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APPLICATION NUMBER:
22442Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-442
Submission Code	SN016
Letter Date	12/08/2010
Stamp Date	12/08/2010
PDUFA Goal Date	06/08/2011
Reviewer Name	Xu Wang, M.D., Ph.D.
Review Completion Date	05/12/2011
Established Name	Hydrocodone and pseudoephedrine
(Proposed) Trade Name	Rezira™ Oral Solution
Therapeutic Class	Antitussive/decongestant
Applicant	Cypress Pharmaceuticals, Inc.
Priority Designation	S
Formulation	Oral solution
Dosing Regimen	For adults 18 years of age and older: 5 mL every 4 to 6 hours as needed, not to exceed 4 doses (20 ml) in 24 hours
	 (b) (4)
Indication	Relief of cough and nasal congestion associated with 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 application. The development program for the proposed drug product is a clinical pharmacology program. The proposed drug product Rezira™ Oral Solution depends on the bioequivalence to the reference drug Hycodan for hydrocodone and to OTC monograph ingredient pseudoephedrine 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 Rezira™ and the reference drugs, showing that the 90% CI of ratios of AUC and C_{max} for the two components in Rezira™ vs. reference drugs are within the 80 - 125% goal post for bioequivalence.

Rezira™ Oral Solution is an immediate release oral solution, containing 5 mg hydrocodone bitartrate and 60 mg pseudoephedrine hydrochloride per 5 mL. It is proposed as a fixed dose combination product containing an antitussive and nasal decongestant. The proposed indication is “Relief of cough and nasal congestion associated with common cold” for adults 18 years of age and older. The proposed indication is guided by the indication from reference drug Hycodan and OTC monograph language for indication for pseudoephedrine.

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 Rezira™ 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 ██████████^{(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 Rezira™ 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. (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. 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 pseudoephedrine is the same as the dose in the Agency's approved OTC monograph. Since there are no new safety signals with these ingredients, and the doses that are proposed in the combination product are the doses that were declared by the agency to be safe and effective for OTC use, no additional PK data is necessary to support these doses. 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.

In the previous review cycle, the Division had discussed with the Applicant regarding the concerns of lacking PK and safety data 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, including timelines of the planned pediatric studies, was submitted on May 6, 2010. The partial pediatric waiver request and the pediatric study plan were submitted to the Pediatric Review Committee (PeRC) meeting on May 26, 2010. The PeRC agreed with the waiver of studies in children less than 6 years of age and a deferral for patients 6 to 17 years of age, with recommendations to incorporate efficacy assessments and population PK in the proposed safety study.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This is the second complete response submission, 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 Rezira™ and another drug product of the Applicant, ZUTRIPRO (NDA 22-439), 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 Rezira™ Oral Solution (NDA 22-442) and ZUTRIPRO Oral Solution (NDA 22-439) are exactly same formulations except that ZUTRIPRO consists of one more active ingredient (chlorpheniramine), demonstration of bioequivalence for the hydrocodone and pseudoephedrine components in the bioequivalence study supporting ZUTRIPRO relative to respective reference products is applicable to this product as well. This approach was discussed in the pre-NDA meeting and the Agency agreed that this approach is acceptable.

The 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. In the original NDA submission, the Applicant provided the AERS database search results for post-marketing spontaneous adverse events associated with hydrocodone and pseudoephedrine.

1.3.2 Efficacy

No clinical efficacy studies were submitted to support this application. This is a 505(b)(2) application using clinical pharmacology studies to support approval. The Agency's previous efficacy and safety findings of the approved hydrocodone NDA (Hycodan) and the OTC monograph for pseudoephedrine are being used to substantiate the efficacy and safety of this 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, chlorpheniramine, and pseudoephedrine. 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) and three reference drugs A, B, and C, respectively. In subjects taking the test drug (ZUTRIPRO), 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 acetaminophen (HC/ACT), hydrocodone plus other ingredients, pseudoephedrine (PSE), pseudoephedrine plus other ingredients. There were no new safety signals revealed through the search of AERS database for post-marketing adverse events.

The Applicant compiled five literature references for information relevant to safety of hydrocodone 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 hydrocodone and pseudoephedrine. The literature survey revealed no new safety signals for hydrocodone and pseudoephedrine. 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 on March 31, 2011. There are no animal studies and clinical safety studies conducted for the proposed drug and the proposed drug has not been manufactured and marketed. There are no new safety data included in the safety update.

1.3.4 Dosing Regimen and Administration

The proposed drug product contains 5 mg hydrocodone bitartrate and 60 mg pseudoephedrine hydrochloride per 5 mL. It is proposed as a prescription drug combination of antitussive and nasal decongestant. The indication is for relief of cough and nasal congestion associated with common cold. The proposed dosage is (b) (4) (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 the clinical pharmacology study S08-0179 in the original NDA submission (NDA 22-439/NDA 22-442 N-000) showed that the subjects' exposure for hydrocodone in the 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 the test drug and the OTC monograph chlorpheniramine and pseudoephedrine solutions. More information regarding possible drug-drug interaction affecting the hydrocodone exposure in the Rezira™ Oral Solution may be found

Clinical Review, NDA 22-442 SN016, Rezira™ (hydrocodone bitartrate and pseudoephedrine hydrochloride) Oral Solution, Cypress Pharmaceuticals, Inc. 12/08/2010, Xu Wang, M.D., Ph.D.

in the Clinical Pharmacology Review [NDA 22-439/NDA 22-442, Clinical Pharmacology Review, Elizabeth Shang, Ph. D., R. Ph.].

