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*APPLICATION NUMBER:*  
**204307Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

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Reviewer Name	Xu Wang, M.D., Ph.D.
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Established Name	Hydrocodone bitartrate and chlorpheniramine maleate
(Proposed) Trade Name	Vituz Oral Solution
Therapeutic Class	Antitussive/antihistamine
Applicant	Cypress Pharmaceuticals, Inc.
Priority Designation	S
Formulation	Oral solution
Dosing Regimen	For adults 18 years of age and older: 5 ml every 4-6 hours as needed, not to exceed 4 doses 20 ml in 24 hours
Indication	Relief of cough and symptoms associated with upper respiratory allergies or the common cold
Intended Population	Adults 18 years of age and older

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## 1 EXECUTIVE SUMMARY

### 1.1 Recommendation on Regulatory Action

I recommend an “Approval” action for this NDA. The development program for the proposed drug product is a clinical pharmacology program. The proposed drug product Vituz Oral Solution depends on the bioequivalence to the reference drug Hycodan for hydrocodone and to OTC monograph ingredient chlorpheniramine to support its efficacy and safety. No clinical efficacy studies were submitted to support this application. The clinical pharmacology study demonstrated that the bioequivalence between the proposed drug product Vituz and the reference drugs, showing that the 90% CI of ratios of AUC and  $C_{max}$  for the two components in Vituz vs. reference drugs are within the 80 - 125% goal post for bioequivalence.

Vituz Oral Solution is an immediate release oral solution, containing 5 mg hydrocodone bitartrate and 4 mg chlorpheniramine maleate per 5 mL. It is proposed as a fixed dose combination product containing an antitussive and antihistamine. The proposed indication is for relief of cough associated with common cold, and relief of symptoms associated with upper respiratory allergies. The proposed indications are guided by the indication from reference drug Hycodan and OTC monograph language for indication for chlorpheniramine. The proposed dose regimen is 5 ml every 4-6 hours as needed, not to exceed 4 doses 20 ml in 24 hours for adults 18 years of age and older.

### 1.2 Recommendation on Postmarketing Actions

#### 1.2.1 Risk Management Activity

The Applicant did not submit a risk management plan for the proposed drug product. Routine post-marketing surveillance is recommended to monitor the adverse events associated with the use of Vituz Oral Solution. If a signal of abuse, misuse, overdose and addiction is identified, further abuse liability assessment may need to be conducted.

#### 1.2.2 Required Phase 4 Commitments

Hydrocodone is a controlled substance that is known to have a certain level of abuse potential. The Controlled substances Staff (CSS) recommended in a consult for another hydrocodone containing cough and cold product that the Applicant conduct well designed animal and human studies to characterize the abuse potential of the proposed combination drug [Memorandum, Consult on NDA (b) (4), Controlled Substance Staff, March 27, 2009]. In an Agency regulatory briefing regarding the abuse potential safety testing for hydrocodone cough and cold combination products on June 12, 2009, the consensus was that abuse liability studies were not required prior to approval of these drug products but that studies may be necessary on a case-by-case basis if a signal is detected post-marketing.

No special Phase 4 commitments are recommended at this time. A routine post-marketing surveillance is recommended to monitor the adverse events associated with the use of Vituz Oral Solution. If a signal of abuse, misuse, overdose and addiction is identified, further abuse liability assessment may need to be conducted.

### 1.2.3 Other Phase 4 Requests

The clinical pharmacology studies to support this NDA were conducted in adults 18 years of age and older, and the proposed drug is indicated for adults 18 years of age and older. The Applicant requested a partial waiver for pediatric studies below 6 years of age because that hydrocodone is contraindicated in children less than 6 years of age due to the risk of fatal respiratory depression. Pediatric studies in population from 6 to under 18 years of age for pharmacokinetics and safety data in this age group are required.

The proposed dose for chlorpheniramine is the same as the dose in the Agency's approved OTC monograph. Since the dose proposed in the combination product is within the doses that were declared by the Agency to be safe and effective for OTC use, no additional PK data is necessary to support the chlorpheniramine dose. Hydrocodone was approved under DESI and is currently labeled for use in children down to 6 years of age, however, safety concerns of dose-related respiratory depression 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 under 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 that the sponsor establish the appropriate dose of hydrocodone for the pediatric (under 18) population. Therefore, pharmacokinetic data for proper dose selection, and safety data are needed in the pediatric population.

In the review process of NDA 22-439 Zutripro (hydrocodone bitartrate, pseudoephedrine hydrochloride and chlorpheniramine maleate) Oral Solution and NDA 22-442 Rezira (hydrocodone bitartrate and pseudoephedrine hydrochloride) Oral Solution, the Division discussed with the Applicant regarding the concerns of lacking PK and safety data of hydrocodone in the pediatric population. The Applicant agreed to conduct PK and safety studies in the pediatric population from 6 to under 18 years of age. A pediatric study plan that currently supports NDAs 22-439 and 22-442 and would also support the present NDA 204-307, including timelines of the planned pediatric studies, was submitted under NDA 22-439. On May 26, 2010 the Pediatric Review Committee (PeRC) meeting agreed with the waiver of studies in children less than 6 years of age and a deferral for studies in patients 6 to 17 years of age, with a recommendation to incorporate efficacy assessment and population PK in the proposed safety study.

Even though NDA 204-307 relies on the same PK study as the related NDAs, 22-439 and 22-442, because it is a separate NDA, the request for the partial pediatric study waiver in children less than 6 years of age and the deferral of PK and safety study in patients 6 to 17 years of age,

which were already agreed to by PeRC for the related NDAs, were submitted to PeRC again and discussed at the PeRC meeting on October 10, 2012. The PeRC maintained its position on the partial waiver of studies in children less than 6 years of age. For the deferral of the pediatric studies in patients 6 to 17 years of age, however, the PeRC recommended that the Division request the Applicant conduct a full development program including dose-ranging and replicate factorial design efficacy studies. Their rationale was that the overall efficacy data for cough and cold drugs in the pediatric population were not robust, and a well designed pediatric efficacy study would provide much needed pediatric efficacy data for chlorpheniramine. This reviewer agrees that the robustness of the available efficacy data for cough and cold drugs in pediatric population might not be up to current standards. But the current OTC monograph, in which the proposed chlorpheniramine dose is generally considered safe and effective, is still the regulatory base in evaluating the cough and cold drugs. Because a pediatric safety study is requested due to the safety concerns of hydrocodone, it is appropriate to add the efficacy assessment for the proposed drug, as recommended by PeRC at the May 26, 2010 meeting. However, it seems not necessary to require a stand alone efficacy study for the proposed drug at this time.

### **1.3 Summary of Clinical Findings**

#### **1.3.1 Brief Overview of Clinical Program**

This is a clinical pharmacology program, in which the Applicant included results of one clinical pharmacology study. The clinical pharmacology study 11058503 is an open-label bioavailability and drug interaction study to evaluate the relative bioavailability of the test drug product to the reference drugs hydrocodone, chlorpheniramine, and pseudoephedrine. This study has been conducted to support the proposed drug product Vituz and another drug product of the Applicant, NDA 22-439, Zutripro (hydrocodone bitartrate, pseudoephedrine hydrochloride and chlorpheniramine maleate) Oral Solution, which is an immediate release triple combination oral solution, containing 5 mg hydrocodone bitartrate, 4 mg chlorpheniramine maleate, and 60 mg pseudoephedrine hydrochloride per 5 mL. Because Vituz Oral Solution (NDA 204-307) and Zutripro Oral Solution (NDA 22-439) are exactly the same formulations except that Zutripro consists of one more active ingredient (pseudoephedrine), demonstration of bioequivalence for the hydrocodone and chlorpheniramine 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 clinical pharmacology study 11058503 is also used to support a third drug product of the Applicant, NDA 22-442, Rezira (hydrocodone bitartrate and pseudoephedrine hydrochloride) Oral Solution, which is an immediate release combination oral solution, containing 5 mg hydrocodone bitartrate and 60 mg pseudoephedrine hydrochloride per 5 mL. NDA 22-439 Zutripro Oral Solution and NDA 22-442 Rezira Oral Solution were approved on June 8, 2011.

The Applicant submitted a Summary of Clinical Safety including the safety data from the clinical pharmacology study and a literature survey to provide support for the safety of the proposed drug

product. The Applicant provided the AERS database search results for post-marketing spontaneous adverse events associated with hydrocodone and chlorpheniramine.

### 1.3.2 Efficacy

No clinical efficacy studies were submitted to support this application. This is a 505(b)(2) application using bioequivalence approach to support approval. The Agency's previous findings of efficacy and safety of the approved hydrocodone NDA (Hycodan) and the OTC monograph for chlorpheniramine are being used to substantiate the efficacy and safety of this triple combination product.

### 1.3.3 Safety

The Applicant provided a Summary of Clinical Safety including the safety data from the clinical pharmacology study 11058503 and a literature survey in the present complete response submission. In the original NDA submission, the Applicant provided the AERS database search results for post-marketing spontaneous adverse events associated with hydrocodone and chlorpheniramine. Safety was assessed through adverse events in the study 11058503 conducted in 112 adult subjects. There were no deaths or other serious adverse events in the clinical pharmacology study 11058503. There were 23 (21.7%), 18 (18.0%), 3 (3.0%), and 10 (9.6%) subjects reported adverse events for the test drug Zutripro (hydrocodone bitartrate, pseudoephedrine hydrochloride and chlorpheniramine maleate) Oral Solution and three reference drugs A (hydrocodone), B (pseudoephedrine), and C (chlorpheniramine), respectively. In subjects taking the test drug product Zutripro Oral Solution, somnolence was the most common adverse event (15), followed by headache (3) and dizziness (2). All adverse events were mild or moderate in nature. A review of the adverse event list showed that the majority of the adverse events spontaneously resolved without special treatment. Only one adverse event received not-specified drug treatment, and 22 adverse events received not-specified non-drug therapy. The adverse events occurred in the clinical pharmacology study 11058503 did not reveal a new safety signal.

The search for post-marketing adverse events from the AERS database covered the period from October, 2007 through March, 2008. The AERS database search used terms of hydrocodone (HC), hydrocodone plus chlorpheniramine (HC/CPM), hydrocodone plus acetaminophen (HC/ACT), chlorpheniramine plus pseudoephedrine (CPM/PSE), pseudoephedrine (PSE), chlorpheniramine plus other ingredients, pseudoephedrine plus other ingredients, and other combination products. There were no new safety signals revealed through the search of AERS database for post-marketing adverse events.

