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RESEARCH**

*APPLICATION NUMBER:*

**22442Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	May 27, 2011
<b>From</b>	Anthony G. Durmowicz, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	22-442
<b>Supplement#</b>	
<b>Applicant</b>	Cypress
<b>Date of Submission</b>	December 8, 2010
<b>PDUFA Goal Date</b>	June 8, 2011
<b>Proprietary Name / Established (USAN) names</b>	Rezira/hydrocodone bitartrate and pseudoephedrine hydrochloride
<b>Dosage forms / Strength</b>	Oral Solution/5 mg and 60 mg, respectively, in each 5 ml
<b>Proposed Indication(s)</b>	1. (b) (4) relief of cough 2. (b) (4) relief of nasal congestion due to the common cold
<b>Recommended Action:</b>	Approval

### 1. Introduction

This current submission by the Applicant dated December 8, 2010, is a complete response to a second Complete Response action taken on June 11, 2010, by the Division on this 505(b)(2) new drug application for use of a hydrocodone bitartrate and pseudoephedrine hydrochloride combination oral solution (proposed name Rezira) with a proposed indication for the (b) (4) relief of cough and nasal congestion due to the common cold. Initially proposed for adults (b) (4) during the last review cycle the Applicant was notified that due to safety concerns regarding the use of the narcotic, hydrocodone, in children, additional pharmacokinetic and safety data would need to be obtained (b) (4)

The original 505(b)(2) new drug application (NDA 22-439) was submitted by Cypress Pharmaceuticals, Inc. on November 7, 2008. The Applicant had submitted another related NDA (NDA 22-439) the previous day for a 3-ingredient product comprised of hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride (proposed name Zutripro). These 2 NDAs shared the same clinical pharmacology program and were reviewed in the same review timeline. During that first review cycle, while the clinical pharmacology program established bioequivalence for the chlorpheniramine and pseudoephedrine components of the combination product, it failed to demonstrate the bioequivalence for the hydrocodone component necessary to support approval of the applications and a Complete Response action was taken on both NDAs on September 10, 2009. Subsequently, the Applicant submitted a complete response on December 10, 2009, with the results of another clinical pharmacology study which, upon initial review, appeared to demonstrate bioequivalence of the hydrocodone ingredient in the combination product to the reference hydrocodone solution. However, based on findings from the inspections conducted by the Division of Scientific Investigations (lack of source documentation for stability experiments at the analytical site and falsification of records for the extraction of subject

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samples and incomplete validation documentation at the clinical research site) the data from the bioequivalence studies were judged to be unacceptable and a second Complete Response action was taken on June 11, 2010, citing deficiencies identified during the inspection. In the current submission dated December 8, 2010, the Applicant has addressed the deficiency noted in the June 11, 2010, Complete Response letter by submitting the results of another clinical pharmacology/bioavailability study to support this 2-ingredient combination product (Rezira). The newly submitted study data have demonstrated the bioequivalence of each component of the 3-ingredient cough/cold combination oral solution test drug (Zutripro, NDA 22-439) to each of the respective reference drugs (hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride) and, as such, also support the approval of the 2-ingredient hydrocodone and pseudoephedrine combination oral solution which is the subject of this review. This review will summarize the Division's assessments of the responses provided by the Applicant to the deficiencies outlined in the June 11, 2010, Complete Response letter, most notably lack of demonstration of bioequivalence between the Applicant's proposed combination product oral solution and the individual reference drug products, hydrocodone and pseudoephedrine. Summaries will also be provided for applicable discipline-specific sections.

## 2. Background

The product under development is one of the hydrocodone-containing cough/cold products belonging to a group of previously illegally marketed products. According to the Agency's Federal Register notice [(published on October 1, 2007 [Docket No. 2007N-0353], all manufacturers of hydrocodone-containing products had to stop manufacturing these products by December 31, 2007. The Agency has encouraged manufacturers of these and other unapproved products to submit NDAs to obtain approval for marketing these products in the United States. This application is to market a combination product containing hydrocodone bitartrate and pseudoephedrine hydrochloride, as an immediate release oral solution containing 5 mg and 60 mg of hydrocodone and pseudoephedrine, per 5 mL respectively. Pseudoephedrine is a well known sympathomimetic amine used for nasal decongestion and is listed in the OTC monograph (21 CFR 341.40).