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 Special Populations

There were no studies in special populations for Rezira™ 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) (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 Rezira™ 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 pseudoephedrine. The drug product contains 5 mg hydrocodone bitartrate and 60 mg pseudoephedrine hydrochloride per 5 mL. It is proposed as a prescription drug combination of antitussive and decongestant. The indication is for relief of cough and nasal congestion associated with common cold. The sponsor's proposed name is Rezira™ Oral Solution. 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) Codeprex Extended-Release Suspension (NDA 21-369, UCB, Inc.), 4) Advil Allergy/Sinus Tablets (NDA 21441, Wyeth Consumer Products), 5) Mucinex D Tablets (NDA 21-585, Adams Respiratory Therapeutics), 6) Tavist Allergy/Sinus/Headache Tablets (NDA 21-082, Novartis), and 7) 21 CFR 341.20 for pseudoephedrine hydrochloride. Of note, reliance on Tussionex or Codeprex is not necessary to determine safety or efficacy of this application, as the information that the sponsor cites from these labels to support their labeling, is information that comes from the published literature. Subsequent to the complete response action for the original NDA application, the Hycodan syrup manufactured by Endo Pharmaceuticals was discontinued from the market (not for reasons of safety or efficacy). The Applicant needed to conduct another bioavailability study and used the hydrocodone bitartrate/homatropine methylbromide syrup developed by HI-TECH Pharma as the reference for the bioavailability study. 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). Hydrocodone 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

- Children less than 6 years of age: The administration of hydrocodone in children less than 6 years of age is contraindicated due to the risk of respiratory depression [Reference to NDA 19-111, Tussionex Pennkinetic product labeling].

Pseudoephedrine (PSE) is considered to be GRASE as an oral nasal decongestant [21 CFR 341.20] in the following age groups at the following oral doses [21 CFR 341.80(d)]:

- Adults and children 12 years of age and over: 60 mg every 4 to 6 hours, NTE 240 mg in 24 hours
- Children 6 to under 12 years of age: 30 mg every 4 to 6 hours, NTE 120 mg in 24 hours
- Children 2 to under 6 years of age: 15 mg every 4 to 6 hours, NTE 60 mg in 24 hours
- Children under 2 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 nasal decongestant 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) M-001, MR, Charles E. Lee, M.D., 9/25/2006. 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). There are other generic Hydrocodone products as antitussive drugs on the market. These are Hydrocodone Compound (ANDA 88-017), Tussicaps (ANDA 77-273), Tussion (ANDA 88-506), and Homatropine Methylbromide and Hydrocodone Bitartrate Tablet and Syrup (ANDA 40295, ANDA 40-613, ANDA 88-008).

Pseudoephedrine is readily available non-prescription monograph drug, being considered to be generally recognized as safe and effective (GRASE) at OTC monograph doses for the temporary relief of nasal congestion. In addition to pseudoephedrine, phenylephrine is another available non-prescription nasal decongestant. Nasal decongestants 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 for cough (Tussionex Pennkinetic, NDA 19-111) and generic antitussive drugs Hydrocodone Compound (ANDA 88-017), Tussicaps (ANDA 77-273), Tussion (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, (b) (4) 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].

Pseudoephedrine is currently approved in the United States in tablets (Afrinol, NDA 18191), in combination with chlorpheniramine (Chlor-Trimeton, NDA 18397), with ibuprofen and chlorpheniramine (Advil Allergy Sinus Caplet, NDA 21441), and with guaifenesin (Mucinex™ D, NDA 21585). These products are extended release formulations. Pseudoephedrine 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).

Pseudoephedrine is an OTC monograph drug of oral nasal decongestant [21 CFR 341.20]. Pseudoephedrine can be unlawfully used to make the illicit drug methamphetamine. The

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.

This second Complete Response resubmission was filed on December 8, 2010, in which the Applicant presents results from a clinical pharmacology study 11058503.

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 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 (b) (4) (b) (4) (b) (4) 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)

(b) (4) The in-process tests used are pH, appearance, density, and viscosity. A detailed review of the CMC portion of the application may be found in the ONDQA review [NDA 22-439/NDA 22-442 N-000, ONDQA Review, Xiaobin Shen, Ph.D.].

Hydrocodone bitartrate dihydrate 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)

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

The proposed drug product Rezira™ is a non-sterile oral solution. (b) (4)

(b) (4)

(b) (4) The product quality microbiology reviewer recommends an approval from a quality microbiology standpoint [NDA 22-439/NDA 22-442 N-000, Product Quality Microbiology Review, Denise Miller, Microbiologist, March 16, 2009].

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 product pseudoephedrine. The Applicant's drug development program for Rezira™ 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 pseudoephedrine. In the original NDA submission and the first complete response resubmission, the Applicant presented two clinical pharmacology studies S08-0179 and SAM-09-1010, which have been reviewed in previous NDA review cycles and were determined "not acceptable" to support the NDA submission. This second complete response submission includes one new 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 assess characterize the exposure of hydrocodone immediate release solution in fasted, healthy, adult subjects. In the original NDA submission, the Applicant presented one clinical pharmacology study S08-0179, which is not included in this review because it has been reviewed in the original NDA review cycle. Table 1 summarizes 2 clinical pharmacology studies.

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	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

	Homatropine)			
	5 mL pseudoephedrine solution, 60 mg			
	5 mL chlorpheniramine solution, 4 mg			

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 pseudoephedrine.

