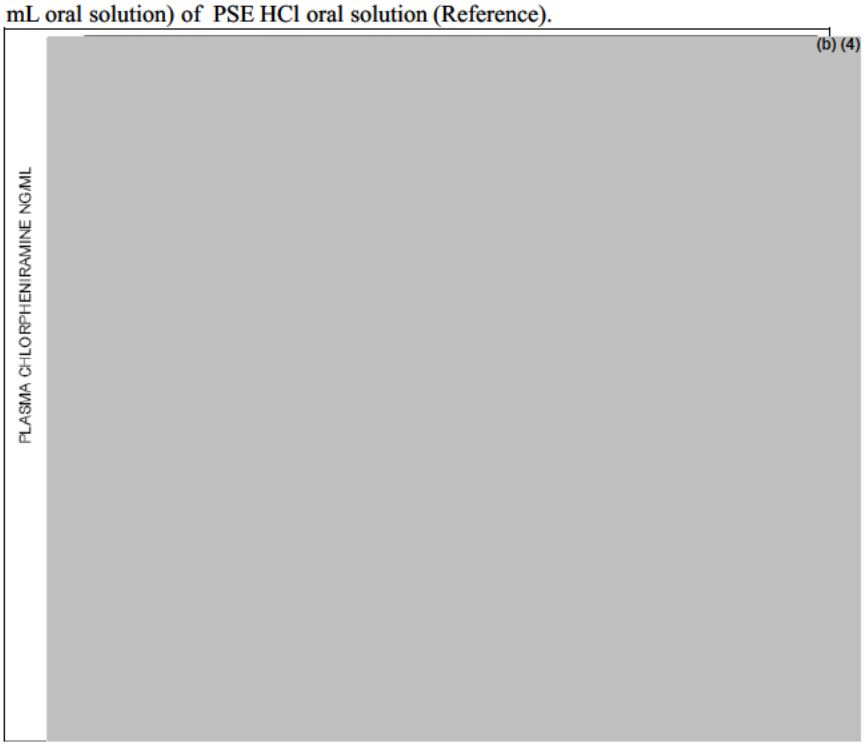



**Figure 3.** Mean plasma concentration time profile for CPM following single dose administration of 5 mL of Test and

5 mL (4 mg per 5 mL oral solution) of CPM oral solution (Reference).

**Table 1.** Summary of mean PK parameters following single dose administration of the treatments

| **Treatments (Dose, Dosage Form, Route) [Product ID]** | **Drug** | **Mean Parameters (± SD)** | | | | |
|---|---|---|---|---|---|---|
| | | **AUC (ng·h/ mL)** | **AUC (ng·h/ mL)** | **$C_{max}$ (ng/mL)** | **$T_{max}$ (h)** | **$t_{½}$ (h)** |
| 5 mg HCB 60 mg PSE **Trt A**: (1 dose, 5 mL oral solution) [P08001] 4 mg CHL | HC | (b) (4) | | | | |
| | PSE | | | | | |
| | CPM | | | | | |
| **Trt B**: (1 dose, 5 mL oral solution) [P08043] 60 mg PSE | PSE | | | | | |
| **Trt C**: (1 dose, 5 mL oral solution) [P08045] 4 mg CPM | CPM | | | | | |
| **Trt D**: (1 dose, 5 mL oral solution) [400804NV] 5 mg HYC | HYC | | | | | |

**Table 2.** Summary of statistical analysis of the log-transformed data

| Comparison | PK parameter | Point estimates (ratio of geometric means) | 90% CI |
|---|---|---|---|
| Test product/Hycodan TRT A/D | AUC t<br>AUCinf<br>Cmax | (b) (4) | |
| Test product/PSE (TRT A/B) | AUC t<br>AUCinf<br>Cmax | | |
| Test product/CPM (TRT A/C) | AUC t<br>AUCinf<br>Cmax | | |

# Office of Clinical Pharmacology

## *New Drug Application Filing and Review Form*

**General Information About the Submission**

| | Information | | Information |
|---|---|---|---|
| **NDA Number** | 22 442 | **Brand Name** | REZIRA™ (b) Oral Solution |
| **OCP Division** | II | **Generic Name** | (Hydrocodone Bitartrate, and Pseudoephedrine Hydrochloride) Oral Solution |
| **Medical Division** | DPAP | **Drug Class** | Cough suppressant/nasal decongestant |
| **OCPB Reviewer** | Sandra Suarez Sharp | **Indication(s)** | (b) (4) relief of cough and for the (b) (4) relief of nasal congestion due to the common col (b) (4) |
| **OCP Team Leader (Acting)** | Wei Qiu | **Dosage Form** | Oral Solution |
| **PM Reviewer** | | **Dosing Regimen** | The proposed dosing regimen is 5 mL every 4 6 h, as needed, NTE 4 doses (20 mL) in 24 h in adults (b) (4) (b) (4) |
| **Date of Submission** | November 7, 2008 | **Route of Administration** | Oral |
| **Estimated Due Date of OCP Primary Review** | April 2009 | **Sponsor** | Cyrpess |
| **PDUFA Due Date** | Sep 7, 2009 | **Priority Classification** | s |
| **Division Due Date** | July 10, 2009 | | |