The development program for this application is based on demonstration of bioequivalence to the reference ingredients of the combination product. Since hydrocodone is not a monograph product, clinical studies would normally be required to support a combination product containing hydrocodone and other active ingredients in order to demonstrate the contribution of each component to the combination product as required by regulation (21CFR 300.50). However, because of the prior regulatory precedent of approving Tussionex Pennkinetic (the combination of hydrocodone and chlorpheniramine) with clinical pharmacology data only, combination products containing hydrocodone and other monograph active ingredients that are permitted monograph combinations can be developed under a clinical pharmacology program only. Therefore, clinical efficacy and safety studies may not be necessary to support this combination product provided that the applicant carries out a satisfactory clinical pharmacology program.

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Of note is that Hycodan [ENDO Pharmaceuticals] was the hydrocodone reference product agreed upon and used in the clinical pharmacology study submitted in first review cycle. During the initial review cycle, the manufacturer of Hycodan [ENDO Pharmaceuticals] discontinued marketing Hycodan solution; however, the discontinuation was not because of safety or efficacy concerns. The Orange Book now lists the hydrocodone product from Hi Tech Pharma (ANDA 040613) as the RLD for hydrocodone bitartrate syrup. Subsequently, the Applicant used Hi-Tech Pharma's product as the reference for hydrocodone in their bioavailability studies upon the advice of the Agency since Hycodan solution was no longer available, however Hycodan is still the reference drug for reliance for safety and efficacy of hydrocodone.

### 3. CMC/Device

The proposed product is an aqueous oral solution containing hydrocodone bitartrate 5 mg and pseudoephedrine hydrochloride 60 mg, per 5 mL. Inactive ingredients (excipients) include citric acid, sodium citrate, sodium saccharin, sucrose, glycerin, propylene glycol, and methylparaben and propylparaben (b) (4). The product is grape flavor and will be available in 16 oz white HDPE bottles as the commercial product and (b) (4) bottles as physicians' samples. The two active substances are USP ingredients that have been previously assessed to support other NDA applications in the past.

The manufacturing of the drug product and drug substance and manufacturing/testing site inspections have been judged as acceptable. Stability data support a 24 month expiry. There are no outstanding product quality issues.

### 4. Nonclinical Pharmacology/Toxicology

No new non-clinical pharmacology/toxicology studies were required or performed for this application.

### 5. Clinical Pharmacology/Biopharmaceutics

As a response to previous deficiencies outlined in the previous Complete Response letters, the Applicant submitted one clinical pharmacology study in this resubmission in order to demonstrate the bioequivalence of their hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride combination cough and cold product (Zutripro) to each of the respective individual reference products. In doing so, the data would also support the hydrocodone and pseudoephedrine 2-ingredient product, Rezira. Study 11058503 was a single dose, 4-period crossover, relative bioavailability study in 112 healthy volunteers to assess the bioequivalence between the test drug and the reference drugs. Four study arms were:

- Zutripro Oral Solution (hydrocodone, pseudoephedrine, and chlorpheniramine oral solution 5 mg/60 mg/4 mg)
- Hi-Tech Pharma's hydrocodone bitartrate /homatropine methylbromide Syrup (5 mg/1.5 mg per 5 mL, ANDA 40-613)

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- Pseudoephedrine hydrochloride oral solution, 60 mg/5 ml (manufactured by (b) (4), manufactured for Cypress Pharmaceutical, Inc.)
- Chlorpheniramine maleate oral solution, 4 mg/5 ml (manufactured by (b) (4), manufactured for Cypress Pharmaceutical, Inc.).

The study was performed under fasted conditions and the following pharmacokinetic variables were calculated for each treatment:  $AUC_{0-t}$ ,  $AUC_{0-inf}$ ,  $C_{max}$ ,  $T_{max}$ ,  $K_{el}$ , and  $T_{1/2}$ .

Bioequivalence, defined as the 90% CI of ratios of AUC and  $C_{max}$  for all three components in the combination product (Zutripro) compared to the individual reference products being within 80 - 125%, was demonstrated in Study 11058503. These data also support the bioequivalence of the proposed 2-ingredient hydrocodone and pseudoephedrine combination product, Rezira. The summary of bioequivalence statistics on pharmacokinetic parameters for hydrocodone, chlorpheniramine, and pseudoephedrine are provided in Table 1.