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) (b) (4) during March 7-11, 2011. 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 (b) (4) (b) (4) to that was recorded (b) (4) (b) (4) 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 the complete response submission. A summary of data from the Applicant's clinical pharmacology study follows below. Detailed information can be found in the Clinical Pharmacology Review [NDA 22-439/NDA 22-442, Clinical Pharmacology Review, Elizabeth Shang, Ph. D., R. Ph.].

The formulation of Hydrocodone/Chlorpheniramine/Pseudoephedrine Oral Solution is displayed in Table 2. The experimental formulation is manufactured and supplied (b) (4).

Table 2 Formulation of Hydrocodone/Chlorpheniramine/Pseudoephedrine 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 USP	(b) (4)	(b) (4)	(b) (4)
Polyethylene glycol USP	(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)
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 (b) (4) manufactured for Cypress Pharmaceutical, Inc.) and 4) chlorpheniramine oral solution, 4 mg/5 ml (manufactured by (b) (4) manufactured for Cypress Pharmaceutical, Inc.). The study was per 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 test drug (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 the test drug (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
ZUTRIPRO 5mL (N=100)					
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
Reference 5 mL (N=98)					
Hi-Tech's Hydrocodone	72063.25	69723.40	11364.25	1.22	5.01
Reference 5 mL (N=100)					
Pseudoephedrine	1926.70	1813.41	204.90	1.67	5.53
Reference 5 mL (N=97)					
Chlorpheniramine	174224.49	155681.52	6789.48	3.86	22.61
Ratio of ZUTRIPRO vs. reference (90% CI)					
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)

Reviewer's comment:

The original NDA was submitted on November 6, 2008 (NDA 22-439/22-442 N-000). In the original NDA, Hycodan (NDA 5-213, approved March 23, 1953) was used as the RLD for hydrocodone in the bioavailability study. Subsequent to the complete response action on the application, the manufacture of Hycodan syrup (Endo) discontinued marketing of Hycodan syrup, therefore, the sponsor used Hi-Tech Pharma's Hydrocodone Bitartrate /Homatropine Methylbromide Syrup as the reference for hydrocodone in their bioavailability study.. In the original NDA, the Applicant submitted the results of a pharmaceutical study (S08-0179) showing that the hydrocodone component in the proposed drug product was not bioequivalent to the reference drug, because the ratio of C_{max} between the test drug and Hycodan was outside of the bioequivalence range of 80 - 125% (see Table 4 and 5 below). Since the pseudoephedrine in the proposed drug product has been bioequivalent to the RLD, as demonstrated in the study S08-0179 in the original NDA submission, the Applicant evaluated only the BE of hydrocodone component in the current complete response submission. Since Hycodan has since been discontinued, the Applicant used the hydrocodone syrup product by HI-TECH Pharma (a generic product) to determine the bioavailability of the hydrocodone component in the Applicant's combination product.

Table 4 Pharmacokinetics results. Study S08-0179

(b) (4)

Table 5 Comparison of PK, Study S08-0179

(b) (4)

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 and pseudoephedrine. No clinical efficacy studies were conducted to support this application.

6.1 Indication

The proposed indication for this product follows below:

Rezira™ Oral Solution is for relief of cough and nasal congestion associated with common cold. The indications of the reference drug Hycodan and OTC monograph indication for pseudoephedrine are referenced for the proposed indication for Rezira™.

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 and pseudoephedrine [m2, Section 2.7.4, pages 26 - 32].]

The AERS database search used terms of hydrocodone (HC), hydrocodone plus acetaminophen (HC/ACT), pseudoephedrine (PSE), 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 five literature references for information relevant to safety of hydrocodone 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 pseudoephedrine. 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 on March 31, 2011. There are no animal studies and clinical safety studies conducted for the proposed drug and the proposed drug has not been manufactured and marketed. There are no new safety data included in the safety update.

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). 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 and three reference drugs A, B, and C, respectively (Table 6). 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.

Table 6 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
Subject with any AE	23 (21.7)	18 (18.0)	3 (3.0)	10 (9.6)
Respiratory disorders				
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)
Skin & subcutaneous disorders				
Pruritus	1 (0.9)	0	0	0
Hot flush	0	1 (1.0)	0	1 (1.0)
GI disorders				
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
General & administ. site disorders				
Fatigue	1 (0.9)	0	0	0
Pain	1 (0.9)	0	0	0
Musculoskeletal & connective tissue disorder				
Back pain	1 (0.9)	0	0	0
Nervous system disorders				
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)
Psychiatric disorder				

Euphoric mood	1 (0.9)	0	0	0
Investigations				
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: (b) (4), manufactured for: Cypress Pharmaceutical, Inc.)

Reference C: 5 mL of pseudoephedrine HCl oral solution, 60 mg per 5 mL (manufactured by: (b) (4), 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 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 hydrocodone¹. 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 2005². Although hydrocodone dosages as an antitussive are much

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

lower than that of analgesics, hydrocodone-containing medications should be prescribed and administered with caution.

Pseudoephedrine is a sympathomimetic amine used as an oral nasal decongestant. It can be unlawfully used to make illicit drug methamphetamine³. The Combat Methamphetamine Act, signed into law by President Bush on March 9, 2005, restricts the access of pseudoephedrine by requiring retailers to place drug products with pseudoephedrine behind the counter, limiting a person's daily and monthly purchases, and requiring buyers' identification and signature for each purchase. The potential of unlawfully using pseudoephedrine in the proposed drug to make methamphetamine is addressed by the access restriction required in the Combat Methamphetamine Act.