The Applicant compiled nine literature references for information relevant to safety of hydrocodone, chlorpheniramine, and pseudoephedrine in general. The references included the product labeling of the reference drug Hycodan, Cochrane reviews, and articles published in peer reviewed journals. There were no studies related to safety of products containing all three ingredients. The literature survey revealed no new safety signals for hydrocodone and chlorpheniramine. The result of the literature review is provided in the Section 8.6 of this review.

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), the Applicant submitted a 120-day safety update under NDA 22-439, Zutripro (hydrocodone bitartrate, pseudoephedrine hydrochloride and chlorpheniramine maleate) Oral Solution (SN 0026). The safety update consisted of the most recent PSUR's submitted for the approved Zutripro product. There were no new data regarding safety of hydrocodone and chlorpheniramine included in the safety update.

#### 1.3.4 Dosing Regimen and Administration

The proposed drug product contains 5 mg hydrocodone bitartrate, 4 mg chlorpheniramine maleate, and 60 mg pseudoephedrine hydrochloride per 5 mL. It is proposed as a prescription drug combination of antitussive, antihistamine and decongestant. The proposed indications are:

(b) (4)  
The proposed dosage is one teaspoon (5 mL) every 4 to 6 hours as needed, not to exceed (NTE) 4 doses (20 mL) in 24 hours for adults 18 years of age and older.

#### 1.3.5 Drug-Drug Interactions

There is no drug-drug interaction study conducted in this NDA submission. The result of a clinical pharmacology study (S08-0179) submitted in NDA 22-439) showed that the subjects' exposure for hydrocodone in the proposed drug hydrocodone, chlorpheniramine, and pseudoephedrine oral solution was lower than that in the reference drug product Hycodan. This suggests that there may be drug-drug interaction between hydrocodone and chlorpheniramine and/or pseudoephedrine in the proposed drug formulation. However, the result of the clinical pharmacology study 11058503 in current complete response submission, the exposure of hydrocodone in the proposed combination product is within the bioequivalence range compared to hydrocodone in the single-ingredient product. There were no differences in chlorpheniramine and pseudoephedrine exposure between Vituz Oral Solution and the OTC monograph chlorpheniramine and pseudoephedrine solutions. More information regarding possible drug-drug interaction affecting the hydrocodone exposure in the Vituz Oral Solution may be found in the Clinical Pharmacology Review [NDA 204-307, Clinical Pharmacology Review, Arun Agrawal, Ph. D.].

Use of MAO inhibitors or tricyclic antidepressants with hydrocodone may increase the effect of either the antidepressant or hydrocodone. Concurrent use of opioids, antihistamines, anti-psychotics, anti-anxiety agents or other CNS depressants including alcohol concomitantly with hydrocodone may result in additive CNS depression. The Applicant's proposed labeling appropriately addresses the potential these drug-drug interactions.

#### 1.3.6 Specific Populations

There were no studies in specific populations for Vituz Oral Solution in this submission to review. The Applicant's proposed labeling indicates that the product is a pregnancy category C drug for the lack of adequate and well-controlled studies in pregnant women. As with other opioids, use of hydrocodone during labor can produce respiratory depression in the neonate. The

Applicant's proposed labeling states that [REDACTED] (b) (4)

[REDACTED] A literature search shows a report that two infants exposed to hydrocodone through breast milk while mothers were taking hydrocodone as an analgesic. Caution should be exercised when Vituz Oral Solution is administered to nursing mothers. The information about the hydrocodone excreted in breast milk and the potential risks of hydrocodone use in nursing women should be added to the proposed labeling.

*Reviewer's comment:*

*On March 11, 2008, FDA published a Public Health Advisory and a Healthcare Professionals Information sheet addressing the risk of a long-acting hydrocodone-containing cough product in patients younger than the approved age group of 6 years and older. FDA has received reports of life-threatening adverse events and death in patients, including children, who have received a long-acting hydrocodone-containing cough product.*

*[<http://www.fda.gov/cder/drug/advisory/hydrocodone.htm>,*

*<http://www.fda.gov/cder/drug/InfoSheets/HCP/hydrocodoneHCP.htm>].*

## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

The Applicant has developed an immediate release oral solution formulation of hydrocodone and chlorpheniramine. The drug product contains 5 mg hydrocodone bitartrate and 4 mg chlorpheniramine maleate per 5 mL. It is proposed as a prescription drug combination of antitussive and antihistamine. The proposed indications are: [REDACTED] (b) (4)

[REDACTED] The sponsor's proposed name is Vituz Oral Solution. The proposed dosage is one teaspoon (5 mL) every 4 to 6 hours as needed, not to exceed (NTE) 4 doses (20 mL) in 24 hours for adults 18 years of age and older. This is a 505(b)(2) application and the Applicant has provided an electronic submission.

As a basis for the 505(b)(2) submission route, the Applicant cited the following reference listed drugs (RLDs) and OTC monographs in their original NDA submission: 1) Hycodan (Hydrocodone Bitartrate /Homatropine Methylbromide Syrup (5 mg/1.5 mg per 5 mL), NDA 05-213, 2) Tussionex Extended-Release Suspension (NDA 19111, UCB, Inc.), 3) Zutripro Oral Solution (NDA 22-439, Cypress), 4) Rezira Oral Solution (NDA 22-442, Cypress), and 5) 21 CFR 341.12 for chlorpheniramine. Of note, reliance on Tussionex is not necessary to determine safety or efficacy of this application, as the information that the sponsor cites from the label to support their labeling, is information that comes from the published literature. Because the Hycodan syrup manufactured by Endo Pharmaceuticals was discontinued from the market (not for reasons of safety or efficacy), the Applicant conducted the clinical pharmacology study using the hydrocodone bitartrate/homatropine methylbromide syrup developed by HI-TECH Pharma as the reference drug for hydrocodone. HI-TECH Pharma's product is a generic drug (ANDA 40-613).

Hydrocodone (HC) is a commonly used antitussive. The safety and effectiveness of HC as a prescription drug for the symptomatic relief of cough are supported by DESI review and by the

FDA approved product Hycodan (NDA 5-213). HC is an opioid, a schedule II controlled substance as a single ingredient (21 CFR 1308.12), a schedule III controlled substance if in combination with active non-narcotic ingredients and if the product contains not more than 300 milligrams of hydrocodone per 100 milliliters or not more than 15 milligrams per dosage unit (21 CFR 1308.13), and a prescription drug product (21 CFR 1306.15).

Hydrocodone Syrup (HC 5 mg plus homatropine methylbromide (HTM) 1.5 mg) was classified in the DESI review as safe and effective for prescription drug for the symptomatic relief of cough (DESI Notice #5123). Hycodan has the following approved dosage (Hycodan product labeling):

- Adults: One teaspoonful of the syrup (5 mg HC) every 4 to 6 hours as needed; not to exceed (NTE) 6teaspoonfuls (30 mg HC) in 24 hours
- Children 6 to 12 years of age: One-half (1/2) teaspoonful of the syrup (2.5 mg HC) every 4 to 6 hours as needed; NTE 3 teaspoonfuls (15 mg HC) in 24 hours

Chlorpheniramine (CPM) is considered to be generally recognized as safe and effective (GRASE) as an antihistamine [21 CFR 341.12] in the following age groups at the following oral doses [21 CFR 341.72]:

- Adults and children 12 years of age and older: 4 mg every 4 to 6 hours, NTE 24 mg in 24 hours
- Children 6 to under 12 years of age: 2 mg every 4 to 6 hours, NTE 12 mg in 24 hours
- Children under 6 years of age: consult a doctor

The monograph considers the combination of any single monograph oral antitussive drug (such as codeine phosphate) with any single antihistamine (such as chlorpheniramine) to be a permitted combination [21 CFR 341.40].

*Reviewer's comment:*

*Hydrocodone, a schedule II controlled substance and a prescription drug, is not an OTC monograph antitussive. Therefore, the proposed combinations of HC/PSE/GU is not in compliance with the OTC monograph (21CFR 341.40), and clinical studies would normally be required to provide the evidence of safety and efficacy of the proposed products as the regulation requires (21CFR 300.50).*

*However, there is a regulatory precedent regarding the combination of HC with an OTC monograph product, which can be found in detail in Medical Officer Review, IND (b) (4) Briefly, during the FDA deliberations on the approvability of Tussionex Pennkinetic extended release suspension (NDA 19-111) at the Center Level the FDA determined that clinical studies are not necessary for the combination of HC and a permitted OTC monograph ingredient. The development program for Tussionex Pennkinetic was comprised of 3 bioavailability studies and no clinical studies. Based on this prior precedent, the Division has accepted the conclusion that for a HC combination product containing monograph active ingredients, a drug development program does not need to establish the efficacy, safety, or the contribution of HC or an OTC monograph ingredient to the*

*efficacy and safety of the combination product, provided that bioequivalence can be established with the reference products.*

## **2.2 Currently Available Treatment for Indications**

Hydrocodone is currently approved in the United States in tablet and syrup as an immediate release antitussive drug (Hycodan, NDA 5-213, approved on March 23, 1943). On February 4, 2009, Endo Pharmaceuticals (the maker of Hycodan) informed FDA that manufacture of Hycodan syrup was discontinued on May 14, 2008 and Hycodan tablet manufacture was discontinued on January 4, 2008. The discontinuation of Hycodan manufacture was not because of reasons of safety or efficacy. The last lot of drug expired on December 31, 2008 (syrup) and January 31, 2009 (tablets). Endo Pharmaceuticals did not withdraw the NDAs for Hycodan products and therefore, can resume marketing the products again in the future. Hydrocodone is also approved in combination with chlorpheniramine in an extended release suspension for cough (Tussionex Pennkinetic, NDA 19-111). Hydrocodone is also available in immediate release solutions in combination with pseudoephedrine (NDA 22-442) and with chlorpheniramine and pseudoephedrine (NDA 22-439). There are other generic Hydrocodone products as antitussive drugs on the market. These are Hydrocodone Compound (ANDA 88-017), Tussicaps (ANDA 77-273), Tussigon (ANDA 88-506), and Homatropine Methylbromide and Hydrocodone Bitartrate Tablet and Syrup (ANDA 40295, ANDA 40-613, ANDA 88-008).