Clin. Pharm. Information

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | X | | | |
| **Tabular Listing of All Human Studies** | X | | | |
| **HPK Summary** | X | | | |
| **Labeling** | X | | | |
| **Reference Bioanalytical and Analytical Methods** | X | | | |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | | | | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| ***Healthy Volunteers-*** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **Patients-** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |

| | | | | |
|---|---|---|---|---|
| **Dose proportionality -** | | | | |
| fasting / non fasting single dose: | | | | |
| fasting / non fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In vivo effects on primary drug: | | | | |
| In vivo effects of primary drug: | | | | |
| In vitro: | | | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| **PD:** | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD:** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Meta analysis: | | | | |
| Data sparse: | | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability:** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | **1** | **x** | | Study (S08 0179):"A Relative Bioavailability and Drug Drug Interaction Study of Hydrocodone, Pseudoephedrine, and Chlorpheniramine Oral Solution (5 mg/60 mg/4 mg per 5 mL), Pseudoephedrine Oral Solution (60 mg per 5 mL), Chlorpheniramine Oral Solution (4 mg per 5 mL) and Hycodan® Syrup (5 mg Hydrocodone Bitartrate/1.5 mg Homatropine Methylbromide per 5 mL) Under Fasted Conditions" |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies:** | | | | |
| **Dissolution:** | | | | |
| **(IVIVC):** | | | | |
| **Bio-wavier request based on BCS** | | | | |
| **BCS class** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies:** | | | | |
| **QTC STUDIES (PHASE 1)** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | | | | |
| **Total Number of Studies** | **x** | **1** | | |

| | | | | |
|---|---|---|---|---|
| **Filability and QBR comments** | | | | |
| | **"X" if yes** | Comments | | |
| **Application filable ?** | X | Reasons if the application is not filable (or an attachment if applicable)<br>For example, is clinical formulation the same as the to be marketed one? | | |
| **Comments sent to firm ?** | | Comments have been sent to firm (or attachment included). FDA letter date if applicable.<br>Please see Clinical Pharmacology filing review for deficiencies. | | |
| **QBR questions (key issues to be considered)** | 1. Is REZIRA™ (b (Hydrocodone Bitartrate and Pseudoephedrine Hydrochloride) Oral Solution equivalent to the reference products (Hycodan PSE oral solutions)?<br>2. What is the degree of drug drug interaction between HC and PSE in the combination product REZIRA™ (b ?<br>**3.** What is the effect of food on the bioavailability of REZIRA™ (b | | | |
| **Other comments or information not included above** | | | | |
| **Primary reviewer Signature and Date** | | | | |
| **Secondary reviewer Signature and Date** | | | | |

## 4.2 Clinical Pharmacology Review on Submission 0000 (Study S08-0179)

## CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| **NDA:** | 22-442 |
| **Type:** | 505 (b) (2) |
| **Brand Name:** | REZIRA [redacted] Oral Solution |
| **Generic Name:** | Hydrocodone and Pseudoephedrine Oral Solution |
| **Indication:** | [redacted] relief of cough and for the [redacted] relief of nasal congestion due to the common cold. |
| **Dosage Form:** | Solution |
| **Route of Administration:** | Oral |
| **Strength:** | Each [redacted] (5 mL) of REZIRA [redacted] Oral Solution contains: hydrocodone bitartrate, USP, 5 mg; and pseudoephedrine hydrochloride, USP, 60 mg. |
| **Dosing regimen:** | Adults [redacted]<br>• [redacted] (5 mL) every 4 to 6 hours as needed, not to exceed 4 doses (20 mL) in 24 hours.<br>[redacted] |
| **Applicant:** | Cypress Pharmaceuticals |
| **OCP Division:** | Division of Clinical Pharmacology 2 |
| **Clinical Division:** | Division of Pulmonary and Allergy Products (ONP-570) |
| **Submission Date:** | November 17, 2008 |
| **Reviewer:** | Sheetal Agarwal, Ph.D. |
| **Team Leader:** | Sally Choe, Ph. D. |

## TABLE OF CONTENTS

## 1.0 Executive summary

This is a 505 (b) (2) NDA for an oral solution containing hydrocodone bitartrate and pseudoephedrine hydrochloride (5 mg and 60 mg per 5 mL respectively). The proposed proprietary name for this product is REZIRA [(b) (4)] Oral Solution. Hydrocodone bitartrate is approved for the [(b) (4)] relief of cough in HYCODAN (NDA 05-213), chlorpheniramine maleate is an accepted antihistamine in the OTC Monograph (21 CFR §341.12), and pseudoephedrine HCl is an accepted nasal decongestant in the OTC Monograph (21 CFR §341.20).

The proposed indication is for [(b) (4)] relief of cough; and for the [(b) (4)] relief of nasal congestion due to the common cold.

## 1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the submitted Clinical Pharmacology information for NDA 22-442 for the proposed indication and finds it unacceptable. The hydrocodone component of the test product, [(b) (4)] Oral Solution, is not bioequivalent to the reference listed drug (RLD), Hycodan® Syrup in the submitted pivotal relative bioavailability study for this 505 (b) 2 NDA application.

## 1.2 Phase 4 Commitments

Not applicable.

## 1.3 Summary of Important Clinical Pharmacology Findings

The Clinical Pharmacology package submitted for this NDA consisted of a single relative bioavailability and drug-drug interaction study (Study S08-0179) conducted under NDA 22-439 in 25 healthy adult volunteers for [(b) (4)] Oral Solution, a fixed dose combination (FDC) oral solution containing hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride (5 mg, 4 mg, and 60 mg per 5 mL respectively). Both NDAs, 22-439 (for [(b) (4)] Oral Solution and 22-442 (for REZIRA [(b) (4)] Oral Solution) were submitted at the same time to the Agency. The objectives of the clinical study were to determine and compare the rate and extent of absorption of hydrocodone from [(b) (4)] Oral Solution to that from Hycodan® Syrup (RLD); and to evaluate the drug-drug interaction impact of pseudoephedrine on hydrocododone and chlorpheniramine in [(b) (4)] Oral Solution, and chlorpheniramine on pseudoephedrine, and chlorpheniramine in [(b) (4)] Oral Solution. Because [(b) (4)] Oral Solution and REZIRA [(b) (4)] Oral Solution are exactly same formulations except for one active ingredient, i.e., chlorpheniramine in [(b) (4)] Oral Solution, the sponsor used the study results from S08-0179 to demonstrate bioequivalence between REZIRA [(b) (4)] Oral Solution and Hycodan® Syrup for hydrocodone. As discussed in the pre-NDA meeting minutes, the Agency agreed this

approach is acceptable. Besides this study, no additional studies (relative BA or DDI) were conducted employing REZIRA (b) (4) Oral Solution.