The proposed Rezira™ (hydrocodone and pseudoephedrine) 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 milk⁴. 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 Rezira™ 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 frequently reported as adverse events associated with hydrocodone and pseudoephedrine 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.

3 www.streetdrugs.org, accessed on March 5, 2009

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

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 [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 [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 Rezira™ 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 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), pseudoephedrine (PSE), and pseudoephedrine plus other ingredients. Table 7 summarizes the results of the AERS search covering the period from October 2007 through March 2008.

Table 7 Post-marketing adverse events (AERS database, Oct. 2007 to March, 2008)

Adverse event	HC	HC/CPM	HC/ACT	CPM/PSE	PSE	PSE/other
Total adverse events	37	2	160	6	40	19
<6 years	1	0	1	1	15	7
6-<12 years	0	1	0	2	0	5
≥12 years	28	1	88	1	21	5
Age unknown	8	0	71	2	4	2
Misuse/overdose/error	8	0	11	0	12	3
Death	29	0	123	0	33	6
Suicide	12	0	94	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. There were 33 and 6 death reports for pseudoephedrine and pseudoephedrine plus other ingredients, respectively. The data also reflect suicide cases in pseudoephedrine use.

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 a new safety signal for hydrocodone and pseudoephedrine.

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 8 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	25.2
	Min, Max	18.4, 30.0

*Body Mass Index (kg/m²)

(Source: NDA 21-747, N020, m5, Section 14.1, Demographic Data, page 67)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Not applicable

7.2.2.3 Literature

The Applicant compiled five literature references for information relevant to safety of hydrocodone and pseudoephedrine in general [NDA 22-439/22-442 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, pseudoephedrine and chlorpheniramine. 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 pseudoephedrine. The AERS database and literature search revealed no new safety signals for hydrocodone and pseudoephedrine at proposed doses. Given the extensive experience with use of hydrocodone as an antitussive and pseudoephedrine as a nasal decongestant, 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 120-day safety update on March 31, 2011 (NDA 22-439, SN026). There are no animal studies and clinical safety studies conducted for the proposed drug and the proposed drug has not been manufactured and marketed. 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 Rezira™ Oral Solution. The proposed drug product contains 5 mg hydrocodone bitartrate and 60 mg pseudoephedrine hydrochloride per 5 mL. It is proposed as a prescription combination drug product of antitussive and decongestant. The proposed indication is “Relief of cough and nasal congestion associated with common cold.” The proposed dosage is

(b) (4) (b) (4) (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 the clinical pharmacology study S08-0179 in the original NDA submission (NDA 22-439/22-442 N-000) 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 is within the bioequivalence range compared to the RLD. There were no differences in pseudoephedrine exposure between the test drug and the OTC monograph pseudoephedrine solution. More information regarding possible drug-drug interaction affecting the hydrocodone exposure in the Rezira™ Oral Solution may be found in the Clinical Pharmacology Review. [NDA 22-439/NDA 22-442, Clinical Pharmacology Review, Elizabeth Shang, Ph. D., R. Ph.]

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.

8.3 Special Populations

There were no studies in special populations for Rezira™ 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)

(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 Rezira™ 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.

8.4 Pediatrics

The clinical pharmacology study 11058503 included no pediatric subjects. In the original NDA submission, the Applicant conducted the post-marketing adverse event search in AERS for hydrocodone and pseudoephedrine 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 frequently reported in pediatric age groups of under 6 and 6 to 12 years of age pseudoephedrine drugs, because it 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 pseudoephedrine 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. FDA has received reports of life-threatening adverse events and death in patients, including children, who have received 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>].

(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 pseudoephedrine is the same as the dose in the Agency's approved OTC monograph pseudoephedrine products. Since there are no new safety signals with these ingredients, and the doses that are proposed in the combination product are the doses that were declared by the agency to be safe and effective for OTC use, no additional PK data is necessary to support these doses. 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 be requested to conduct PK and safety studies in the pediatric population from 6 to under 18 years of age.

Reviewer's comment:

The Division had a telephone-conference with the Applicant conveying the concerns of lacking PK and safety data 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, including timelines of the planned pediatric studies, was submitted on May 6, 2010. The partial pediatric waiver request and the pediatric study plan were submitted to the Pediatric Review Committee (PeRC) meeting scheduled for May 26, 2010. The PeRC agreed with the waiver of studies in children less than 6 years of age and a deferral for patients 6 to 17 years of age, with recommendations to incorporate efficacy assessments and population PK in the proposed safety study.

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)^{1,2} 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 patients³. OTC monograph, Cochran reviews, and controlled trials have demonstrated that pseudoephedrine^{4,5} is safe and effective as a decongestant in treatment of symptoms of common cold.

Reference

1. Endo Pharmaceuticals. HYCODAN (Hydrocodone Bitartrate and Homatropine Methylbromide) Tablet and Syrup Prescribing Information. 2003.
2. Eddy NB, Halbach H, Braenden OJ. Synthetic substances with morphine-like effect: clinical experience; potency, side-effects, addiction liability. Bull World Health Organ 1957; 17(4- 5):569-863.
3. Homsy J, Walsh D, Nelson KA, Sarhill N, Rybicki L, Legrand SB et al. A phase II study of hydrocodone for cough in advanced cancer. Am J Hosp Palliat Care 2002; 19(1):49-56.
4. Taverner D, Latte J. Nasal decongestants for the common cold. Cochrane Database Syst Rev 2007;(1):CD001953.
5. Facts and Comparisons 4.0. Oral Monograph: Pseudoephedrine HCl. Available at: http://online.factsandcomparisons.com/MonoDisp.aspx?monoID_fandc-hcp12309&#monoTab. 2007.