Chlorpheniramine is available as a non-prescription monograph drug, being considered to be generally recognized as safe and effective (GRASE) at OTC monograph dose for the temporary relief of allergy symptoms. A large number of antihistamines (both over the counter and prescription) are available on the market. Examples include diphenhydramine, loratadine, desloratadine, and fexofenadine. Also antihistamines are available as combination products with a variety of cough and cold preparations.

## **2.3 Availability of Proposed Active Ingredient in the United States**

Hydrocodone is currently available in combination with chlorpheniramine in an extended release suspension (Tussionex Pennkinetic, NDA 19-111), with pseudoephedrine in immediate release solution (Rezira, NDA 22-442) and with chlorpheniramine and pseudoephedrine immediate release solution (Zutripro, NDA 22-439), and generic antitussive drugs Hydrocodone Compound (ANDA 88-017), Tussicaps (ANDA 77-273), Tussigon (ANDA 88-506), and Homatropine Methylbromide and Hydrocodone Bitartrate Tablet and Syrup (ANDA 40-295, ANDA 40-613, ANDA 88-008). In addition, hydrocodone is available in the United States in tablet and capsule formulations as analgesic medications at higher doses than antitussives, such as Vicoprofen (NDA 20-716), Vicodin and Vicodin HP (ANDA 88-058, ANDA 40-117), Lortab (ANDA 40100, ANDA 87-722), and Anexsia (ANDA 40-405, ANDA 40-409, ANDA 89-729, ANDA 40-686, ANDA 89-160). There have been multiple illegally marketed hydrocodone-containing products in the U.S. market. The FDA announced its intention to take enforcement actions against unapproved drug products containing hydrocodone bitartrate if such drug products are manufactured and marketed on or after October 31, 2007 [Federal Register Vol. 72, No 189, October 1, 2007].

Chlorpheniramine is currently approved in the United States in tablets (Chlor-trimeton, NDA 07638), in combination with pseudoephedrine and ibuprofen Advil Allergy/Sinus Tablets NDA 21441). These products are extended release formulations. Chlorpheniramine is also available in the United States in immediate release formulations and is considered to be GRASE at OTC monograph doses.

## 2.4 Important Issues With Pharmacologically Related Products

Hydrocodone is a semi-synthetic opioid that has the potential for abuse. Dependence and tolerance may develop upon repeated administration. Hydrocodone is a schedule II controlled substance as a single ingredient (21 CFR 1308.12), a schedule III controlled substance if in combination with active non-narcotic ingredients and if the product contains not more than 300 milligrams of hydrocodone per 100 milliliters or not more than 15 milligrams per dosage unit (21 CFR 1308.13), and a prescription drug product (21 CFR 1306.15).

## 2.5 Presubmission Regulatory Activity

The Applicant had a pre-IND meeting on January 14, 2008 with the Division to discuss the plans to develop several immediate release combination oral solutions of hydrocodone, pseudoephedrine, chlorpheniramine, and phenylephrine. The Division's comments in the pre-IND meeting which relate to this application are summarized as follows [Pre-IND Meeting Minutes, February 6, 2008]:

- A 505(b)(2) pathway would be an acceptable approach for the planned combination drug products.
- The bioequivalence should be demonstrated between hydrocodone in the proposed products and an approved hydrocodone antitussive drug product (e.g. Hycodan) by conducting bioequivalence studies.
- The drug-drug interaction between hydrocodone and other active pharmacological ingredients should be addressed. This information may be provided from the literature or by conducting pharmacokinetic drug-drug interaction studies.

The Applicant submitted an opening IND on April 11, 2008 for the proposed Hydrocodone, Chlorpheniramine, and Pseudoephedrine Oral Solution (IND 102,146), and subsequently submitted a 505(b)(2) NDA for the triple combination drug product Zutripro (hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride) Oral Solution on November 06, 2008. The original NDA submission included results of a clinical pharmacology study S09-0179, in which the Clinical Pharmacology review team found that the hydrocodone  $C_{max}$  for the proposed drug product was out of the 80 -125% goal post of bioequivalence [NDA 22-439/22-442, 74-day Letter, January 23, 2009]. The chlorpheniramine and pseudoephedrine in Zutripro Oral Solution were bioequivalent to the OTC monograph reference products chlorpheniramine and pseudoephedrine. The Division issued a Complete Response Letter on September 18, 2009, stating that the deficiency in the original NDA submission can be addressed by either conducting a single dose clinical pharmacology study to establish the bioequivalence of Zutripro Oral Solution to RLD, or conducting a clinical development program with clinical efficacy and safety studies to support the proposed drug product.

On December 10, 2009, the Applicant submitted the first Complete Response resubmission including results of a clinical pharmacology study SAM-09-1010. In this study, the exposure of hydrocodone in the proposed combination product was within the bioequivalence range compared to hydrocodone in the RLD. However, based on the deficiencies identified in the analytical site inspections, the Division of Scientific Investigation (DSI) concluded that “the bioequivalence data for Study SAM-09-1010 submitted in the NDA are questionable” and “Study S-08-0179 should not be accepted for review.” [Memorandum, DSI Report on an Audit of Study SAM-09-1010, Martin K. Yau, Ph. D. 5/05/2010; and Memorandum, DSI Report on an Audit of Study S-08-0179, Martin K. Yau, Ph. D. 5/20/2010]. Subsequently, the clinical pharmacology review team decided that “the results of bioequivalence studies from studies S-08-0179 and SAM-09-1010 are not acceptable.” [[NDA 22-439, SN009, Addendum to Clinical Pharmacology Review, Elizabeth Y. Shang, Ph. D., R. Ph. 5/25/2010]. A CR letter was issued on June 11, 2010, in which the Applicant was given two choices to address the deficiency: conduct another single-dose clinical pharmacology study to establish the bioequivalence of the proposed oral solution products to the reference products, or conduct a clinical development program with clinical efficacy and safety studies to support the proposed oral solution products.

Subsequently, the second Complete Response resubmission of NDA 22-439 was filed on December 8, 2010, in which the Applicant presented results from a clinical pharmacology study (#11058503). In addition to supporting NDA 22-439, the clinical pharmacology study 11058503 is also used to support two drug products of the Applicant, NDA 22-442 Rezira (hydrocodone bitartrate and pseudoephedrine hydrochloride) Oral Solution that was filed at the same time with NDA 22-439, and NDA 204-307 Vituz (hydrocodone bitartrate and chlorpheniramine maleate) Oral Solution that was filed on April 23, 2012. NDA 22-439 Zutripro Oral Solution and NDA 22-442 Rezira Oral Solution were approved on June 8, 2011.

### 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

#### 3.1 CMC (and Product Microbiology, if Applicable)

The drug product is an oral aqueous solution containing hydrocodone bitartrate USP 5 mg, chlorpheniramine maleate USP 4 mg, and pseudoephedrine hydrochloride USP 60 mg per 5 mL. This is an immediate release formulation. The excipients in the test formulation include glycerin, propylene glycol, sucrose, methylparaben, propylparaben, citric acid, sodium citrate, sodium saccharin, and Grape Flavor (b) (4). The proposed combination drug product is manufactured by Great Southern Laboratories, 10863 Rockley Road, Houston, TX 77099. The Applicant certified that the facility, equipment, methods, and controls used in the manufacture, packaging, holding and testing of drug products and their components are in conformance with Current Good Manufacturing Practice as defined in 21 CFR 210 and 211 [m3, Section 2.1, page 3]. The methods of manufacturing are relatively straight forward. (b) (4)



(b) (4) A detailed review of the CMC portion of the application may be found in the ONDQA review [NDA 204-307, ONDQA Review, Xiaobin Shen, Ph.D.].

Hydrocodone bitartrate (b) (4) is a white or slightly yellow-white color powder. It is fairly soluble in water and but not soluble in ether and chloroform and pH of a 2% Aqueous solution is about 3.6. Hydrocodone bitartrate USP used in the test formulation is manufactured by (b) (4)

Chlorpheniramine maleate USP used in the test formulation is manufactured by (b) (4)

Pseudoephedrine hydrochloride USP used in the test formulation is manufactured by (b) (4)

The proposed drug product Vituz is a (b) (4) oral solution. (b) (4) methylparaben and propylparaben at target concentrations of (b) (4) and (b) (4) w/v, respectively. (b) (4)

The product quality microbiology reviewer recommends an approval from a quality microbiology standpoint [NDA 204-307, Product Quality Microbiology Review, Steven Donald, Microbiologist].

### 3.2 Animal Pharmacology/Toxicology

No new animal data or toxicology data were submitted. No new pre-clinical toxicology studies were required or performed for this application.

## 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

### 4.1 Sources of Clinical Data

The application was submitted under Section 505(b)(2) of the Food, Drug & Cosmetic Act, which permits approvals to be based on the Agency's previous findings of efficacy and safety of approved or OTC monograph reference products. This application relies on the Agency's previous findings of efficacy and safety of the proposed drug product to the reference drug Hycodan and the monograph products chlorpheniramine. The Applicant's drug development program for Vituz Oral Solution is based on establishing that their combination product produces exposures that are equivalent to that of approved and marketed products for hydrocodone and to that of OTC monograph dose of chlorpheniramine. The bioequivalent data come from one clinical pharmacology study 11058503. There were no clinical efficacy or safety studies in this application.

## 4.2 Table of Clinical Studies

The Applicant has submitted the results from study 11058503, a single-dose, 4-period, relative bioavailability study, to characterize the exposure of hydrocodone, chlorpheniramine, and pseudoephedrine immediate release solution in fasted, healthy, adult subjects. Table 1 summarizes the clinical pharmacology study.

**Table 1. Summary of Clinical Pharmacology Study 11058503**

Study number	Treatment	Study design	Diagnosis, subjects' age	Materials submitted
11058503	Test drug: 5 ml Zutripro (5 mg HC/ 4 mg CPM/ 60 mg PSE)  Reference drug: 5 mL Hi-Tech Syrup (5 mg HC/1.5 mg Homatropine)  5 mL pseudoephedrine solution, 60 mg  5 mL chlorpheniramine solution, 4 mg	Randomized, single dose, 4-period cross over with a 7-day washout period between dosing	112 healthy males and females, 18-62 yrs of age	Study report

## 4.3 Review Strategy

This is a review of the safety data from study 11058503, and of the data from AERS database for post-marketing and spontaneous adverse event reports and the literature review for hydrocodone and chlorpheniramine.