Study S08-0179 was an open-label, single-dose, randomized, four period cross-over study under fasted conditions. The dosing regimen and the statistical summary are presented below. This reviewer has reanalyzed the PK information submitted for this pivotal relative BA study by employing WinNonLin version 5.2 to obtain the noncompartmental PK parameters and perform the BE analysis. The results of this reanalysis are in agreement with the results submitted by the sponsor.

**Dosing Regimen**

- 5 mL dose of hydrocodone, pseudoephedrine, and chlorpheniramine oral solution (5 mg / 60 mg / 4 mg per 5 mL) **(Treatment A)**
- 5 mL dose of pseudoephedrine oral solution (60 mg per 5 mL) (**Treatment B**)
- 5 mL dose of chlorpheniramine oral solution (4 mg per 5 mL) (**Treatment C**)
- 5 mL dose of Hycodan® Syrup (5 mg hydrocodone bitartrate / 1.5 mg homatropine methylbromide per 5 mL) (**Treatment D**)

Bioequivalence Comparison Summary Statistics of PK Parameters for hydrocodone bitartrate:

| | Test/Ref ratio (%) | 90% CI | |
|---|---|---|---|
| | | Lower | Upper |
| AUC 0-inf | (b) (4) | | |
| AUC 0-t | | | |
| Cmax | | | |

Overall, the test product (b) (4) Oral Solution is not bioequivalent to the corresponding reference product for hydrocodone, Hycodan syrup. The lower limit of the 90% CI of the geometric mean of Cmax for hydrocodone was (b) (4), which is outside of the 80% 125% bioequivalence range. Based on this conclusion, it can therefore be concluded that the subject of this NDA, REZIRA (b) (4) Oral Solution is also not bioequivalent to the corresponding reference product for hydrocodone, Hycodan syrup. No information on exposure response relationship could be found for hydrocodone as evidence to support that a lower Cmax will not affect its efficacy as a cough depressant. Therefore, unless the sponsor can provide convincing evidence to demonstrate that a shift in Cmax will not affect the efficacy, the test product, REZIRA (b) (4) Oral Solution, cannot be considered bioequivalent to the reference product, Hycodan® Syrup (RLD).

The other two components of the test product (b) (4) Oral Solution, chlorpheniramine and pseudoephedrine are equivalent in terms of both rate and formation to the corresponding test products respectively. The geometric means as well as the 90% CI limits for both chlorpheniramine and pseudoephedrine are well within the 80-125% limits for all the three PK parameters measured, i.e., Cmax, AUClast and AUCinf with respect to those of the reference products. Based on this conclusion, it can therefore be

concluded that the pseudoephedrine component of REZIRA (b) (4) Oral Solution is also bioequivalent to the corresponding reference product for pseudoephedrine.

## 2.0 Question Based Review

## 2.1 General Attributes of the Drug

### 2.1.1 *What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?*

Hydrocodone and pseudoephedrine are not currently approved as a combination product in the United States, but each is offered as an approved product or a part of a combination product. Hydrocodone is marketed as Hycodan® syrup, a fixed dose combination oral syrup product containing homatropine methylbromide 1.5 mg/5 ml and hydrocodone bitartrate 5 mg/5 ml under NDA 005213, held by Endo Pharmaceuticals, Inc.) and is a prescription product and pseudoephedrine (pseudoephedrine hydrochloride; 21 CFR 341.20) is marketed as Advil® Allergy Sinus, a fixed dose combination oral suspension product containing 100 mg/ 5 ml ibuprofen, 15 mg/5 ml of pseudoephedrine hydrochloride and 1mg/5 ml chlorpheniramine maleate respectively, and both are over-the-counter (OTC) products.

Hydrocodone bitartrate has been available for over 50 years, demonstrating a long history of use in humans, with an initial approval of Hycodan® Syrup (NDA 005213) in 1943. In 2007, FDA ordered companies making unapproved hydrocodone drug products to cease manufacturing such products on or before December 31, 2007, and for those companies marketing unapproved hydrocodone products labeled for use in children younger than 6 years of age to stop manufacturing and distributing the products by October 31, 2007. The Agency removed these unapproved products from the market, indicating that NDAs should subsequently be submitted. As a result, Cypress submitted a new drug application for REZIRA (b) (4) Oral Solution (hydrocodone bitartrate nd pseudoephedrine hydrochloride) submitted in this NDA.

Cypress submitted IND 102,177 for this and other proposed combination products on April 15, 2008. A type B pre-IND meeting was held on 01/17/2008 to discuss the sponsor's concerns and the meeting minutes for this meeting can be found in DARRTS.

### 2.1.2 *What are the highlights of the properties of the drug or the formulation as they relate to clinical pharmacology review?*

***Hydrocodone Bitartrate*** is available as a fine white or slightly yellow-white powder. It is soluble in water (1 g dissolves in 16 g of water), slightly soluble in alcohol (1 g dissolves in 150 g of 95% ethanol), and almost insoluble in ether and chloroform. The pH of a 2% aqueous solution is approximately 3.6.

***Pseudoephedrine Hydrochloride*** is a white to almost white crystalline powder. It is freely soluble in water. The pH of an aqueous solution is 5.0  6.0 and its pKa is 9.9.