**Table 1. Summary Statistics on Bioequivalence of Hydrocodone, Pseudoephedrine, and Chlorpheniramine Following Single Dose Administration of 5 mL Zutripro Oral Solution and the Respective Reference Solutions**

PK parameters	$AUC_{0-inf}$ (pg.hr/mL) Geometric Mean	$AUC_{0-t}$ (pg.hr/mL) Geometric Mean	$C_{max}$ (pg/mL) Geometric Mean
<b>ZUTRIPRO 5mL (N=100)</b>			
Hydrocodone	69747.27	67540.16	10290.79
Pseudoephedrine	1943.05	1824.27	207.17
Chlorpheniramine	181409.61	159719.72	6923.48
<b>Reference 5 mL (N=98)</b>			
Hi-Tech's Hydrocodone	72063.25	69723.40	11364.25
<b>Reference 5 mL (N=100)</b>			
Pseudoephedrine	1926.70	1813.41	204.90
<b>Reference 5 mL (N=97)</b>			
<b>Chlorpheniramine</b>	174224.49	155681.52	6789.48
<b>Ratio of ZUTRIPRO vs. reference (90% CI)</b>			
Hydrocodone	0.97 (0.95 – 0.99)	0.97 (0.95 – 0.99)	0.91 (0.88 – 0.93)
Pseudoephedrine	1.01 (0.98 – 1.04)	1.01 (0.98 – 1.03)	1.01 (0.99 – 1.03)
Chlorpheniramine	1.04 (1.02 – 1.07)	1.03 (1.00 – 1.05)	1.02 (0.99 – 1.05)

## 6. Clinical Microbiology

This is a non-sterile solution product for oral ingestion. The product contains methylparaben and propylparaben at target concentrations (b) (4)

(b) (4) There are no outstanding microbiology issues with the formulation.

## 7. Clinical/Statistical- Efficacy

The application relies on a comparison of the bioavailability of the proposed drug product to that of approved reference products Hycodan (the actual hydrocodone product used was a generic version of Hycodan since that product is no longer marketed) and the OTC monograph products pseudoephedrine. No clinical efficacy studies were conducted.

## 8. Safety

The safety of the product is based on establishing bioequivalence of the product compared to the approved reference products. In addition, for the original NDA submission, the Applicant conducted a review of the literature, and a search of the AERS database for post-marketing safety information for the individual ingredients and any combination thereof, for the period from October 2007 through March 2008. For this resubmission, the safety update dated March 31, 2011 consisted of information obtained through another literature search conducted from October 2, 2010, to March 1, 2011. These searches did not reveal any new safety signals.

## 9. Advisory Committee Meeting

An advisory committee meeting is not necessary for this application. The active ingredients present in this product are well known as individual drug substances, and as previously discussed, based on the current monograph and the Agency's prior precedent, the combination of products of these classes are accepted for the proposed indications.

## 10. Pediatrics

The (b) (4) Applicant requested a waiver for children under 6 years of age. (b) (4)

(b) (4) The request for waiver for children under 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). It would be appropriate to waive studies for pediatric patients less than 6 years of age because of this safety concern. However, although hydrocodone is currently labeled for use in children down to 6 years of age, safety concerns regarding dose-related respiratory depression identified over the last few years raises the issue of the need to be assured of the most appropriate dose for the pediatric population. Dose-related respiratory depression including fatalities due to respiratory failure has been reported with the use of hydrocodone in children. Several of these cases were associated with overdose, and led to the revised labeling currently in the single-ingredient and combination hydrocodone products; i.e. that hydrocodone is contraindicated in children less than 6 years of age and that the dose should be administered with an accurate measuring device. In view of this dose-related safety concern, it is appropriate to require the sponsor to establish the appropriate dose of hydrocodone for the pediatric (less than 18 years) population. Hydrocodone was approved under Drug Efficacy Study Implementation (DESI) review and the basis for the dose selection

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for the pediatric population is unclear. The dose of pseudoephedrine in the proposed combination product is the same as the doses in the Agency's approved OTC cough/cold monograph. Since the Agency is not aware of any new safety concerns with these ingredients at these doses and the current monograph is still in effect, the proposed doses for pseudoephedrine in this combination solution should be acceptable; however pharmacokinetic (PK) data for adequate dose selection and additional safety data should be required for the hydrocodone component. The need for additional PK and safety data for the pediatric (under 18 years of age) population was discussed with the Applicant during the second review cycle and at that time they submitted a plan to conduct a pharmacokinetic study and a safety study in the pediatric (6 to 17 years of age) population in the future. The Applicant's proposed pediatric plan and the Division's PREA assessment were presented to PeRC on May 26th, 2010. The 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.