## 4.4 Data Quality and Integrity

This is a clinical pharmacology program. The clinical pharmacology team requested the Division of Scientific Investigation (DSI) audit for both clinical study site and bioanalytics site of the study 11058503. The inspection of clinical portion was conducted at Novum Pharmaceutical Research Services, Houston, TX during February 15-28, 2011. This inspection identified no deficiencies. The inspection of analytical portion was conducted at (b) (4). DSI identified several deficiencies during this inspection, and issued an FDA Form 483 (Inspection Observations) on March 11, 2011. These deficiencies were involving improper documentation of sample processing steps and a deviation of the sample storage temperature from that is specified per protocol ( $-80 \pm 10^{\circ}\text{C}$ ) to that was recorded ( $-60$  to  $-90^{\circ}\text{C}$ ) in the laboratory documentation. After evaluating the written response from the Applicant to the FDA Form 483, DSI issued a Memorandum on April 14, 2011, recommended that "the clinical and analytical data generated in study 11058503 be accepted for the review." [Memorandum, DSI Report on an Audit of Study 11058503, Sripal R. Mada, Ph. D., April 14, 2011]

#### 4.5 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 [m5, Section 5.2, page 9].

#### 4.6 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 Applicant stated that the clinical investigator of the clinical pharmacology study in this application certified that he did not disclose any proprietary interest in the proposed product. The clinical investigator certified that he was not a recipient of significant payments defined in 21 CFR 54.2(f) [m1, FDA Form 3454, page 1].

### 5 CLINICAL PHARMACOLOGY

There is one clinical pharmacology study in this second Complete Response resubmission. A summary of data from the Applicant's clinical pharmacology study follows below. Detailed information can be found in the Clinical Pharmacology Review [NDA 204-307, Clinical Pharmacology Review, Arun Agrawal, Ph. D.].

The formulation of test drug product Zutripro Oral Solution is displayed in Table 2. The proposed drug Vituz Oral Solution in the present NDA submission has the same formulation except that Zutripro consists of one more active ingredient (pseudoephedrine). The experimental formulation is manufactured and supplied by Great Southern Laboratories at Houston, TX.

**Table 2 Formulation of Zutripro Oral Solution**

Ingredient	% w/v	mg/5 mL	Mg/480 mL
Hydrocodone bitartrate USP	(b) (4)	5.0	480
Chlorpheniramine Maleate USP	(b) (4)	4.0	384
Pseudoephedrine hydrochloride USP	(b) (4)	60	5,760
Sucrose NF*	(b) (4)	(b) (4)	(b) (4)
Glycerin (b) (4) USP	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Methylparaben NF*	(b) (4)	(b) (4)	(b) (4)
Propylparaben NF*	(b) (4)	(b) (4)	(b) (4)
Citric acid anhydrate USP	(b) (4)	(b) (4)	(b) (4)
Sodium citrate USP	(b) (4)	(b) (4)	(b) (4)
Sodium saccharin USP	(b) (4)	(b) (4)	(b) (4)
Grape flavor (b) (4)	(b) (4)	(b) (4)	(b) (4)
Purified water USP	(b) (4)	(b) (4)	(b) (4)

NF = National Formulary (Source: m2, Section 2.3, page 5)

Study 11058503 was a single dose, 4-period crossover, relative bioavailability study to assess the bioequivalence between the test drug and the reference drugs. Four study arms were: 1) Zutripro Oral Solution (hydrocodone, pseudoephedrine, and chlorpheniramine oral solution 5 mg/60 mg/4

mg), 2) Hi-Tech Pharma’s Hydrocodone Bitartrate /Homatropine Methylbromide Syrup (5 mg/1.5 mg per 5 mL, ANDA 40-613), 3) pseudoephedrine oral solution, 60 mg/5 ml (manufactured by Great Southern Laboratories, manufactured for Cypress Pharmaceutical, Inc.), and 4) chlorpheniramine oral solution, 4 mg/5 ml (manufactured by Great Southern Laboratories, manufactured for Cypress Pharmaceutical, Inc.). The study was performed under a fasted condition. A total of 112 healthy volunteers were enrolled, and 98 subjects completed the study. The following pharmacokinetic variables were calculated for each treatment:  $AUC_{0-t}$ ,  $AUC_{0-inf}$ ,  $C_{max}$ ,  $T_{max}$ ,  $K_{el}$ , and  $T_{1/2}$ .

For Zutripro Oral Solution, 21 blood samples were collected from each subject during each period of the study prior to dosing (0), then at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, 48 and 72 hours after dosing for analysis of hydrocodone, pseudoephedrine and chlorpheniramine. For Hi-Tech Pharma’s Hydrocodone Oral Solution, 18 samples were collected from each subject during each period of the study prior to dosing (0), then at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16 and 24 hours post dose for analysis of hydrocodone only. For pseudoephedrine oral solution, 18 samples were collected from each subject during each period of the study prior to dosing (0), then at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16 and 24 hours post dose for analysis of pseudoephedrine only. For chlorpheniramine oral solution, 21 samples were collected from each subject during each period of the study prior to dosing (0), then at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, 48 and 72 hours after dosing for analysis of chlorpheniramine only.

Table 3 shows the PK measurements of the study 11058503. The Applicant compared the PK of hydrocodone, pseudoephedrine, and chlorpheniramine between Zutripro and the reference drugs. The comparison shows that the 90% CI of ratios of AUC and  $C_{max}$  for all three components in Zutripro are within the 80 - 125% goal post for bioequivalence.

**Table 3 Pharmacokinetics results, Study 11058503**

PK parameters	$AUC_{0-inf}$ (pg.hr/mL) Geometric Mean	$AUC_{0-t}$ (pg.hr/mL) Geometric Mean	$C_{max}$ (pg/mL) Geometric Mean	$T_{max}$ (hr) Mean	$t_{1/2}$ (hr) Mean
<b>Zutripro 5mL (N=100)</b>					
Hydrocodone	69747.27	67540.16	10290.79	1.38	4.92
Pseudoephedrine	1943.05	1824.27	207.17	1.78	5.61
Chlorpheniramine	181409.61	159719.72	6923.48	3.47	24.14
<b>Reference 5 mL (N=98)</b>					
Hi-Tech’s Hydrocodone	72063.25	69723.40	11364.25	1.22	5.01
<b>Reference 5 mL (N=100)</b>					
Pseudoephedrine	1926.70	1813.41	204.90	1.67	5.53
<b>Reference 5 mL (N=97)</b>					
Chlorpheniramine	174224.49	155681.52	6789.48	3.86	22.61
<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)		

(Source: NDA 22-439 N-020, m5, Section 5.3.1.2.2, page 9-17)

## **6 INTEGRATED REVIEW OF EFFICACY**

This application is supported by the bioequivalence of the proposed drug product and the approved hydrocodone product (Hi-Tech Pharma's Hydrocodone Bitartrate /Homatropine Methylbromide Syrup, ANDA 40-613) and OTC monograph drug chlorpheniramine. No clinical efficacy studies were conducted to support this application.

### **6.1 Indication**

The Applicant's proposed indications for Vituz Oral Solution are: Relief of cough associated with common cold; Relief of symptoms associated with upper respiratory allergies.

## **7 INTEGRATED REVIEW OF SAFETY**

The Applicant submitted a Summary of Clinical Safety including the safety data from the clinical pharmacology study 11058503 and a literature survey. The safety was assessed through adverse events in the study 11058503. The safety data from this clinical pharmacology study in adult subjects did not identify a safety signal. Study 11058503 was conducted in 112 subjects, and the adverse event data from the study is not enough to evaluate the association of adverse events and gender or race/ethnicity.

The post-marketing adverse event reports from the search result of AERS database covering the period from October 2007 through March 2008, and a brief literature review for safety of hydrocodone, pseudoephedrine, and chlorpheniramine [m2, Section 2.7.4, pages 26 - 32].

The AERS database search used terms of hydrocodone (HC), hydrocodone plus chlorpheniramine (HC/CPM), hydrocodone plus acetaminophen (HC/ACT), chlorpheniramine plus pseudoephedrine (CPM/PSE), pseudoephedrine (PSE), chlorpheniramine plus other ingredients, pseudoephedrine plus other ingredients, and other combination products. There were no new safety signals revealed through the search of AERS database for post-marketing adverse events.

The Applicant compiled nine literature references for information relevant to safety of hydrocodone, pseudoephedrine, and chlorpheniramine in general. The references included the product labeling of the reference drug Hycodan, Cochrane reviews, and articles published in peer reviewed journals. There were no studies related to safety of products containing all three ingredients. The literature survey revealed no new safety signals for hydrocodone, pseudoephedrine, and chlorpheniramine. The result of the literature review is provided in the Section 8.6 of this review.

## 7.1 Methods and Findings

### 7.1.1 Deaths

There was no death in the clinical pharmacology study 11058503 in this application.

### 7.1.2 Other Serious Adverse Events

There was no serious adverse event occurred in the clinical pharmacology study 11058503 in this application.

### 7.1.3 Dropouts and Other Significant Adverse Events

A total of 112 healthy volunteers were enrolled into the clinical pharmacology study 11058503, 98 subjects received all four treatments. There were 12 subjects discontinued voluntarily by not returning to the study site at different stage of the study. One subject dropped off the study due to vomiting after taking the reference drug hydrocodone (reference A). One subject discontinued the study due to headache after taking the test drug Zutripro Oral Solution. There was no significant adverse event in the clinical pharmacology study in this application.

### 7.1.4 Other Search Strategies

No other search strategies were used in this application.