The proposed drug product, REZIRA (b) (4) (Hydrocodone Bitartrate and Pseudoephedrine

Hydrochloride) Oral Solution (REZIRA [(b) (4)] Oral Solution), is a clear, colorless to light yellow liquid with a grape odor. Each milliliter of the solution contains 1.0 mg of hydrocodone bitartrate and 12 mg of pseudoephedrine hydrochloride as the active ingredients. The route of administration is oral. Based on a discussion in the pre-IND meeting held on 01/14/08, the sponsor has removed [(b) (4)] (that could have affected the BA of the three components as discussed in the meeting) from the proposed product.

The unit composition, function, and quality of each component in the drug product are presented below:

**Table 2.3.P-1. Unit Composition of REZIRA-D 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 | [(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.

### 2.1.3 *What are the proposed mechanism(s) of action and therapeutic indication(s)?*

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. In excessive doses, hydrocodone, like other opium derivatives, will depress respiration. The effects of hydrocodone in therapeutic doses on the cardiovascular system are insignificant. Hydrocodone can produce miosis, euphoria, and physical and psychological dependence.

Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine hydrochloride is recognized as an effective agent for the relief of nasal congestion due to allergic rhinitis. 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.

The proposed indication is [redacted] relief of cough and for the [redacted] relief of nasal congestion due to the common cold.

### 2.1.4 *What are the proposed dosage and route of administration?*

Adults [redacted]

- [redacted] (5 mL) every 4 to 6 hours as needed, not to exceed 4 doses (20 mL) in 24 hours.

[redacted]

Each [redacted] (5 mL) of REZIRA [redacted] Oral Solution contains: hydrocodone bitartrate, USP, 5 mg; and pseudoephedrine hydrochloride, USP, 60 mg.

## 2.2 General Clinical Pharmacology

### 2.2.1 *What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?*

Based on the pre-IND meeting discussion with the Agency, the sponsor has requested for a waiver of the *in vivo* bioequivalence requirement for the proposed REZIRA [redacted] Oral Solution based on the fact that there are no major differences between this formulation and that of Cypress' proposed [redacted] Oral Solution. Hence, bioequivalence would be determined by comparing hydrocodone bitartrate in Cypress' proposed [redacted] Oral Solution with HYCODAN syrup. Therefore, in this submission for the REZIRA [redacted] Oral Solution, the sponsor has referenced one study that was conducted for a NDA submission of a triple combination product., i.e. Study S08-0179, which was a bioequivalence/bioavailability study and drug-drug interaction study for Cypress' proposed [redacted] Oral Solution (NDA 22-439). As far as drug-drug interaction for the proposed REZIRA [redacted] Oral Solution is concerned; no additional studies were conducted employing REZIRA [redacted] Oral Solution to address that concern.

The objectives of the clinical study were to determine and compare the rate and extent of absorption of hydrocodone from [redacted] Oral Solution to that from Hycodan Syrup (RLD) in healthy volunteers; and to evaluate the drug-drug interaction impact of pseudoephedrine on hydrocododone and chlorpheniramine in [redacted] Oral Solution, and chlorpheniramine on pseudoephedrine, and chlorpheniramine in [redacted] Oral Solution. This was an open-label, single-dose, randomized, four period cross-over study under fasted conditions. The dosing regimen and the statistical summary are presented below.

No clinical study to determine safety and efficacy of the product was carried out in this NDA. The sponsor is relying for safety and efficacy on Agency's DESI review findings for Hycodan syrup, NDA 05-213.

### 2.2.2 *Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?*

Hydrocodone and pseudoephedrine in the plasma samples were measured.

### 2.2.3 *What are the characteristics of the exposure-response relationship (dose response, concentration-response)?*

No exposure-response relationship was characterized in this submission.

### 2.2.4 *What are the single dose and multiple dose PK parameters in healthy subjects?*

Single oral doses of hydrocodone and pseudoephedrine were administered in healthy volunteers under fasting conditions. The PK parameters are presented below in tables 1 and 2. No multiple dose PK studies were conducted.

**Table 1: Pharmacokinetic Parameters for Hydrocodone Bitartrate after Single-dose Administration in Cypress Clinical Study S08-0179:**

| Mean Parameters (± SD) | Cypress Clinical *Study S08-0179* | |
|---|---|---|
| | N = 25 | |
| | Age Range: 18 – 54 | |
| | Test Product A (HCB/CHL/PSE) 5 mg Dose | Test Product D (HYCODAN®) 5 mg Dose |
| $AUC_{0-\infty}$ (ng·h/mL) | (b) (4) | |
| $AUC_{0-t}$ (ng·h/mL) | | |
| $C_{max}$ (ng/mL) | | |
| $T_{max}$ (h) | | |
| $t_{½}$ (h) | | |
| $K_{el}$ (1/h) | | |

**Table 2: Pharmacokinetic Parameters for Pseudoephedrine HCl after Single-dose Administration in Cypress Clinical Study S08-0179:**

| Study | Cypress Clinical *Study S08-0179* | |
|---|---|---|
| N | 25 | |
| Age Range | 18 – 54 | |
| Composition | Test Product A (HCB/CHL/PSE) Solution | Test Product B (PSE) Solution |
| Dose | 60 mg | 60 mg |
| Mean Parameters (± SD) | | |
| $AUC_{0-\infty}$ (ng·h/mL) | (b) (4) | |
| $AUC_{0-t}$ (ng·h/mL) | | |
| $C_{max}$ (ng/mL) | | |
| $T_{max}$ (h) | | |
| $t_{½}$ (h) | | |
| $K_{el}$ (1/h) | | |

### 2.2.5 *What are the ADME characteristics of the drugs involved?*

No ADME characterization for hydrocodone and pseudoephedrine was carried out in this NDA submission. However, relevant information related to the three drugs from literature review (conducted by the sponsor) is presented below:

Hydrocodone is not extensively protein bound, binding to plasma protein at a range between 19% and 45%. The mean peak serum concentration (Cmax) of hydrocodone is 23.6 ± 5.2 ng/mL when administered as an oral dose of 10 mg. Maximum serum levels are reached in 1.3 ± 0.3 hours and the elimination half-life (t1/2) was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism, including O-demethylation, N-demethylation, and 6-keto reduction to the corresponding 6-α- and 6-ß-hydroxy metabolites. Hydromorphone, a potent opioid, is formed from the O-demethylation of hydrocodone and contributes to the total analgesic effect of hydrocodone.