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 Rezira^{(b) (4)} Oral Solution is expected being similar to the risks of other hydrocodone-containing antitussives. In a consult for another hydrocodone containing drug product^{(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 (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 Rezira (b) (4) Oral Solution. If a signal of abuse, misuse, overdose and addiction is identified, further abuse liability assessment should be conducted.

9 OVERALL ASSESSMENT

9.1 Conclusions

The Applicant seeks the approval of Rezira™ Oral Solution based on a clinical pharmacology program to demonstrate the bioequivalence to the reference drug and to OTC monograph product. No clinical efficacy and safety studies were submitted to support this application. The results of bioequivalence studies submitted in this second complete response submission show that the proposed combination drug product is bioequivalent to the reference drug for hydrocodone and OTC monograph product for pseudoephedrine.

The proposed indication for Rezira™ Oral Solution is “Relief of cough and nasal congestion associated with common cold.” The proposed indications are guided by the indication from reference drug Hycodan and OTC monograph language for indication of pseudoephedrine.

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 pseudoephedrine and chlorpheniramine are the same as the doses in the Agency’s approved OTC monograph for these products. Since there are no new safety signals with these ingredients, and the doses that are proposed in the combination product are the doses that were declared by the agency to be safe and effective for OTC use, no additional PK data is necessary to support these doses. 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 (b) (4)

(b) (4) In the previous review cycle, the Division had discussed with the Applicant regarding the concerns of lacking PK and safety data 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, including timelines of the planned pediatric studies, was submitted on May 6, 2010. The partial pediatric waiver request and the pediatric study plan were submitted to the Pediatric Review Committee (PeRC) meeting on May 26, 2010. The PeRC agreed with the waiver of studies in children less than 6 years of age and a deferral for patients 6 to 17 years of age, with recommendations to incorporate efficacy assessments and population PK in the proposed safety study.

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 Rezira™ Oral Solution depends on the bioequivalence to the reference drug Hycodan for hydrocodone and to OTC monograph ingredient pseudoephedrine 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 Rezira™ and the reference drugs, showing that the 90% CI of ratios of AUC and C_{max} for the two components in Rezira™ 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 (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 Rezira™ - (b) (4) 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 pseudoephedrine 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 pseudoephedrine is the same as the dose in the Agency’s approved OTC monograph pseudoephedrine products. Since there are no new safety signals with these ingredients, and the doses that are proposed in the combination product are the doses that were declared by the agency to be safe and effective for OTC use, no additional PK data is necessary to support these doses. 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 PK and safety studies in the pediatric population from 6 to under 18 years of age.

9.4 Labeling Review

The proposed labeling has been reviewed in the previous review cycle. The Division had revised the proposed labeling and sent it to the Applicant in the Complete Response letter on June 11, 2010. The proposed labeling in this CR resubmission is reviewed in comparison with the Division's revision and focus on new data from the study 11058503 and safety update.

The proposed package insert was submitted in Physician's Labeling Rule (PLR) format. The Division of Drug Marketing, Advertising, and Communication at the Office of Surveillance and Epidemiology (DDMAC/OSE) has been consulted regarding the product labeling and the DDMAC's comments have been incorporated into the labeling revision.

Detailed draft labeling review has been conducted as appended below.

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

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

/s/

XU WANG
05/13/2011

ANTHONY G DURMOWICZ
05/13/2011

MEDICAL OFFICER REVIEW			
Division Of Pulmonary, Allergy, and Rheumatology Products (HFD-570)			
APPLICATION:	NDA 22-439 S020 NDA 22-442 S016	TRADE NAME:	(b) (4) (b) (4) Rezira
APPLICANT/SPONSOR:	Cypress Pharmaceutical, Inc.	USAN NAME:	hydrocodone, chlorpheniramine, and pseudoephedrine oral solution;
MEDICAL OFFICER:	Xu Wang, M.D., Ph.D.		hydrocodone and pseudoephedrine oral solution
TEAM LEADER:	Anthony G. Durmowicz, M.D.	CATEGORY:	cough suppressant, antihistamine, decongestant
DATE:	January 20, 2011	ROUTE:	oral
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
Dec 8, 2010	Dec 8, 2010	NDA 22-439 S020 NDA 22-442 S016	Second CR Resubmission
RELATED APPLICATIONS			
<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>	
Nov 6, 2008	NDA 22-439 S000	Original NDA submission	
Dec 10, 2009	NDA 22-439 S009	First CR Resubmission	
<p>REVIEW SUMMARY: This is a 505(b)(2) application. The Applicant, Cypress Pharmaceutical Inc, submitted this application to support two immediate release oral solution combination products, NDA 22-439 (b) (4) (b) (4) (containing hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride 5, 4, and 60 mg, respectively, per 5 ml) and NDA 22-442 Rezira (containing hydrocodone bitartrate and pseudoephedrine hydrochloride 5 and 60 mg, respectively, per 5 ml).</p> <p>This is a clinical pharmacology program. The submission is the second CR resubmission. On 11/06/2008, Cypress submitted original NDA 22-439 and NDA 22-442. The clinical pharmacology study showed that the hydrocodone component in the proposed oral solution products was not bioequivalent to the reference Hycodan oral solution, in that the 90% CIs of the geometric mean ratio of Cmax for hydrocodone bitartrate in the proposed oral solution products is outside of the 80 -125% goal post for bioequivalence. Complete Response (CR) letters were issued on 09/18/2009. On 12/10/2009, Cypress filed CR resubmission. An audit performed by the Agency identified deficiencies both in the conduct of the study and in the methods used at the analytical sites, and the bioequivalence data cannot be relied upon to establish bioequivalence of the proposed drug products to the reference products. CR letters were issued on 06/11/2010.</p> <p>In the present submission, the Applicant submitted a single clinical bioavailability study (11058503) with (b) (4) (b) (4) in healthy adults to evaluate the relative bioavailability of the test drug product to the reference drugs hydrocodone, chlorpheniramine, and pseudoephedrine. 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 Cmax. Nausea, dizziness, and headache were the most common adverse events reported in the study. There were no deaths or serious adverse events reported during the study.</p> <p>The submission is adequate to allow for clinical review.</p> <p>OUTSTANDING ISSUES: none</p>			
RECOMMENDED REGULATORY ACTION			
NDA/SUPPLEMENTS:	FILABLE	X	NOT FILABLE
	APPROVAL	APPROVABLE	NOT APPROVABLE
OTHER ACTION:	COMMENTS FOR SPONSOR	X	

