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RESEARCH**

*APPLICATION NUMBER:*  
**204307Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	January 24, 2013
<b>From</b>	Anthony G. Durmowicz, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	204307
<b>Supplement#</b>	
<b>Applicant</b>	Cypress Pharmaceuticals
<b>Date of Submission</b>	April 24, 2012
<b>PDUFA Goal Date</b>	February 24, 2013
<b>Proprietary Name / Established (USAN) names</b>	Vituz/hydrocodone bitartrate and chlorpheniramine maleate
<b>Dosage forms / Strength</b>	Oral Solution/5 mg and 4 mg, respectively, in each 5 ml
<b>Proposed Indication(s)</b>	Relief of cough and symptoms associated with upper respiratory allergies or the common cold
<b>Recommended Action:</b>	Approval

### 1. Introduction

This 505(b)(2) new drug application (NDA 204307) submission by Cypress Pharmaceuticals received April 24, 2012, for a hydrocodone bitartrate (HC) and chlorpheniramine maleate (CH) combination oral solution with a proposed indication for the temporary relief of cough and symptoms due to upper respiratory allergies or a common cold. This is a clinical pharmacology-based program that relies on the demonstration of bioequivalence of the proposed HC and CH combination product to that of approved reference product, Hycodan (the actual hydrocodone product used was a generic version of Hycodan since that product is no longer marketed) and the OTC monograph product chlorpheniramine.

This product is related to and shares the same clinical pharmacology program as two other NDAs previously submitted by Cypress, NDA 22-439, a 3-ingredient combination product comprised of hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride (tradename Zutripro) and NDA 22-442, a 2-ingredient combination product of hydrocodone bitartrate and pseudoephedrine hydrochloride (tradename Rezira). After two complete response actions based on a lack of demonstration of bioequivalence and failure of an inspection by the Division of Scientific Investigations, the two products were approved on June 8, 2011. As mentioned, the clinical pharmacology study data used to support approval of Zutripro (demonstration of the equivalence of each component of the 3-ingredient cough/cold combination oral solution test drug to each of the respective reference drugs (hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride) is being used to support approval of this 2-ingredient HC and CH combination product. This review will outline the clinical pharmacology program used to support approval as well as summarize applicable discipline-specific reviews.

## 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 chlorpheniramine maleate, as an immediate release oral solution containing 5 mg and 4 mg of HC and CH, per 5 mL respectively. Chlorpheniramine is a well known antihistamine used to treat symptoms associated with upper respiratory allergies and is listed in the OTC monograph (21 CFR 341.12).

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 (an extended release combination of hydrocodone and chlorpheniramine) with clinical pharmacology data only, combination products containing hydrocodone and other monograph active ingredients that are permitted monograph combinations have been allowed to 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.

Of note is that Hycodan [ENDO Pharmaceuticals] was the hydrocodone reference product initially agreed to during the course of the development period for the 3 related combination products. However, ENDO Pharmaceuticals subsequently discontinued marketing Hycodan solution, but not because of safety or efficacy concerns. The Orange Book then listed 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. However, Hycodan is still the reference drug for reliance for safety and efficacy of hydrocodone.

## 3. CMC/Device

The proposed product is an aqueous clear to light yellow (b)(4) oral solution containing hydrocodone bitartrate 5 mg and chlorpheniramine maleate 4 mg, per 5 mL. The product contains methylparaben and propylparaben at target concentrations of (b)(4)

From the CMC microbiology standpoint, Cypress responded adequately to several requests in the 74-day letter regarding antimicrobial preservative effectiveness testing, microbial limits testing, and testing for the presence of *B. cepacia*. There are no outstanding CMC microbiology issues with the formulation.

The hydrocodone component is manufactured by (b) (4) and referenced to DMF (b) (4) which was last reviewed in May, 2012 by Dr. Gil Jong Kang and found adequate. The chlorpheniramine component is manufactured by (b) (4) and referenced to DMF (b) (4). This DMF was last reviewed in Feb, 2012 by Dr. Gil Jong Kang and deemed adequate. The status of the DMF's facilities for both the hydrocodone and chlorpheniramine components is acceptable to CDER Compliance (overall EES recommendation dated January 2, 2013 was acceptable). Inactive ingredients (excipients) include citric acid, glycerin, grape flavor, propylene glycol, water, sodium citrate, sodium saccharin, and sucrose with methylparaben and propylparaben (b) (4). The product will be available in 16 oz white HDPE bottles as the commercial product (b) (4).