Pseudoephedrine is a sympathomimetic amine that acts as an α-adrenergic agonist. It is indicated for use as a nasal decongestant. Pseudoephedrine does not produce rebound congestion, as a single product or in combination with other ingredients. Frequently, it is used in combination products with analgesics, antihistamines, antitussives and expectorants. The Tmax for pseudoephedrine following 60 mg or 120 mg doses is from 1.4 to 2 hours. Administration of a single large dose of 180 mg pseudoephedrine increases Tmax to 3 hours. The reported t1/2 is 4-8 hours for pseudoephedrine.

## 2.3 General Biopharmaceutics

### 2.3.1 *What is the relative bioavailability of the formulations (reference and test) based on the pivotal BE studies?*

**Study S08-0179** was a relative bioavailability study of hydrocodone, pseudoephedrine, and chlorpheniramine oral solution (5 mg/60 mg/4 mg per 5 mL), Pseudoephedrine Oral Solution (60 mg per 5 mL), Chlorpheniramine Oral Solution (4 mg per 5 mL) and Hycodan® Syrup (5 mg hydrocodone bitartrate/1.5 mg homatropine methylbromide per 5 mL) under fasted conditions. The dosing regimen and PK summary is presented below.

**Dosing Regimen**

• 5 mL dose of hydrocodone, pseudoephedrine, and chlorpheniramine oral solution (5 mg / 60 mg / 4 mg per 5 mL) **(Treatment A)**
• 5 mL dose of pseudoephedrine oral solution (60 mg per 5 mL) (**Treatment B**)
• 5 mL dose of chlorpheniramine oral solution (4 mg per 5 mL) (**Treatment C**)
• 5 mL dose of Hycodan® Syrup (5 mg hydrocodone bitartrate / 1.5 mg homatropine methylbromide per 5 mL) (**Treatment D**)

Overall, the test product (b) (4) Oral Solution is not bioequivalent to the corresponding reference product for hydrocodone, i.e., Hycodan syrup since the hydrocodone component from the fixed dose combination oral solution product failed to meet the bioequivalence criterion (Fig.1.). The lower limit of the 90% CI of the geometric mean of $C_{max}$ for hydrocodone was (b) (4), which is outside of the 80% 125% bioequivalence range (Table 3). Treatment arm A which tests effect of chlorpheniramine and pseudoephedrine on the pharmacokinetics of hydrocodone, in addition to addressing the the relative BA property of the test product in comparison with the reference product, also addresses an important drug-drug interaction concern. The result from this study indicating that the hydrocodone exposure from the sponsor's product is not equivalent to the reference product could be an indication of a potential drug-drug interaction among the three components such that the hydrocodone exposure is affected by the other two components, chlorpheniramine and pseudoephedrine of the combination product. Therefore, extrapolating this result to REZIRA (b) (4) Oral Solution, it is possible that pseudoephedrine when administered together with hydrocodone may alter the PK of hydrocodone.

However, the other two components of the test product (b) (4) Oral Solution. i.e. chlorpheniramine (not shown here since irrelevant to this NDA) and pseudoephedrine (Fig.2) are equivalent in terms of both rate and formation to the corresponding test products. The geometric means as well as the 90% CI limits for pseudoephedrine are well within the 80-125% limits for all the three PK parameters measured, i.e., Cmax, AUClast and AUCinf with respect to reference (Table 4).

**Fig.1: Linear Plot of Mean Plasma Hydrocodone Concentrations *vs.* Time after Single-dose Administration in Cypress Clinical Study S08-0179:**


**Table 3: Bioequivalence Comparison Summary Statistics of Pharmacokinetic Parameters for Hydrocodone Bitartrate after Single-dose Administration in Cypress Clinical Study S08-0179:**

| Drug Analyte N = 25 | Geometric Mean | | Test/Reference Ratio (%) | 90% Confidence Limits | | Intra-Subject CV (%) | Power |
|---|---|---|---|---|---|---|---|
| | Test[a] | Reference[b] | | Lower | Upper | | |
| $AUC_{0-\infty}$ (ng·h/mL) | (b) (4) | | | | | | |
| $AUC_{0-t}$ (ng·h/mL) | | | | | | | |
| $C_{max}$ (ng/mL) | | | | | | | |

**Fig.2: Linear Plot of Mean Plasma Pseudoephedrine Concentrations *vs.* Time after Single-dose Administration in Cypress Clinical Study S08-0179:**


**Table 4: Bioequivalence Comparison Summary Statistics of Pharmacokinetic Parameters for Pseudoephedrine HCl after Single-dose Administration in Cypress Clinical Study S08-0179:**

| Drug Analyte N = 25 | Geometric Mean | | Test/Reference Ratio (%) | 90% Confidence Limits | | Intra-Subject CV (%) | Power |
|---|---|---|---|---|---|---|---|
| | Test[a] | Reference[b] | | Lower | Upper | | |
| $AUC_{0-\infty}$ (ng·h/mL) | (b) (4) | | | | | | |
| $AUC_{0-t}$ (ng·h/mL) | | | | | | | |
| $C_{max}$ (ng/mL) | | | | | | | |

### 2.3.2 *What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?*

No specific PK studies to determine the effect of food on the disposition of hydrocodone, and pseudoephedrine were conducted in this submission. As a post meeting comment to the pre-IND meeting, (can be found in the pre-IND meeting minutes dated 01/14/08 in DARRTS) the Agency had agreed that no food effect study was needed with the proposed oral solution formulation (b) (4)

## 2.4 Analytical Section

### 2.4.1 *What bioanalytical methods are used to assess concentrations?*

The analytical portion of the Cypress Pharmaceuticals, Inc. Protocol No. S08-0179 was conducted at (b) (4) for hydrocodone and chlorpheniramine and at (b) (4) for pseudoephedrine.