### 7.1.5 Common Adverse Events

In the clinical pharmacology study 11058503, there were 23 (21.7%), 18 (18.0%), 3 (3.0%), and 10 (9.6%) subjects reported adverse events for the test drug Zutripro Oral Solution and three reference drugs A (hydrocodone), B (pseudoephedrine), and C (chlorpheniramine), respectively (Table 6). In subjects taking Zutripro Oral Solution, somnolence was the most common adverse event (15), followed by headache (3) and dizziness (2). All adverse events were mild or moderate in nature. A review of the adverse event list showed that the majority of the adverse events spontaneously resolved without special treatment. Only one adverse event received not-specified drug treatment, and 22 adverse events received not-specified non-drug therapy. The adverse events occurred in the clinical pharmacology study 11058503 did not reveal a new safety signal.

**Table 4 Adverse events in Study 11058503**

Adverse event*	Number (%) of subjects			
	Zutripro N=106	Reference A N=100	Reference B N=101	Reference C N=104
<b>Subject with any AE</b>	<b>23 (21.7)</b>	<b>18 (18.0)</b>	<b>3 (3.0)</b>	<b>10 (9.6)</b>
<b>Respiratory disorders</b>				
Cough	1 (0.9)	0	0	0
Nasal congestion	1 (0.9)	0	0	0
Rhinorrhea	0	0	0	1 (1.0)
Throat irritation	1 (0.9)	0	0	1 (1.0)

<b>Skin &amp; subcutaneous disorders</b>				
Pruritus	1 (0.9)	0	0	0
Hot flush	0	1 (1.0)	0	1 (1.0)
<b>GI disorders</b>				
Dry mouth	1 (0.9)	0	0	0
Nausea	0	7 (7.0)	0	1 (1.0)
Toothache	0	1 (1.0)	0	0
Vomiting	0	1 (1.0)	0	0
<b>General &amp; administ. site disorders</b>				
Fatigue	1 (0.9)	0	0	0
Pain	1 (0.9)	0	0	0
<b>Musculoskeletal &amp; connective tissue disorder</b>				
Back pain	1 (0.9)	0	0	0
<b>Nervous system disorders</b>				
Dizziness	2 (1.8)	8 (8.0)	1 (1.0)	4 (3.9)
Headache	3 (2.8)	0	0	3 (2.9)
Photophobia	1 (0.9)	0	0	0
Somnolence	15 (15.2)	5 (5.0)	2 (2.0)	5 (4.8)
<b>Psychiatric disorder</b>				
Euphoric mood	1 (0.9)	0	0	0
<b>Investigations</b>				
Increased ALT	1 (0.9)	0	0	0
Increased blood glucose	0	1 (1.0)	0	0

Reference A: 5 mL of hydrocodone bitartrate and homatropine methylbromide syrup, 5 mg/1.5 mg per 5 mL (manufactured by Hi-Tech Pharmacal Co., Inc.)

Reference B: 5 mL of chlorpheniramine maleate oral solution, 4 mg per 5 mL (manufactured by: Great Southern Laboratories, manufactured for: Cypress Pharmaceutical, Inc.)

Reference C: 5 mL of pseudoephedrine HCl oral solution, 60 mg per 5 mL (manufactured by: Great Southern Laboratories, manufactured for: Cypress Pharmaceutical, Inc.)

(Source: m5, Section 12.0, page 62)

*Reviewer's comment:*

*These data do not identify a safety signal. Because of the small number of the subjects, there was no meaningful information in differences in adverse events in gender, age, and race/ethnicity.*

### 7.1.6 Less Common Adverse Events

Adverse events occurring in the clinical pharmacology study in adults are reviewed in Section 7.1.5. Less common adverse events did not suggest a safety signal.

### 7.1.7 Laboratory Findings

Laboratory examinations were not safety endpoints in the clinical pharmacology study of this application.

### 7.1.8 Vital Signs

Vital sign assessments were conducted before and at the end of the clinical pharmacology study. No clinically significant changes from baseline data were reported.

### 7.1.9 Electrocardiograms (ECGs)

ECGs were not performed in the clinical pharmacology study of this application.

#### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

Hydrocodone is a controlled substance that is known to have a certain level of abuse potential. Adams EH, Breiner S, Cicero TJ, et al. reported a 12-month study in chronic pain patients that showed an abuse rate of 1.2% for hydrocodone<sup>1</sup>. Manchikanti reported data regarding the drug-related ED visits in 2005, collected by the Drug Abuse Warning Network (DAWN). The data show that hydrocodone/combinations accounted for 51,225 (6.27%) of the 816,696 total illicit drug-related ED visits in 2005<sup>2</sup>. Although hydrocodone dosages as an antitussive are much lower than that of analgesics, hydrocodone-containing medications should be prescribed and administered with caution.

The proposed drug Vituz (hydrocodone bitartrate and chlorpheniramine maleate) Oral Solution is a prescription drug, which provides limitation to its accessibility for the unlawful use.

#### 7.1.14 Human Reproduction and Pregnancy Data

No human reproduction and pregnancy data were collected in the clinical pharmacological study. The Applicant has not observed or reported adverse events associated with drug exposure during pregnancy in the post-marketing surveillance. The Applicant's proposed labeling indicates that the product is a pregnancy category C drug for the lack of adequate and well-controlled studies in pregnant women. A report revealed 2 cases of hydrocodone excretion in breast milk<sup>3</sup>. The infants of the mothers who were taking hydrocodone received an estimated 3.1% and 3.7% of the maternal weight-adjusted dosage. The absolute hydrocodone doses the infants received were 8.58 mcg/kg and 3.07 mcg/kg per day. One infant (18-day-old) became groggy and slept for most of the day while the mother was taking 20 mg hydrocodone every 4 hours. The infant's symptoms improved when mother decrease her hydrocodone dose by half. Another infant (5-week-old) became cyanotic and required intubation while the mother was taking hydrocodone and methadone for migraine headache. The infant was positive for opioids in urinary test and responded well to naloxone treatment. There are no reports of hydrocodone in breast milk while a mother takes hydrocodone at a much lower antitussive dosage. The prescribers and patients should be aware of the potential hydrocodone excretion into breast milk and use Vituz with caution.

#### 7.1.16 Overdose Experience

There is no overdose experience reported in the clinical pharmacological study 11058503. In the original NDA submission, the Applicant searched the AERS database covering the period from October 2007 through March 2008 and the result showed that overdose/misuse/error were

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1 Adams EH, Breiner S, Cicero TJ, et al. J Pain Symptom Manage. May 2006;31(5):465-476

2 Manchikanti L. Pain Physician 2007;10:399-424

3 Anderson PO, Sauberan JB, Lane JR, et al. Breastfeeding Med March 2007;2(1):10-14

frequently reported as adverse events associated with hydrocodone drug products. The AERS database search and literature review did not differentiate whether the hydrocodone was taken as antitussives or at much higher dosages as analgesics. The Applicant identified no new pattern of overdose for the ingredients of the proposed drug.

*Reviewer's comment:*

*The potential for abuse including overdose with hydrocodone is well recognized. However, the Applicant has not provided specific data in the NDA to evaluate the abuse potential of the proposed combination drug. In a consult for another hydrocodone containing combination drug product (NDA [REDACTED] (b) (4)), Controlled Substance Staff (CSS) recommended that the Applicant conduct well designed animal and human studies to characterize the abuse potential of the proposed combination drug [Memorandum, Consult on NDA [REDACTED] (b) (4) Controlled Substance Staff, March 27, 2009]. In an Agency regulatory briefing regarding the abuse potential safety testing for hydrocodone cough cold combination products on June 12, 2009, the consensus was not to require these studies for approval. If there are safety signals post-marketing the issue of the need for these types of studies can be revisited.*

### 7.1.17 Postmarketing Experience

The proposed drug product Vituz Oral Solution has not been marketed. There have been multiple illegally marketed hydrocodone-containing products in the U.S. market. The FDA has announced its intention to take enforcement actions against unapproved drug products containing hydrocodone bitartrate if such drug products are manufactured and marketed on or after October 31, 2007 [Federal Register Vol. 72, No 189, October 1, 2007].

The post-marketing experiences were obtained from AERS database search covering pseudoephedrine, chlorpheniramine, and hydrocodone drug products, including approved and unapproved drug products containing hydrocodone as antitussives and analgesics. In the original NDA submission, the Applicant submitted the result of the AERS database search for the terms of hydrocodone (HC), hydrocodone plus chlorpheniramine (HC/CPM), hydrocodone plus acetaminophen (HC/ACT), chlorpheniramine plus pseudoephedrine (CPM/PSE), chlorpheniramine plus other ingredients, pseudoephedrine (PSE), pseudoephedrine plus other ingredients, and other combination products. Table 7 summarizes the results of the AERS search covering the period from October 2007 through March 2008.

**Table 5 Post-marketing adverse events (AERS database, Oct. 2007 to March, 2008)**

Adverse event	HC	HC/CPM	HC/ACT	CPM/PSE	CPM/other	PSE	PSE/other
Total adverse events	37	2	160	6	7	40	19
<6 years	1	0	1	1	1	15	7
6-<12 years	0	1	0	2	3	0	5
≥12 years	28	1	88	1	3	21	5
Age unknown	8	0	71	2	0	4	2
Misuse/overdose/error	8	0	11	0		12	3
Death	29	0	123	0	0	33	6
Suicide	12	0	94	0	0	6	0

(Source: NDA 22-439 N-000, m2, Section 2.5.5, page 13)

In searching AERS database covering the period from October, 2007 through March, 2008, the most death cases were from HC/ACT (123 deaths), accounting for 76.88% of the adverse events reported for hydrocodone plus acetaminophen drugs. There were 29 deaths reported for HC alone, accounting for 78.39% of the adverse events reported for hydrocodone drugs. HC/ACT is a fixed dose combination analgesic. Also the overall adverse events and death reports for hydrocodone alone did not differentiate if the hydrocodone was taken as antitussive doses or as much higher analgesic doses. Because the data reflect a large fraction of suicide, the dosage forms of hydrocodone for the deaths and adverse events were most possibly higher than doses as an antitussive. Noticeably, hydrocodone and chlorpheniramine, which is a fixed dose combination antitussive drug product (Tussionex, NDA 19-111 and Tussicaps, ANDA 77-273), had only two adverse events and no death reported.