Stability data support a 24 month expiry. Overall, 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**

Cypress submitted one clinical pharmacology study in this application in order to demonstrate the bioequivalence of the hydrocodone bitartrate and chlorpheniramine maleate components of their proposed HC and CH combination product to their respective individual reference products. The data generated from the study, which included pseudoephedrine as a third drug component, have been used to support the approval of two other related combination cough and cold products, Zutripro, a hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride triple combination product and Rezira, a hydrocodone and pseudoephedrine 2-ingredient product. 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. The 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)
- Pseudoephedrine hydrochloride oral solution, 60 mg/5 ml (manufactured by Great Southern Laboratories, manufactured for Cypress Pharmaceutical, Inc.)
- Chlorpheniramine maleate oral solution, 4 mg/5 ml (manufactured by Great Southern Laboratories, manufactured for Cypress Pharmaceutical, Inc.).

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

Bioequivalence, defined as the 90% CI of ratios of AUC and  $C_{max}$  for all three components in the triple combination product compared to the individual reference products being within 80 - 125%, was demonstrated. As such, these data also support the bioequivalence of the currently proposed 2-ingredient hydrocodone and chlorpheniramine combination product. 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

Not applicable.

## 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 product chlorpheniramine. 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. Subsequent safety updates dated March 31, 2011, and October 15, 2012, submitted during the review of NDA complete responses 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 pediatric plan for this HC/CH combination product (Vituz) was previously agreed to with Cypress at the time of approval of their 2 closely related cough and cold combination products, Zutripro and Rezira, which contain hydrocodone, chlorpheniramine, and pseudoephedrine and hydrocodone and pseudoephedrine, respectively. The rationale for the plan is as follows. The current proposed indication for Vituz is for adults 18 years of age and older, and the Applicant requested a deferral for children 6-17 years of age and a waiver for children under 6 years of age. 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 is 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 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, the Applicant will need to establish the appropriate dose of hydrocodone for children between 6 and 17 years of age. Hydrocodone was approved under Drug Efficacy Study Implementation (DESI) review and the basis for the dose selection for the pediatric population is unclear. The dose of chlorpheniramine (and pseudoephedrine for the Zutripro product) in the 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 chlorpheniramine at the established dose and the current monograph is still in effect, the proposed dose for chlorpheniramine in this combination solution should be acceptable. However, pharmacokinetic (PK) data for adequate dose selection and additional

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safety data in the pediatric population will be required for the hydrocodone component. This rationale and pediatric plan were discussed at a PeRC meeting for the related Zutripro and Rezira products on May 26, 2010, at which time the committee agreed with the proposed plan to waive studies in children less than 6 years of age and to conduct PK and safety studies in patients 6 to 17 years of age with the intent of arriving at an appropriate dose and collecting additional safety data in the pediatric population. The committee recommended that efficacy assessments and population PK measurements be included in the proposed safety study as well. Such general assessment of efficacy in a safety study is appropriate as collection of efficacy data is generally done in a designated safety study. Even though this product's efficacy is supported by the same relative bioequivalency study as the two related Zutripro and Rezira products, because it is a separate application, the same pediatric plan as previously accepted by PeRC and agreed to with the Applicant was once again presented to PeRC on October 10, 2012. At this PERC meeting, the PeRC agreed with the waiver of studies in children less than 6 years of age since hydrocodone is contraindicated in children less than 6 years of age, however, the PeRC changed their recommendation from the previously agreed to PK and safety studies in patients 6 to 17 years of age that cover the other triple and double combination products. Instead the PeRC recommended that the Division require the Applicant conduct a full development program including dose-ranging and replicate factorial design efficacy studies designed to demonstrate the contribution of each individual component to the efficacy of the combination. The main rationale for this requirement was that the overall efficacy data for cough and cold drugs in the pediatric population were not robust, and a well designed pediatric safety and efficacy development program would provide additional pediatric efficacy data for chlorpheniramine. The Division disagrees with the new PeRC recommendation for the following reasons:

- While one could debate the robustness of the available efficacy data for chlorpheniramine and other cough and cold medications in the pediatric population, the proposed chlorpheniramine doses for children 6-17 years of age are within those contained in the current OTC monograph. Since the monograph remains the legal regulatory basis for the determination of safety and efficacy for cough and cold drugs, including chlorpheniramine, the Applicant is not required to conduct a full clinical program to establish what the monograph already has determined to be the safe and effective doses of chlorpheniramine in children.
- There are no new safety concerns for chlorpheniramine in children that have arisen since the previous approval of the related Zutripro product.
- The Applicant is currently conducting PK and safety studies previously accepted by PeRC and the Division for the hydrocodone component in pediatric patients 6-17 years of age for the Zutripro and Rezira products that would also extend to this Vituz hydrocodone and chlorpheniramine combination product

## **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 [REDACTED] (b) (4)

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 initial proposed trade name, [REDACTED] (b) (4) was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and deemed unacceptable based on [REDACTED] (b) (4). Subsequently, Cypress proposed the tradename, Vituz, which was reviewed by DMEPA and found acceptable.

### **Physician Labeling**

The physician labeling was reviewed and revised based on similar approved labels for the Applicant's related cough and cold combination products, Zutripro and Rezira and current labeling for similar cough and cold combination products. 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.

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 DMPP and DDMAC. The Division and Applicant have agreed on final carton and container labeling.

### **Patient Labeling and Medication Guide**

## 13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The Applicant has submitted the clinical pharmacology study report which had previously been used to establish the bioequivalence and support approval of Zutripro, their hydrocodone 5 mg, chlorpheniramine 4 mg, and pseudoephedrine 60 mg/ per 5 mL triple combination oral solution. Because the current proposed drug product exists as a solution with the only difference between it and Zutripro being the lack of pseudoephedrine, the same clinical pharmacology study may be used to establish the bioequivalence the hydrocodone and chlorpheniramine components of the proposed HC and CH combination product to their respective reference drugs. By establishing bioequivalence, the program is able to rely on previous Agency determinations of the safety and efficacy of hydrocodone bitartrate and chlorpheniramine maleate in the proposed combination product for the relief of cough symptoms associated with upper respiratory tract allergies 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, approval for children 6-17 years of age will be dependent upon the results of 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 chlorpheniramine combination product, 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 are necessary prior to extending the indication to the pediatric population.

- 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

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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 continued safety concerns for hydrocodone in the pediatric population, the Applicant will need to conduct PK and safety studies to establish the appropriate dose and collect additional safety data 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 the then proposed name (b) (4) product in children 6-17 years of age was originally submitted on May 6, 2010, and resubmitted in this complete response. These studies are the same as those currently being conducted for the related Zutripro and Rezira products, NDAs 22-439 and 22-432, respectively. The Division feels the completion of those studies will fulfill the PREA requirement for the Vituz product as well. The Applicant was contacted regarding the time lines of the studies and confirmed the time lines will be the same as for the Zutripro and Rezira products. The studies and time lines are outlined below:

1. Conduct a study to assess the pharmacokinetics of each Vituz drug component (hydrocodone and chlorpheniramine) in approximately 25-35 children ages 6-17 years with symptoms of the common cold. The study will be conducted with a formulation containing hydrocodone, chlorpheniramine, and pseudoephedrine. The results of this study will be used to determine the appropriate dose of the combination product to evaluate in a safety study in children ages 6-17 years.

- Final Protocol Submission: September 30, 2011
- Study Completion: December 31, 2013
- Final Report Submission: June 30, 2014

2. Conduct a study to assess the safety of Vituz (hydrocodone and chlorpheniramine combination product oral solution) in approximately 400-450 children 6-17 years of age with symptoms of the common cold. The study will be conducted with a formulation containing hydrocodone, chlorpheniramine, and pseudoephedrine. The dose used in this study will be based upon the results of the pharmacokinetic study in children ages 6-17 years.

- Final Protocol Submission: September 30, 2014
- Study Completion: December 31, 2015
- Final Report Submission: September 30, 2016

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01/31/2013