1. GENERAL INFORMATION

This is a 505(b)(2) application. The Applicant, Cypress Pharmaceutical Inc, submitted this application to support two immediate release oral solution combination products, NDA 22-4439 (b) (4) (b) (4) (containing hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride 5, 4, and 60 mg, respectively, per 5 ml) and NDA 22-442 Rezira (containing hydrocodone bitartrate and pseudoephedrine hydrochloride 5 and 60 mg, respectively, per 5 ml). The proposed indication for (b) (4) is for (b) (4) and for Rezira is for (b) (4) relief of cough and the (b) (4) relief of nasal congestion due to the common cold.

As a basis for the 505(b)(2) submission route, the Applicant cites the following reference listed drugs (RLDs) and OTC monographs: 1) Hycodan Tablets and Syrup¹ (NDA 05-213, Endo Pharmaceuticals), 2) Tussionex Extended-Release Suspension (NDA 19-111, UCB, Inc.), 3) Codeprex Extended-Release Suspension (NDA 21-369, UCB, Inc.), 4) Advil Allergy/Sinus Tablets (NDA 21-441, Wyeth Consumer Products), 5) Mucinex D Tablets (NDA 21-585, Adams Respiratory Therapeutics), 6) Tavist Allergy/Sinus/Headache Tablets (NDA 21-082, Novartis), 7) 21 CFR 341.12 for chlorpheniramine maleate, and 8) 21 CFR 341.20 for pseudoephedrine hydrochloride.

The application is provided electronically.

2. CLINICAL DEVELOPMENT PROGRAM

This is a clinical pharmacology program. The Applicant conducted a single clinical bioavailability study (11058503) with (b) (4) in healthy adult volunteers. The objective of the study was to evaluate the relative bioavailability of the test drug product to the reference drugs hydrocodone, chlorpheniramine, and pseudoephedrine. There are no clinical efficacy and safety studies included in the submission.

Reviewer's comments:

The submitted clinical study is to support NDA 22-439 (b) (4) (hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride 5, 4, and 60 mg, per 5 ml) and NDA 22-442 Rezira (hydrocodone bitartrate and pseudoephedrine hydrochloride 5 and 60 mg, per 5 ml). Separate clinical reviews will be written for the two applications. However, regulatory review meetings for the two applications will be conducted in tandem.

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

¹ Hycodan is not available in the market because the manufacturer has discontinued its marketing. The Applicant used hydrocodone solution manufactured by Hi-Tech as the RLD in the place of Hycodan, which had been accepted by the clinical pharmacology review team [NDA 22-439 Clinical pharmacology Review, Elizabeth Y. Shang, Ph.D., R.Ph. 7/20/2009]. Hi-Tech's hydrocodone solution (ANDA 40-613) was approved in reference to Hycodan (NDA 5-213).

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 is sufficient to support the proposed combination drug products, provided can be established with the reference products.

3. FOREIGN MARKETING AND REGULATORY HISTORY

Cypress submitted the opening IND for (b) (4) and Rezira on April 15, 2008 (IND 102,177). A pre-IND meeting for this application was held on January 14, 2008 as (b) (4) with the Division. (b) (4)

(b) (4) 1) liquid solution
products containing pseudoephedrine (b) (4) developed under IND 102,177, (b) (4)

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.

On November 6, 2008, Cypress submitted original NDA 22-439 and NDA 22-442. The clinical pharmacology study submitted to support the two applications show that the hydrocodone component in the proposed oral solution products is not bioequivalent to the reference Hycodan oral solution, in that the 90% CIs of the geometric mean ratio of C_{max} for hydrocodone bitartrate in the proposed oral solution products is outside of the 80 -125% goal post for bioequivalence. Complete Response (CR) letters were issued on September 18, 2009.

On December 10, 2009, Cypress filed Complete Response resubmission for the two NDAs. An audit performed by the Agency of the bioequivalence studies identified deficiencies both in the conduct of the study and in the methods used at the analytical sites. Therefore, the bioequivalence studies cannot be relied upon to establish bioequivalence of the proposed drug products to the reference products. CR letters were 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.