*Reviewer's comment:*

*The AERS database search shows the death rate is high in the AE reports for hydrocodone and combination drugs containing hydrocodone. The death reports reflected a large fraction of suicide cases. Also, hydrocodone is known to be used in symptomatic treatment for many end stage diseases. Without the knowledge of dosage forms, diseases, co-administered medications, a simple search of AERS, a spontaneous post-marketing adverse event reporting database, does not provide meaningful safety information for hydrocodone use. The data showed that hydrocodone and chlorpheniramine combination, as an antitussive formulation, had only two adverse events and no death report.*

*The post-marketing adverse event data search from AERS did not identify new safety signals for hydrocodone and chlorpheniramine.*

## 7.2 Adequacy of Patient Exposure and Safety Assessments

In the clinical pharmacology study 11058503, a total of 112 healthy, adult subjects aged 19 to 65 years were enrolled and 98 subjects received all four treatments. Fourteen subjects dropped off at different stage of the study. The demographic characteristics of the subjects are shown in Table 8.

This is a clinical pharmacology study. The subject number of the study for safety assessment is relatively small. The efficacy and safety of the proposed drug is supported by DESI review for hydrocodone and by OTC monograph for pseudoephedrine and chlorpheniramine.

**Table 6 Demographic characteristics of subjects in Study 11058503**

		All subjects, N=98
Gender	Males	58 (59.2%)
	Females	40 (40.8%)
Race	Caucasian	10 (10.2%)
	Black	69 (70.4%)
	Asian, Native Americans	2 (2.0%)
	Others	17 (17.4%)
Ethnicity	Hispanic	17 (17.4%)
	Not Hispanic	81 (82.7%)
Age	Mean	32.3
	Min, Max	19, 65
	BMI*	Mean

Min, Max	18.4, 30.0
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\*Body Mass Index (kg/m<sup>2</sup>)

## 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Not applicable

### 7.2.2.3 Literature

The Applicant compiled nine literature references for information relevant to safety of hydrocodone, pseudoephedrine, and chlorpheniramine in general [NDA 22-439 N-000, m2, Section 2.5.7, page 14]. The reference included the product labeling of the reference drug product Hycodan, Cochrane reviews, and articles published on the peer reviewed journals. There were no studies related to safety of products containing all three ingredients. The literature survey revealed no new safety signals for hydrocodone, chlorpheniramine, and pseudoephedrine. The result of the literature review is provided in the Section 8.6 of this review.

## 7.2.3 Adequacy of Overall Clinical Experience

This submission includes a single-dose clinical pharmacology study that provided a fairly limited amount of safety information. The efficacy and safety of the proposed drug is supported by DESI review for hydrocodone and by OTC monograph for chlorpheniramine. The AERS database and literature search revealed no new safety signals for hydrocodone and chlorpheniramine at proposed doses. Given the extensive experience with use of hydrocodone as an antitussive and chlorpheniramine as an antihistamine, this reviewer concludes that the overall clinical exposure to the proposed drug is adequate.

## 7.2.9 Additional Submissions, Including Safety Update

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), the Applicant submitted a safety update under the NDA 204-307 SN0006 on October 15, 2012. There are no new safety data included in the safety update.

## **7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions**

In the clinical pharmacology study, the number of subjects treated was small and AEs were infrequent. No new safety concerns have become apparent in the clinical study.

## **8 ADDITIONAL CLINICAL ISSUES**

### **8.1 Dosing Regimen and Administration**

The application is for Vituz Oral Solution. The proposed drug product contains 5 mg hydrocodone bitartrate and 4 mg chlorpheniramine maleate per 5 mL. It is proposed as a

prescription drug combination of antitussive and antihistamine. The indications are (b) (4)

The proposed dosage is one teaspoon (5 mL) every 4 to 6 hours as needed, not to exceed (NTE) 4 doses (20 mL) in 24 hours for adults 18 years of age and older.

## 8.2 Drug-Drug Interactions

There is no drug-drug interaction study conducted in this NDA submission. The result of a clinical pharmacology study (S08-0179) in NDA 22-439 showed that the subjects' exposure for hydrocodone in the proposed drug hydrocodone, chlorpheniramine, and pseudoephedrine oral solution was lower than that in the reference drug product Hycodan. This suggests that there may be drug-drug interaction between hydrocodone and chlorpheniramine and/or pseudoephedrine in the proposed drug formulation. However, the result of the clinical pharmacology study 11058503 showed that the exposure of hydrocodone is within the bioequivalence range compared to the RLD. There were no differences in chlorpheniramine exposure between Vituz Oral Solution and the OTC monograph chlorpheniramine solution.

Use of MAO inhibitors or tricyclic antidepressants with hydrocodone may increase the effect of either the antidepressant or codeine. Concurrent use of opioids, antihistamines, anti-psychotics, anti-anxiety agents or other CNS depressants including alcohol concomitantly with hydrocodone may result in additive CNS depression. The Applicant's proposed labeling appropriately addresses the potential these drug-drug interactions.

More information regarding possible drug-drug interaction affecting the hydrocodone exposure in the Vituz Oral Solution may be found in the Clinical Pharmacology Review [NDA 204-307, Clinical Pharmacology Review, Arun Agrawal, Ph. D.].

## 8.3 Specific Populations

There were no studies in special populations for Vituz Oral Solution in this submission to review. The Applicant's proposed labeling indicates that the product is a pregnancy category C drug for the lack of adequate and well-controlled studies in pregnant women. As with other opioids, use of hydrocodone during labor can produce respiratory depression in the neonate. The Applicant's proposed labeling states that (b) (4)

A literature search shows a report that two infants exposed to hydrocodone through breast milk while mothers were taking hydrocodone as an analgesic. Caution should be exercised when Vituz is administered to nursing mothers.

## 8.4 Pediatrics

The clinical pharmacology study 11058503 included no pediatric subjects. The Applicant conducted the post-marketing adverse event search in AERS for hydrocodone and chlorpheniramine covering the period from October, 2007 through March, 2008 for age groups of under 6, 6 to under 12, and 12 years and above. The most adverse events for hydrocodone were in the age group of 12 years and above. However, adverse events were reported in pediatric age groups of under 6 and 6 to 12 years of age for chlorpheniramine, because chlorpheniramine is an active ingredient of many OTC cough and cold products. The post-

marketing adverse event data revealed no new pediatric safety concerns for hydrocodone and chlorpheniramine when used for approved indications at approved doses.

On March 11, 2008, FDA published a Public Health Advisory and a Healthcare Professionals Information sheet addressing the risk of a long-acting hydrocodone-containing cough product in patients younger than the approved age group of 6 years and older.

[<http://www.fda.gov/cder/drug/advisory/hydrocodone.htm>, <http://www.fda.gov/cder/drug/InfoSheets/HCP/hydrocodoneHCP.htm>]. FDA has received reports of life-threatening adverse events and death in patients, including children, who have received long-acting hydrocodone-containing cough products. The product labels of marketed hydrocodone products (Hycodan, Tussionex) have indicated that hydrocodone is contraindicated in children less than 6 years of age due to the risk of fatal respiratory depression.

The Applicant requested a partial waiver for the requirement for pediatric studies for Vituz Oral Solution in age groups of birth to under 6 years of age. This reviewer recommends a partial waiver for pediatric studies below 6 years of age because hydrocodone is contraindicated in children less than 6 years of age due to the risk of fatal respiratory depression. Although hydrocodone was approved under DESI and is currently labeled for use in children down to 6 years of age, safety concerns of dose-related respiratory depression 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 have 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 under 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 that the sponsor establish the appropriate dose of hydrocodone for the pediatric (under 18) population. In the review process of NDA 22-439 Zutripro (hydrocodone bitartrate, pseudoephedrine hydrochloride and chlorpheniramine maleate) Oral Solution and NDA 22-442 Rezira (hydrocodone bitartrate and pseudoephedrine hydrochloride) Oral Solution, the Division had discussed with the Applicant regarding the concerns of lacking PK and safety data of hydrocodone in the pediatric population. A pediatric study plan that already covers NDAs 22-439/22-442 and will also cover the present NDA 204-307, including timelines of the planned pediatric studies, was submitted under NDA 22-439. In the pediatric plan, the Applicant agreed to conduct a PK study and a pediatric safety study from 6 to under 18 years of age. On May 26, 2010, the Pediatric Review Committee (PeRC) meeting agreed with the waiver of studies in children less than 6 years of age and a deferral for studies in patients 6 to 17 years of age, with a recommendation to incorporate efficacy assessments and population PK in the proposed safety study.

For the present submission of NDA 204-307, the requests of the partial waiver for pediatric studies in children less than 6 years of age and the deferral of PK and safety studies in patients 6 to 17 years of age, in which the efficacy assessment is incorporated as recommended by PeRC for the related combination products Zutripro and Rezira, were reevaluated at the PeRC meeting on October 10, 2012. The PeRC maintained its position on the partial waiver of studies in children less than 6 years of age. For the deferral of the pediatric studies in patients 6 to 17 years of age, however, the PeRC recommended that the Division request the Applicant conduct a full

development program including dose-ranging and replicate factorial design efficacy studies. Their rationale was that the overall efficacy data for cough and cold drugs in the pediatric population were not robust, and a well designed pediatric efficacy study would provide much needed pediatric efficacy data for chlorpheniramine. This reviewer agrees that the robustness of the available efficacy data for cough and cold drugs in pediatric population might not be up to current standards. But the current OTC monograph, in which the proposed chlorpheniramine dose is generally considered safe and effective, is still the regulatory base in evaluating the cough and cold drugs. Because a pediatric safety study is requested due to the safety concerns of hydrocodone, it is appropriate to add the efficacy assessment for the proposed drug, as recommended by PeRC at the May 26, 2010 meeting. However, it seems not necessary to require a stand alone efficacy study for the proposed drug at this time.

## 8.6 Literature Review

Hydrocodone has been approved as an antitussive for more than 50 years. The proposed drug product is relying on the Agency's finding of safety and efficacy of Hycodan (NDA 5-213, approved on March 23, 1943)<sup>1,2</sup> and subsequent DESI review, to support the efficacy and safety of the hydrocodone in the proposed product. Clinical studies have demonstrated the effectiveness and safety of hydrocodone in treatment of cough symptom in cancer patients<sup>3</sup>. D'Agostino RB, Weintraub M, Russel H, et al. conducted a meta-analysis regarding the efficacy of chlorpheniramine in reducing the severity of runny nose and sneezing. The data of eight placebo-controlled studies demonstrated that the oral dose of 4 mg chlorpheniramine was effective in reducing the severity of runny nose and sneezing in common cold compared to placebo<sup>4</sup>. OTC monographs, Cochran reviews, and controlled trials have demonstrated that chlorpheniramine<sup>5,8,9</sup> and pseudoephedrine<sup>6,7,8,9</sup> are safe and effective as an antihistamine and decongestant in treatment of symptoms of common cold and allergic rhinitis.