## **11. Other Relevant Regulatory Issues**

### **Inspections**

The Division of Scientific Investigation (DSI) conducted an audit for both the clinical study and bioanalytics sites used for this clinical pharmacology program. The inspection of the clinical site was conducted at Novum Pharmaceutical Research Services, Houston, TX during February 15-28, 2011 and identified no deficiencies. The inspection of analytical portion was conducted at (b) (4) during March 7-11, 2011. DSI identified several deficiencies during this inspection involving improper documentation of sample processing steps and a deviation of the sample storage temperature from that specified. The Applicant responded adequately to the deficiencies outlined as a result of the inspection and, subsequently, DSI issued a Memorandum on April 14, 2011, recommending that the clinical and analytical data generated in study 11058503 be accepted for the review. As such, the data for study 11058503 are judged as acceptable to support the clinical pharmacology program.

### **Compliance with Good Clinical Practices**

The clinical pharmacology study in this application was conducted in accordance with Good Clinical Practices, and in particular with the requirements of 21 CFR Part 314.50(3)(i). The Applicant certified that the clinical contractor conducted the study in compliance with Institutional Review Board regulations and with Informed Consent Regulations.

### **Financial Disclosures**

The Applicant certified that there was no financial arrangement with the clinical investigator whereby the value of the compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The clinical investigator certified that he was not a recipient of significant payments defined in 21 CFR 54.2(f).

## 12. Labeling

### Proprietary Name

The proposed trade name Rezira was reviewed and deemed to be acceptable by the Division of Medication Error Prevention and Analysis (DMEPA).

### Physician Labeling

In the previous submission, the physician labeling was reviewed and extensively revised by the review team and conveyed to the Applicant. Changes were made to the Indication section to reflect the population for which it would be used; those with respiratory tract symptoms due to the common cold and respiratory allergies. Another significant change in the proposed labeling was the restriction of the age limit to adults (patients 18 years of age and older) only. As noted in section 10 (Pediatrics), PK and safety data should be obtained in the pediatric population (b) (4).

In this resubmission, the Applicant submitted a label in the Physician's Labeling Rule Format that was consistent with the label discussed during the previous review cycle. During this review cycle minor revisions to the Adverse Reaction and Clinical Pharmacology sections were made as well as minor changes in format and grammar. At the time of this review the final draft product labeling has been agreed to by the Applicant and Division.

### Carton and Immediate Container Labels

A detailed review of the carton and immediate container labels was conducted by the individual disciplines of the Division in consultation with DMEPA and DDMAC. At the time of this review, the final carton and container labels format is under discussion with the Applicant.

### Patient Labeling and Medication Guide

There is no separate patient labeling and medication guide for this product

## 13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

In response to the Complete Response action taken on June 11, 2010, the Applicant submitted the study report for another single-dose clinical pharmacology study which has established the bioequivalence of their hydrocodone 5 mg and pseudoephedrine 60 mg/ per 5 mL oral solution (Rezira) to the two individual reference products. In establishing bioequivalence, the program is able to rely on previous Agency determinations of the safety and efficacy of hydrocodone bitartrate and pseudoephedrine hydrochloride in the proposed combination product for the relief of cough and nasal congestion associated with the common cold when administered to adults 18 years of age and older at a dose of 5 mL by mouth every 4-6 hours as needed, not to exceed 4 doses in a 24 hour period. Therefore the recommendation is for Approval for the adult population. As detailed in Section 10 (pediatrics) above, (b) (4) adequately designed pharmacokinetic and safety studies to be performed as a PREA post-marketing requirement in that population.

- Risk Benefit Assessment

The overall risk and benefit assessment of the proposed hydrocodone and pseudoephedrine combination product (Rezira) based on establishing bioequivalence to the individual reference products and literature and AERS database searches does not suggest an unfavorable risk benefit for these individual ingredients for the adult (18 years and older) population. Since dose-related respiratory depression associated with fatalities from the use of hydrocodone has been reported for the younger population (patients under 18 years of age) additional PK and safety data to support the appropriate dose in the pediatric population is necessary (b) (4)

- Recommendation for Postmarketing Risk Management Activities

Hydrocodone is a controlled substance known to have a certain level of abuse potential. The combination product as proposed will be labeled as a Schedule III narcotic and available by prescription only. At this time, the abuse potential can be managed by appropriate labeling. However, we will monitor for signals of abuse/misuse, overdose, and addiction post approval.

- Recommendation for other Postmarketing Study Commitments

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. For this combination product we are waiving the requirement for children less than 6 years of age 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). Because of the safety concerns for the pediatric population, the Applicant will need to conduct PK and safety studies to evaluate the appropriate dose for patients less than 18 years of age. This issue was discussed with the Applicant during the previous review cycle and a pediatric plan which included studies to assess the PK and safety of Rezira in children 6-17 years of age was submitted on May 6, 2010. At the time of this review an update for the time line for initiation of the studies and submission of the study reports has yet to be agreed upon.

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05/27/2011