The present submission is the second CR resubmission.

Reviewer's comment:

It is unclear if (b) (4) and Rezira were ever marketed abroad and in the US as an unapproved product. If they were, the Applicant should provide safety information and marketing history.

4. 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) [m1.1.2-fda-form-356h]
- Summary [m2.2-introduction to m2.7-summary]
- Clinical technical section
 - Clinical study reports
 - 11058503 [m5.3.1.2.3 clin-stud-rep]
 - Good Clinical Practice certification [m5.3.1.2.3 clin-stud-rep, Section 5 Ethics]
 - Debarment certification [m1.3-administrative-information\1.3.3-debarment-certification]
 - Pediatric use [m1.9.1-request-waiver-pediatric-studies]
- Labeling [m1.14-labeling]
- Case report forms [m5.1.2.3.24\study-report-110580503\crfs]
- Financial disclosure [m1.3-administrative-information\1.3.4-financial-certification-disclosure]

5. CLINICAL STUDIES

There was a single clinical bioavailability study conducted for the drug development program of (b) (4) and Rezira. The study report is appropriately indexed to allow review. A summary of the study follows.

Study 11058503

Study 11058503 was a single center, single dose, 4-period crossover, relative bioavailability study. Study arms included: 1) hydrocodone, pseudoephedrine, and chlorpheniramine oral solution (5 mg/60 mg/4 mg; (b) (4)), 2) pseudoephedrine oral solution, 60 mg/5 ml (manufactured by (b) (4), manufactured for Cypress Pharmaceutical, Inc.), 3) chlorpheniramine oral solution, 4 mg/5 ml (manufactured by (b) (4) 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} , K_{el} , 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.

6. BRIEF REVIEW OF PROPOSED LABELING

The proposed labeling has been reviewed in the previous review cycle. The Division had revised the proposed labeling and sent it to the Applicant in the second Complete Response letter on June 11, 2010. The proposed labeling in this CR resubmission will be reviewed in comparison with the Division's revision and focus on new data from the study 11058503 and safety update.

7. DSI REVIEW AND AUDIT

The clinical pharmacology team has requested a DSI audit of the sites for the clinical pharmacology study 11058503.

Novum Pharmaceutical Research Services [clinical site]
Wilcrest Green Office Park
3320 Walnut Bend Lane
Houston, TX 77042-4712

(b) (4)

8. REVIEW TIMELINE

The schedule for review is provided in Table 1. Write-up will be concomitant with the review process. Clinical review will focus initially on the pivotal clinical pharmacology study, followed by the integrated summary of safety, and any data provided in the safety update. 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 June 8, 2009, and the review will be finalized by May 10, 2011.

Table 1: Review timeline for NDA 22-439 S020/NDA 224-42 S016

Milestone	Target date for completion
Filing and planning meeting	January 20, 2011
Wrap-up meeting	April 25 10, 2011
Labeling T-con	May 10, 2011

Primary review	May 13, 2011
PDUFA Action date (6 months)	June 8, 2011

9. COMMENTS FOR THE SPONSOR

Clarify if your proposed drug products, (b) (4) and Rezira, were ever marketed abroad and in the US as an unapproved product. If they were, the Applicant should provide safety information and marketing history.

Reviewed by:

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

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

cc: Original NDA
HFD-570/Division File
HFD-570/ Durmowicz/Medical Team Leader
HFD-570/Wang/Medical Reviewer
HFD-715/Li/Biometrics Reviewer
HFD-570/Whitehurst/Pharmacology-Toxicology Reviewer
ONDQA/Shen/CMC Reviewer
OCP/Shang/Clinical Pharmacology Reviewer
HFD-570/Bowen/CSO

Clinical Filing Checklist

NDA/BLA Number: 22-439/22-442

Applicant: Cypress

Stamp Date: Dec. 08, 2010

Drug Name: (b) (4)/Rezira

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

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
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			
LABELING					
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			
SUMMARIES					
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			Hycodan; cough and cold monograph
DOSE					
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	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:			X	

	Content Parameter	Yes	No	NA	Comment
	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	
SAFETY					
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 ²) 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 ³ 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

² 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.

³ 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).

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
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	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
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
DATASETS					
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			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
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	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
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.

Reviewing Medical Officer

Date

Clinical Team Leader

Date

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/s/

XU WANG
01/27/2011

ANTHONY G DURMOWICZ
01/27/2011

Summary Review for Regulatory Action

Date	June 11, 2010
From	Lydia Gilbert-McClain, MD,
Subject	Summary Review
NDA/BLA #	22-442
Supplement #	
Applicant Name	Cypress
Date of Submission	December 10, 2009
PDUFA Goal Date	June 11, 2010
Proprietary Name / Established (USAN) Name	REZIRA/hydrocodone, and pseudoephedrine
Dosage Forms / Strength	Oral Solution/5 mg /60 mg in each 5 ml
Proposed Indication(s)	1. (b) (4) relief of cough 2. (b) (4) relief of nasal congestion due to the common cold
Action/Recommended Action for NME:	<i>Complete Response</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Xu Wang, MD, PhD
Pharmacology Toxicology Review	Grace Lee, PhD
CMC Review/OBP Review	Xiaobin, Shen, PhD
Clinical Pharmacology Review	Elizabeth Shang, PhD, R. Ph
DDMAC	Roberta Szydio
DSI	Arindam Dasgupta, PhD
OSE/DMEPA	Felicia Duffy, RN, BSN, MSEd