(b) (4)

### 2.4.2 *For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?*

Total plasma concentrations were measured.

### 2.4.3 *What are the lower and upper limits of quantification (LLOQ/ULOQ)?*

(b) (4)

### 2.4.4 *What are the accuracy, precision, and selectivity at these limits?*


## 2.5 Labeling comments

Not applicable. The label is not reviewed because of the significant deficiency in this application.

## 3.0 Sponsor's proposed labeling

(b) (4)

8 pages of draft labeling have been withheld in full as B(4) CCI/TS immediately following this page

## 4.0 Appendices:

## 4.1 SYNOPSIS OF STUDY S08-0179

| | |
|---|---|
| **SPONSOR:** | Cypress Pharmaceuticals, Inc.<br>135 Industrial Blvd.<br>Madison, MS 39110, USA |
| **NAME OF TEST PRODUCT:** | Hydrocodone bitartrate, psueodephedrine HCl and chlorpheniramine maleate oral solution, 5 mg/60 mg/4 mg |
| **ACTIVE INGREDIENT:** | Hydrocodone, pseudoephedrine and chlorpheniramine |
| **STUDY TITLE:** | A Relative Bioavailability and Drug-Drug Interaction Study of Hydrocodone, Pseudoephedrine, and Chlorpheniramine Oral Solution (5 mg/60 mg/4 mg per 5 mL), Pseudoephedrine Oral Solution (60 mg per 5 mL), Chlorpheniramine Oral Solution (4 mg per 5 mL) and Hycodan® Syrup (5 mg Hydrocodone Bitartrate/1.5 mg Homatropine Methylbromide per 5 mL) Under Fasted Conditions |
| **PRINCIPAL INVESTIGATOR AND STUDY SITE:** | (b) (4) |
| **STUDY DURATION:** 16 May 2008 – 06 July 2008 | |
| **STUDY TYPE:** Phase 1 | |
| **OBJECTIVES:** The objectives of this study were:<br>1) To determine and compare the rate and extent of absorption of hydrocodone from the following products under fasted conditions:<br>a) Hydrocodone, Pseudoephedrine, and Chlorpheniramine Oral Solution (5 mg / 60 mg / 4 mg per 5 mL)<br>b) HYCODAN® Syrup (5 mg hydrocodone bitartrate / 1.5 mg homatropine methylbromide per 5 mL)<br><br>2) To evaluate the drug-drug interaction of pseudoephedrine with hydrocodone and chlorpheniramine from the following products under fasted conditions:<br>a) Hydrocodone, Pseudoephedrine, and Chlorpheniramine Oral Solution (5 mg / 60 mg / 4 mg per 5 mL) | |

b) Pseudoephedrine Oral Solution (60 mg per 5 mL)

3) To evaluate the drug-drug interaction of chlorpheniramine with pseudoephedrine and hydrocodone from the following products under fasted conditions:
   a) Hydrocodone, Pseudoephedrine, and Chlorpheniramine Oral Solution (5 mg / 60 mg / 4 mg per 5 mL)
   b) Chlorpheniramine Oral Solution (4 mg per 5 mL)

**METHODOLOGY:** This was a randomized, four-period crossover, open-label, single dose study conducted under fasting conditions.

Subjects were dosed as two groups (Group 1: Subjects 01 – 23 and Group 2: Subjects 24 – 28) and remained housed for 24 hours post-dose. Following an overnight fast of at least 10 hours, subjects received either a single oral dose of 5 mL (5 mg/4 mg/60 mg per 5 mL oral solution) of the test product, hydrocodone bitartrate/chlorpheniramine maleate/pseudoephedrine HCl oral solution or a single oral dose of 5 mL (60 mg per 5 mL oral solution) of the reference product 1, pseudoephedrine HCl oral solution; or a single oral dose of 5 mL (4 mg per 5 mL oral solution) of reference product 2, chlorpheniramine maleate oral solution; or a single oral dose of 5 mL (5 mg/1.5 mg per 5 mL oral solution) of reference product 3, Hycodan® oral solution. Treatments were administered in a randomly assigned sequence. Following a 14-day washout period, subjects returned to the clinical facility to be dosed with the alternative treatments as per the randomization (see Appendix 16.1.7).

In each study period, serial pharmacokinetic blood samples to measure the hydrocodone, pseudoephedrine and chlorpheniramine concentrations were to be collected at pre-dose and ending with the 24 hour post-dose sample (for those subjects who had received 5 mL (5 mg/ 4 mg/60 mg per 5 mL oral solution) of the test product, hydrocodone bitartrate/chlorpheniramine maleate/pseudoephedrine HCl oral solution or 5 mL (4 mg per 5 mL) of reference product 2, chlorpheniramine maleate oral solution. Blood samples were also collected at study hours 36, 48, 72, and 96).

Plasma samples were sent to the bioanalytical laboratory at [redacted] (b) (4) for determination of hydrocodone, pseudoephedrine and chlorpheniramine plasma concentrations.