### Reference

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7. Facts and Comparisons 4.0. Oral Monograph: Pseudoephedrine HCl. Available at: <http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-hcp12309&#monoTab>. 2007.

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9. Wyeth Consumer Healthcare. Product Monograph for Health Canada: Advil Cold and Sinus Nighttime Caplets (200 mg Ibuprofen, 30 mg Pseudoephedrine HCl, and 2 mg Chlorpheniramine Maleate) DIN Number 02267632. 6-13-2006.

## 8.7 Postmarketing Risk Management Plan

Hydrocodone is a controlled substance that is known to have a certain level of abuse potential. The risk associated with Vituz Oral Solution is expected being similar to the risks of other hydrocodone-containing antitussives. In a consult for another hydrocodone containing drug product (NDA (b) (4)), Controlled Substance Staff (CSS) recommended that the Applicant conduct well designed animal and human studies to characterize the abuse potential of the proposed combination drug [Memorandum, Consult on NDA (b) (4) Controlled Substance Staff, March 27, 2009]. In an Agency regulatory briefing regarding the abuse potential safety testing for hydrocodone cough cold combination products on June 12, 2009, the consensus was that abuse liability studies were not required prior to approval of these drug products but that studies may be necessary on a case-by case basis if a signal is detected.

No special post-marketing risk management plan is recommended at this time. A routine post-marketing surveillance is recommended to monitor the adverse events associated with the use of Vituz Oral Solution. If a signal of abuse, misuse, overdose and addiction is identified, further abuse liability assessment may need to be conducted.

## 9 OVERALL ASSESSMENT

### 9.1 Conclusions

The Applicant seeks the approval of Vituz Oral Solution based on a clinical pharmacology program to demonstrate the bioequivalence to the reference drugs. No clinical efficacy and safety studies were submitted to support this application. The results of bioequivalence study submitted in this second Complete Response resubmission show that the proposed combination drug product is bioequivalent to the reference drug for hydrocodone and OTC monograph products for chlorpheniramine and pseudoephedrine.

The proposed product labeling indications for Vituz Oral Solution are: Relief of cough associated with common cold; Relief of symptoms associated with upper respiratory allergies.

The clinical pharmacology studies to support this NDA were conducted in adults 18 years of age and older. (b) (4) This reviewer recommends a partial waiver for pediatric studies below 6 years of age because that hydrocodone is contraindicated in children less than 6 years of age due to the risk of fatal respiratory depression. The proposed dose for chlorpheniramine is the same as the dose in the Agency's approved OTC monograph for these products. Since there are no new safety signals, and the dose proposed in the combination product is within the doses that were declared by the

agency to be safe and effective for OTC use, no additional PK data is necessary to support the dose of chlorpheniramine. However, although Hydrocodone was approved under DESI and is currently labeled for use in children down to 6 years of age, safety concerns of dose-related respiratory depression 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 under 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 that the sponsor establish the appropriate dose of hydrocodone for the pediatric (under 18) population. Therefore, pharmacokinetic data for proper dose selection, and safety data are needed in the pediatric population. The Applicant will be requested to conduct PK and safety studies in the pediatric population from 6 to under 18 years of age to support the approval of the proposed combination product in this age group. In the review cycle, the Division had discussed with the Applicant regarding the concerns of lacking PK and safety data of hydrocodone in the pediatric population. The Applicant agreed to conduct PK and safety studies in the pediatric population from 6 to under 18 years of age. A pediatric study plan that will cover NDA 22-439/22-442 and the present NDA 204-307, including timelines of the planned pediatric studies, was submitted under NDA 22-439. On May 26, 2010 the Pediatric Review Committee (PeRC) meeting agreed with the waiver of studies in children less than 6 years of age and a deferral for studies in patients 6 to 17 years of age, with a recommendation to incorporate efficacy assessment and population PK in the proposed safety study.

For the present submission of NDA 204-307, the requests for the partial waiver of pediatric studies in children less than 6 years of age and the deferral of PK and safety studies in patients 6 to 17 years of age, in which the efficacy assessment is incorporated as recommended by PeRC, were reevaluated at the PeRC meeting on October 10, 2012. The PeRC maintained its position on the partial waiver of studies in children less than 6 years of age. For the deferral of the pediatric studies in patients 6 to 17 years of age, however, the PeRC recommended that the Division request an efficacy study in addition to the PK and safety study with incorporated efficacy assessment, because the PeRC considered that the overall efficacy data for cough and cold drugs in pediatric population were not robust, and a well designed pediatric efficacy study would provide much needed pediatric efficacy data for chlorpheniramine. This reviewer agrees that the robustness of the available efficacy data for cough and cold drugs in pediatric population might be questionable according to current standards. But the current OTC monograph, in which the proposed chlorpheniramine dose is generally considered safe and effective, is still the regulatory base in evaluating the cough and cold drugs. Because a pediatric safety study is requested due to the safety concerns of hydrocodone, it is appropriate to add the efficacy assessment for the proposed drug, as recommended by PeRC at the May 26, 2010 meeting. However, it seems not necessary to require a stand alone efficacy study for the proposed drug at this time.

## 9.2 Recommendation on Regulatory Action

I recommend an “Approval” action for this NDA application. The development program for the proposed drug product is a clinical pharmacology program. The proposed drug product Vituz Oral Solution depends on the bioequivalence to the reference drug Hycodan for hydrocodone and to OTC monograph ingredient chlorpheniramine to support its efficacy and safety. No clinical efficacy studies were submitted to support this application. The clinical pharmacology study demonstrated that the bioequivalence between the proposed drug product Vituz and the reference drugs, showing that the 90% CI of ratios of AUC and  $C_{max}$  for the active components in Vituz vs. reference drugs are within the 80 - 125% goal post for bioequivalence.

## 9.3 Recommendation on Postmarketing Actions

Hydrocodone is a controlled substance that is known to have a certain level of abuse potential. The Controlled substances Staff (CSS) recommended in a consult for another hydrocodone containing cough and cold product that the Applicant conduct well designed animal and human studies to characterize the abuse potential of the proposed combination drug [Memorandum, Consult on NDA (b) (4) Controlled Substance Staff, March 27, 2009]. In an Agency regulatory briefing regarding the abuse potential safety testing for hydrocodone cough and cold combination products on June 12, 2009, the consensus was that abuse liability studies were not required prior to approval of these drug products but that studies may be necessary on a case-by case basis if a signal is detected.

Routine post-marketing surveillance is recommended to monitor the adverse events associated with the use of Vituz Oral Solution. If a signal of abuse, misuse, overdose and addiction is identified, further abuse liability assessment may need to be conducted.

Although the reference drug for hydrocodone and OTC monograph for chlorpheniramine are approved for children 6 years of age and older, pharmacokinetic (PK) data to support dose selection of the proposed combination drug product are lacking in the pediatric population. The proposed dose for chlorpheniramine is the same as the dose in the Agency’s approved OTC monograph. Since there are no new safety signals, and the proposed dose in the combination product is within the doses that were declared by the agency to be safe and effective for OTC use, no additional PK data is necessary to support the proposed dose. However, although Hydrocodone was approved under DESI and is currently labeled for use in children down to 6 years of age, safety concerns of dose-related respiratory depression 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 have 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 under 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 that the sponsor establish the appropriate dose of hydrocodone for the pediatric (under 18) population. Therefore, pharmacokinetic data for proper dose selection, and safety data are needed in the pediatric population. The Applicant will conduct a PK study and a safety study, in which the efficacy assessment will be incorporated, in the pediatric population from 6 to 17 years of age.

## 9.4 Labeling Review

The proposed labeling is reference to the approved product labeling of NDA 19111 Tussionex (hydrocodone polistirex and chlorpheniramine polistirex) Extended-Release Suspension and NDA 22-439 Zutripro ((hydrocodone bitartrate, pseudoephedrine hydrochloride and chlorpheniramine maleate) Oral Solution, with the component of pseudoephedrine being taken out. The proposed package insert was submitted in Physician's Labeling Rule (PLR) format.

The indication is modified from proposed two indications [REDACTED] (b) (4) [REDACTED] to one indication "Relief of cough and symptoms associated with upper respiratory allergies or the common cold" that is consistent with the indication of Tussionex. The Division of Professional Drug Promotion (DPDP), Office of Prescription Drug Promotion (OPDP), and the Division of Medication Error Prevention & Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE) have been consulted regarding the product labeling and the consultation comments have been incorporated into the labeling revision. Detailed draft labeling review has been conducted as appended below.

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

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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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XU WANG  
01/17/2013

ANTHONY G DURMOWICZ  
01/18/2013



## 1. GENERAL INFORMATION

This is a 505(b)(2) application for an immediate release oral solution combination product containing hydrocodone bitartrate and chlorpheniramine maleate (5 and 4 mg, respectively, per 5 ml). The sponsor is Cypress Pharmaceutical Inc. The proposed name for the product is (b) (4) Oral Solution. The proposed indication is for relief of cough associated with common cold, and relief of symptoms associated with upper respiratory allergies. The application is provided electronically.

As a basis for the 505(b)(2) submission route, the applicant cites the following reference listed drugs (RLDs): 1) Zutripro Oral Solution (NDA 22-439, Cypress Pharmaceutical), 2) Rezira Oral Solution (NDA 22-442, Cypress Pharmaceutical).

## 1. CLINICAL DEVELOPMENT PROGRAM

The clinical pharmacology program for this combination product also supports other two NDAs: Zutripro (NDA 22-439), an oral solution combination of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate, and Rezira (NDA 22-442), an oral solution combination of hydrocodone bitartrate and pseudoephedrine hydrochloride. Since the formulations for the 3 NDAs are exactly the same, except that Zutripro contains 3 active ingredients, Rezira does not contain chlorpheniramine maleate, and the current NDA for (b) (4) does not contain pseudoephedrine hydrochloride, it is acceptable to use the same clinical pharmacology program to support the 3 NDAs.