**NUMBER OF SUBJECTS:** A total of 28 healthy adult subjects participated in this study.

**MAIN DIAGNOSIS FOR ENTRY:** Subjects were asymptomatic, healthy, non-smoking adult subjects between the ages of 18 and 65 years who met the inclusion/exclusion criteria for this study.

| | |
|---|---|
| **TEST PRODUCT:**<br>**(Treatment A)** | Hydrocodone Bitartrate 5 mg per 5 mL / Chlorpheniramine Maleate 4 mg per 5 mL / Pseudoephedrine HCl 60 mg per 5 mL<br>(Cypress Pharmaceuticals, Inc.),<br>Lot No. P08001 |
| **REFERENCE PRODUCT 1:**<br>**(Treatment B)** | Pseudoephedrine HCl 60 mg per 5 mL<br>(Cypress Pharmaceuticals, Inc.),<br>Lot No. P08043 |
| **REFERENCE PRODUCT 2:**<br>**(Treatment C)** | Chlorpheniramine Maleate 4 mg per 5 mL<br>(Cypress Pharmaceuticals, Inc.),<br>Lot No. P08045 |
| **REFERENCE PRODUCT 3:**<br>**(Treatment D)** | HYCODAN®, 5 mg hydrocodone bitartrate/ 1.5 mg homatropine methylbromide per 5 mL,<br>Manufactured for Endo Pharmaceuticals Inc.,<br>Manufactured by Novartis,<br>Lot No. 400804NV |
| **ROUTE OF ADMINISTRATION:** | Oral |

**DURATION OF TREATMENT:** The subjects received 5 mL of the test product, reference product 1, reference product 2, or reference product 3 in each of the treatment conditions over an 8-week period with a 14 day washout period between dosing time points. Total study participation, exclusive of screening, was 46 days.

**PRIMARY EFFICACY VARIABLE:** Not applicable.

**SECONDARY EFFICACY VARIABLE:** Not applicable.

**CRITERIA FOR EVALUATION:**

**Pharmacokinetics:** Blood for pharmacokinetic sampling was obtained from all subjects within 90 minutes prior to dosing (0 hour) and after dose administration at study hours 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 for Treatments A and C and for Treatments B and D at post-dose study hours 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, and 24. Analytical data from the blood samples collected during the study conduct were used to calculate values for the following pharmacokinetic parameters: $AUC_{0-t}$, $AUC_{0-inf}$, $C_{max}$, $T_{max}$, Kel, and $T_{1/2}$

Analyses of variance (ANOVA) were performed on the ln-transformed pharmacokinetic parameters $AUC_{0-t}$, $AUC_{0-inf}$ and $C_{max}$ and on the untransformed pharmacokinetic parameters $AUC_{0-t}$, $AUC_{0-inf}$, $C_{max}$, $T_{max}$, Kel and $T_{1/2}$. The ANOVA model included sequence, formulation and period as fixed effects and subject nested within sequence as a random effect. Sequence was

tested using subject nested within sequence as the error term. A 10% level of significance was used to test the sequence effect. Each analysis of variance included calculation of least-squares means, the difference between adjusted formulation means and the standard error associated with this difference. The above statistical analyses were done using the appropriate SAS® procedure. Additional calculations were performed as needed.

In agreement with the two one-sided test for bioequivalence, 90% confidence intervals for the difference between drug formulation least-squares means (LSM) were calculated for the parameters $AUC_{0-t}$, $AUC_{0-inf}$ and $C_{max}$ using ln-transformed data. The confidence intervals were expressed as a percentage relative to the LSM of the reference formulation.

Ratios of means were calculated using the LSM for ln-transformed $AUC_{0-t}$, $AUC_{0-inf}$ and $C_{max}$. The geometric mean values were expressed as a percentage. The comparisons of interest are: D vs. A (hydrocodone); B vs. A (pseudoephedrine); and C vs. A (chlorpheniramine).

**Safety:** All subjects were monitored throughout the confinement portion of the study. Sitting blood pressure, heart rate, temperature, and respirations were measured at each check-in. Blood pressure, heart rate and respirations were measured at 1, 2, 4, and 24 hours after each dose. Subjects were also queried for adverse events at screening, check-in, during the confinement portion of the study, and at study exit (or early termination). All subjects underwent clinical laboratory testing including hematology, biochemistry, urinalysis, and, for women of childbearing potential, pregnancy tests. Clinical laboratory testing (hematology and serum chemistry) was repeated at study exit. Additionally, vital signs were taken and physical examinations were performed at screening and at study exit (or early termination).