## 2. FOREIGN MARKETING AND REGULATORY HISTORY

Cypress submitted the opening IND on April 15, 2008 (IND 102,177). A pre-IND meeting for this application was held on January 14, 2008 with the Division. The Division's comments in the pre-IND meeting which relate to this application are summarized as follows:

- A 505(b)(2) pathway would be an acceptable approach for the planned combination drug products.
- The bioequivalence should be demonstrated between hydrocodone in the proposed products and an approved hydrocodone antitussive drug product (e.g. Hycodan) by conducting bioequivalence studies.
- The drug-drug interaction between hydrocodone and other active pharmacological ingredients should be addressed. This information may be provided from the literature or by conducting pharmacokinetic drug-drug interaction studies.

Cypress stated that the proposed combination product (b) (4) is not marketed in domestic or foreign markets.

*Reviewer comment: The Agency's DESI review determined that hydrocodone is safe and effective for symptomatic relief of cough. There is regulatory precedent regarding the combination of hydrocodone with a monograph cold, cough, allergy, bronchodilator, and*

*antiasthmatic drug. The precedent was established in response to the NDA for Tussionex Pennkinetic Extended-Release Suspension (NDA 19-111), equivalent to 10 mg hydrocodone plus 8 mg chlorpheniramine maleate/5 ml. The NDA, which included three bioavailability studies and no clinical studies, was approved on December 31, 1987. The decision was made at the Center level. Given this regulatory background, and recognizing that the Agency has determined that both single ingredients are safe and effective for their respective indications, the pK program as the Division recommended is sufficient to support the proposed combination drug products, provided bioequivalence and no drug-drug interactions are demonstrated.*

### **3. ITEMS REQUIRED FOR FILING (21 CFR 314.50)**

The following items pertinent to a clinical review are included in the submission:

- Application form (FDA 356h) [m1\11-forms\112-fda-form-356h]
- Index [index.xml]
- Summary [m2\22-intro and 25-clin-over]
- Clinical technical section
  - Clinical study reports
    - Study 11058503 [m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep]
  - Other pertinent data
    - none
  - Integrated summary of efficacy [m2\27-clin-sum\sum-clin-efficacy-cough-and-cold-relief.pdf]
  - Integrated summary of biopharmacology [m2\27-clin-sum\summary-biopharm.pdf]
  - Integrated summary of safety
    - Integrated summary of safety [m2\27-clin-sum\summary-clin-safety.pdf]
    - Abuse and overdose information [m2\27-clin-sum\summary-clin-safety.pdf]
    - Risk/benefit analysis: not provided
    - Good Clinical Practice certification [m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study-report-s08-0179\report-body.pdf, Section 5 Ethics]
  - Debarment certification [m1\13-administrative-information\133-debarment-certification]
  - Pediatric use [m1\19-pediatric-administrative-information\191-request-waiver-pediatric-studies]
- Labeling [m1\us\114-labeling\1141-draft-labeling]
- Case report forms [m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study-report-s08-0179\crfs]

- Financial disclosure [m1\13-administrative-information\134-financial-certification-disclosure]

#### 4. CLINICAL STUDIES

There was a single clinical bioavailability and drug-drug interaction study conducted for the drug development program of (b) (4) Oral Solution.

Study 11058503 was a single center, single dose, 4-period crossover, relative bioavailability study. Study arms included: 1) hydrocodone, pseudoephedrine, and chlorpheniramine oral solution, 2) pseudoephedrine oral solution, 60 mg/5 ml (manufactured by Great Southern Laboratories, manufactured for Cypress Pharmaceutical, Inc.), 3) chlorpheniramine oral solution, 4 mg/5 ml (manufactured by Great Southern Laboratories, manufactured for Cypress Pharmaceutical, Inc.), and 4) hydrocodone bitartrate and homatropine methylbromide syrup, 5 mg/1.5 mg per 5 mL (manufactured by Hi-Tech Pharmacal Co., Inc.). The study was performed under fasted conditions. A total of 112 healthy volunteers were enrolled, and 98 completed. The following pharmacokinetic variables were calculated for each treatment:  $AUC_{0-t}$ ,  $AUC_{0-inf}$ ,  $C_{max}$ ,  $T_{max}$ ,  $Kel$ , and  $T_{1/2}$ . The 90% confidence intervals about the ratio of the test geometric mean to reference geometric mean are all within the 80-125% limits for  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$ . Nausea, dizziness, and headache were the most common adverse events reported in the study. There were no death or serious adverse events reported during the study.

#### 5. BRIEF REVIEW OF PROPOSED LABELING

The proposed label is based on the approved product label for NDA 22-439, Zutripro (hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate) Oral Solution, and the information regarding pseudoephedrine in the label of Zutripro is tailored out for the proposed combination product of hydrocodone bitartrate and chlorpheniramine.

#### 6. DSI REVIEW AND AUDIT

The DSI conducted an audit for both the clinical study and the bioanalytic sites in the review cycle for Zutripro (NDA 22-439). Some irregularities were found to which the Applicant provided an acceptable response, and the DSI had concluded that the data from study 11058503 could be used to support the NDA. Because this NDA is supported by the same study, there are no new issues that require a DSI review and audit.

#### 7. SUMMARY

This is a 505(b)(2) application for an immediate release oral solution combination product containing hydrocodone bitartrate and chlorpheniramine maleate (5 and 4 mg, respectively, per 5 ml). The sponsor is Cypress Pharmaceutical Inc. The proposed name for the product is (b) (4) Oral Solution. The proposed indication is for relief of cough associated with common cold, and relief of symptoms associated with upper respiratory allergies. As a basis for the 505(b)(2) submission route, the applicant cites the following reference listed drugs (RLDs): 1) Zutripro

Oral Solution (NDA 22-439, Cypress Pharmaceutical), 2) Rezira Oral Solution (NDA 22-442, Cypress Pharmaceutical).

The clinical pharmacology program for this combination product also supports other two NDAs: Zutripro (NDA 22-439), an oral solution combination of hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate, and Rezira (NDA 22-442), an oral solution combination of hydrocodone bitartrate and pseudoephedrine hydrochloride. Since the formulations for the 3 NDAs are exactly the same, except that Zutripro contains 3 active ingredients, Rezira does not contain chlorpheniramine maleate, and the current NDA for (b) (4) does not contain pseudoephedrine hydrochloride, it is acceptable to use the same clinical pharmacology program to support the 3 NDAs.

There was a single clinical bioavailability and drug-drug interaction study conducted for the clinical pharmacology program. Study 11058503 was a single center, single dose, 4-period crossover, relative bioavailability study. Study arms included: 1) hydrocodone, pseudoephedrine, and chlorpheniramine oral solution, 2) pseudoephedrine oral solution, 60 mg/5 ml, 3) chlorpheniramine oral solution, 4 mg/5 ml, and 4) hydrocodone bitartrate and homatropine methylbromide syrup, 5 mg/1.5 mg per 5 mL (manufactured by Hi-Tech Pharmacal Co., Inc.). The study was performed under fasted conditions. A total of 112 healthy volunteers were enrolled, and 98 completed. The following pharmacokinetic variables were calculated for each treatment:  $AUC_{0-t}$ ,  $AUC_{0-inf}$ ,  $C_{max}$ ,  $T_{max}$ ,  $Kel$ , and  $T_{1/2}$ . The 90% confidence intervals about the ratio of the test geometric mean to reference geometric mean are all within the 80-125% limits for  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$ . Nausea, dizziness, and headache were the most common adverse events reported in the study. There were no death or serious adverse events reported during the study.

The proposed label is based on the approved product label for NDA 22-439, Zutripro (hydrocodone bitartrate, pseudoephedrine hydrochloride, and chlorpheniramine maleate) Oral Solution, and the information regarding pseudoephedrine in the label of Zutripro is tailored out for the proposed combination product of hydrocodone bitartrate and chlorpheniramine.

## 8. REVIEW TIMELINE

The PDUFA action date is February 22, 2013. The schedule for review is provided in Table 1. Write-up will be concomitant with the review process. The review will culminate with the proposed label, which will include comparison to the referenced listed products and monographs. The initial draft review will be complete by September 20, 2012, and the final draft review will be completed by October 20, 2012. The Division may take an early action on this NDA before the PDUFA due date.

Table 1: Review timeline for NDA 204-307

Milestone	Target date for completion
Filing and planning meeting	June 8, 2012
Integrated Summary of Efficacy/Safety	August 30, 2012
Initial draft review complete	September 20, 2012

Wrap-up meeting/Label	October 1, 2012
Final draft review complete	October 20, 2012
PDUFA Action date (10 months)	February 22, 2013

## 9. COMMENTS FOR THE SPONSOR

No comment is to be communicated to the sponsor.

Reviewed by:

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Xu Wang, M.D., Ph.D.  
Medical Officer, Division of Pulmonary, Allergy, and Rheumatology Products

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Anthony G. Durmowicz, M.D.  
Medical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products

cc: NDA 204-307  
HFD-570/Division File  
HFD-570/ Durmowicz /Medical Team Leader  
HFD-570/Chowdhury/Director  
HFD-570/Wang/Medical Reviewer  
HFD-715/Li/Biometrics Reviewer  
HFD-570/Whitehurst/Pharmacology-Toxicology Reviewer  
ONDQA/Shen/CMC Reviewer  
OCP/Suarez/Clinical Pharmacology Reviewer  
HFD-570/Han/CSO

### Clinical Filing Checklist

**NDA/BLA Number: 204-307**

**Applicant: Cypress**

**Stamp Date: April 23, 2012**

**Drug Name: (b) (4) Oral  
Solution**

**NDA/BLA Type: 505(b)(2)**

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

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?			X	All components of this combo product are DESI or GRASE
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			Zutripro Oral Solutin and Rezira Oral Solution
<b>DOSE</b>					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
<b>EFFICACY</b>					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?			X	

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
	Pivotal Study #1 Indication:				
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	X			MedDRA Ver 11
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	No deaths or discontinuations due to AEs
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission		X		

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
	discussions?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	No foreign data
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			CRFs submitted for all patients in the study
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_\_ YES \_\_\_**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

None

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Reviewing Medical Officer

Date

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Clinical Team Leader

Date

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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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XU WANG  
07/25/2012

ANTHONY G DURMOWICZ  
07/25/2012