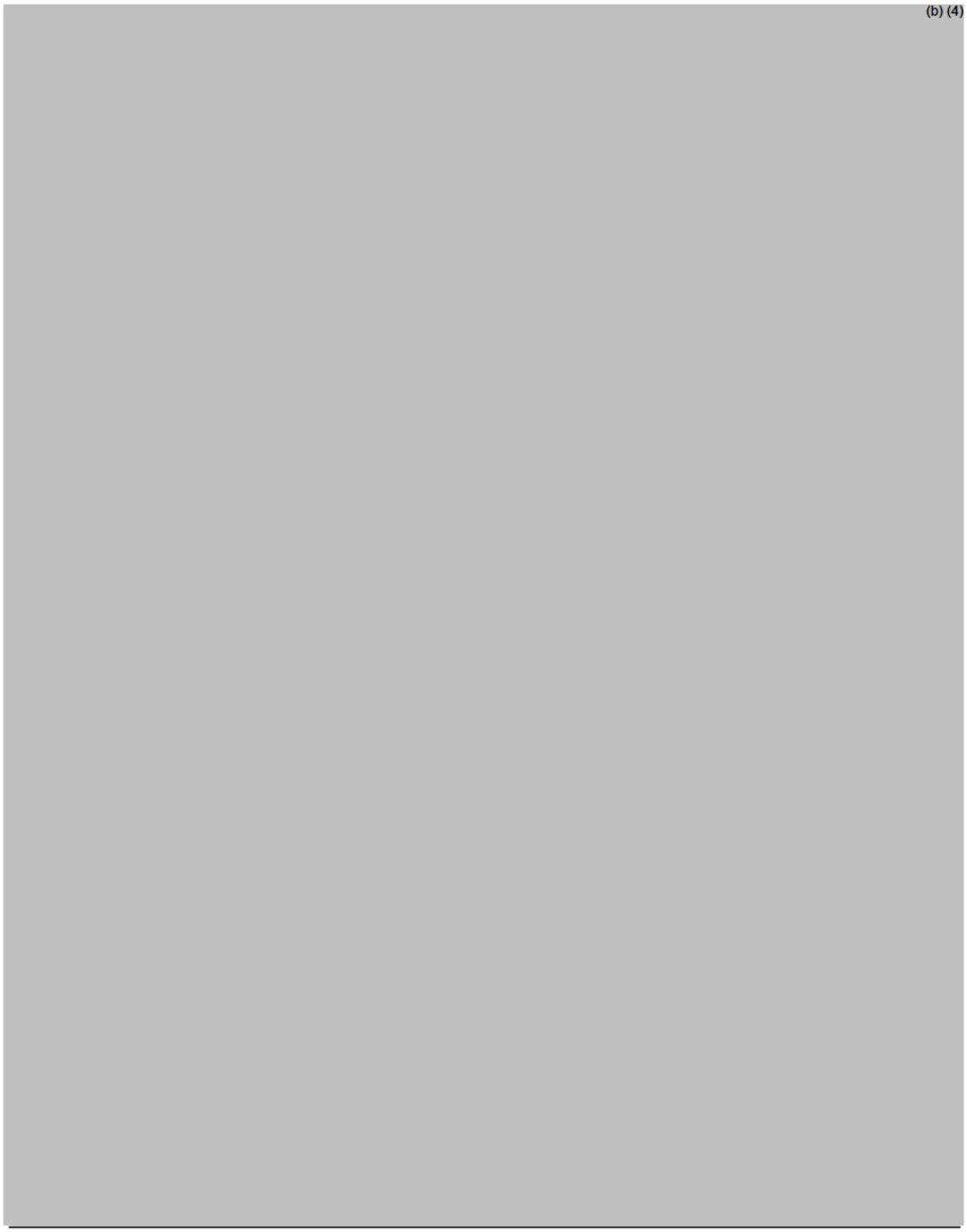
**SUMMARY OF RESULTS:**

**Demographic Summary:** The mean age of the subjects was 29 years (Mean = 29.1 yrs ± 10.2 yrs). Ages ranged from 18 to 54 years. Nineteen (19) males and 9 females were enrolled in the study and a majority of the subjects were white (approximately 64.29%).

**Pharmacokinetic Summary:** The bioanalytical laboratory at (b) (4) determined the hydrocodone, pseudoephedrine and chlorpheniramine plasma concentrations and sent the data to the Statistical Division (b) (4)

Hydrocodone:

(b) (4)


(b) (4)

(b) (4)

**Safety Summary:** No serious adverse events (SAEs) were reported over the course of this study. No subject was discontinued due to an adverse event (AE). Eight (8) subjects (28.6%) reported 27 adverse events (AEs) during the course of the study. Of the 8 subjects who reported AEs, 1 subject (3.8%) experienced an AE following administration of hydrocodone bitartrate/pseudoephedrine HCl/chlorpheniramine maleate 5 mg/60 mg/4 mg; 2 subjects (7.7%) experienced AEs following administration of pseudoephedrine HCl 60 mg, 3 subjects (11.1%) experienced AEs following administration of chlorpheniramine maleate 4 mg and 5 subjects (18.5%) experienced AEs following administration of Hycodan® oral solution. Sixteen (16) of the 27 AEs were reported by 5 subjects after receiving treatment D, Hycodan® oral solution.

Overall, the most common AEs were nausea and headache, each reported by 4 subjects (14.3%) Dizziness was reported by 3 subjects (10.8%) and two (2) subjects (7.1%) experienced vessel puncture site pain. All adverse events were mild or moderate in intensity.

There were no clinically significant findings from an assessment of the clinical laboratory test results, vital signs data, or physical examination results.

**SUMMARY CONCLUSIONS:**

**Pharmacokinetic:** For the log-transformed hydrocodone data, the 90% confidence intervals about the ratio of the Test geometric mean to Reference geometric mean are within the 80% to 125% limits (set by FDA, Guidance for Industry, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations*, Center for Drug Evaluation and Research [CDER], March, 2003) for $AUC_{0-t}$, $AUC_{0-inf}$, but not $C_{max}$.

For the log-transformed pseudoephedrine and chlorpheniramine data, the 90% confidence intervals about the ratio of the Test geometric mean to Reference geometric mean are within the 80% to 125% limits (set by FDA, Guidance for Industry, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations*, Center for Drug Evaluation and Research [CDER], March, 2003) for $AUC_{0-t}$, $AUC_{0-inf}$ and $C_{max}$.

**Safety:** Eight (8) subjects (28.6%) experienced 27 AEs during the course of the study. No serious adverse events (SAEs) were reported over the course of this study. Sixteen (16) of the 27 AEs were reported by 5 subjects after receiving treatment D, Hycodan® oral solution

Overall, hydrocodone bitartrate/pseudoephedrine HCl/chlorpheniramine maleate oral solution,

5 mg/60 mg/4 mg was well tolerated as a single dose of 5 mL (5 mg/60 mg/ 4 mg per 5 mL) administered under fasted conditions. Overall, the most common AEs were nausea and headache, each reported by 4 subjects (14.3%). Dizziness was reported by 3 subjects (10.7%) and two (2) subjects (7.1%) experienced vessel puncture site pain. All adverse events were mild or moderate in intensity.

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BIOPHARMACEUTICS

| 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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ELIZABETH Y SHANG
04/30/2010

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