OND Office of New Drugs
 DDMAC Division of Drug Marketing, Advertising and Communication
 OSE Office of Surveillance and Epidemiology
 DMEPA Division of Medication Error Prevention and Analysis
 DSI Division of Scientific Investigations
 CDTL Cross Discipline Team Leader

1. Introduction

Cypress Pharmaceuticals Inc. submitted a 505 (b) (2) new drug application (NDA 22-442) on November 4th, 2008 (received on November 7th, 2008, CDER stamp date) for use of a combination oral solution comprised of hydrocodone bitartrate and pseudoephedrine hydrochloride oral solution for temporary relief of cough and nasal congestion in adults (b) (4). To support this NDA the Applicant cross-references the clinical pharmacology data for NDA 22-439 the triple combination product containing hydrocodone, chlorpheniramine, and pseudoephedrine. The clinical pharmacology program under NDA 22-439 failed to demonstrate bioequivalence for the hydrocodone component of

the solution. In addition there were several outstanding CMC issues that needed to be addressed before the application could be approved. The Applicant submitted a complete response on December 10th, 2009 with the results of another clinical pharmacology study. The results of that study showed bioequivalence to the hydrocodone ingredient in the combination product to the reference hydrocodone solution. However, based on the findings from the inspections conducted by the Division of Scientific Investigations, the data from the bioequivalence studies are not acceptable for review and this NDA cannot be approved in this cycle. This review will summarize the basis for the regulatory decision on this NDA.

2. Background

The product under development is one of the hydrocodone-containing cough/cold products belonging to a group of previously illegally marketed products. According to the Agency's Federal Register notice, all manufacturers of hydrocodone-containing products had to stop manufacturing these products by December 31, 2007. The Agency has encouraged manufacturers of these and other unapproved products to submit NDAs to obtain approval for marketing these products in the United States. This application is to market a combination product containing hydrocodone bitartrate (HC), and pseudoephedrine hydrochloride (PSE), as an immediate release oral solution containing 5 mg and 60 mg of HC and PSE, per 5 mL respectively. Pseudoephedrine is a well known sympathomimetic amine used for nasal decongestion. PSE is listed in the OTC monograph and although hydrocodone is not a monograph product, the Agency (based on prior precedent) has allowed monograph ingredients to be combined with hydrocodone (an antitussive agent).

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

In the clinical pharmacology study submitted in the original NDA submission, bioequivalence was demonstrated for the pseudoephedrine component of the product but bioequivalence for the hydrocodone ingredient was not demonstrated. Since the study failed to demonstrate bioequivalence, an inspection from the Division of Scientific Investigations (DSI) was not requested in the first review cycle. In the complete response, the applicant submitted another clinical pharmacology study conducted to compare the bioavailability of hydrocodone to the reference hydrocodone product (Hi-Tech Pharma's hydrocodone oral solution formulation). Since the formulation of the product has not changed and the Applicant had previously demonstrated bioequivalence of pseudoephedrine, it was not necessary to repeat the bioavailability assessment for the pseudoephedrine components of the solution. The data showed that bioequivalence for hydrocodone was established and therefore a DSI audit was

conducted. However based on the results of the DSI audit (discussed later in the summary) the data are not acceptable to use in making a regulatory decision on this NDA and the application will be given a complete response.

3. CMC/Device

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

The manufacturing of the drug product and drug substance and the manufacturing site inspections are acceptable. The outstanding product quality issues cited in the initial complete response letter have been adequately addressed and there are no outstanding approvability issues from a CMC standpoint.

4. Nonclinical Pharmacology/Toxicology

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

5. Clinical Pharmacology/Biopharmaceutics

In the initial submission the applicant submitted results of one clinical pharmacology study S08-0179 conducted for the applicant by (b) (4) in 25 adult healthy volunteers to evaluate the rate and extent of exposure of hydrocodone compared to the reference product Hycodan® Syrup, and to evaluate the drug-drug interaction of the three active ingredients HC, CPM, and PSE in the formulation. Since this two-ingredient combination solution is the same formulation as the triple-combination product, the same clinical pharmacology study conducted for NDA 22-439 would be used to support the NDA for the 2-ingredient product. Study S08-0179 was an open-label, single-dose, randomized, four period cross-over study under fasted conditions. The results showed that hydrocodone was not bioequivalent to the reference product Hycodan syrup (Endo Pharmaceuticals Inc) but the other ingredients in the solution CPM, and PSE were bioequivalent to their respective test products.

In the complete response, the Applicant submitted the results of another clinical pharmacology study SAM-09-1010 conducted by (b) (4). A total of 152 healthy volunteers were enrolled in this study and the study was of similar design (open-label, single-dose, randomized, cross-over study under fasted conditions) to study S08-0179 except that study SAM-091010 was a 2-period cross-over design to evaluate the bioequivalence of hydrocodone in their proposed product and the reference drug. The study showed that the hydrocodone in the Applicant's formulation is bioequivalent to the hydrocodone in the reference product (Hi Tech Pharma's hydrocodone oral solution). The clinical pharmacology team reviewed and agreed with the Applicant's analysis results and these findings could have been acceptable for approval of the NDA if the results of the DSI inspections showed that the study conduct and

analytical methods used were adequate to allow us to use these data to support the NDA. However, the findings from the DSI audit (discussed further in section 11) indicate that these clinical pharmacology results cannot be used to support the NDA.

6. Clinical Microbiology

This is a non-sterile solution product for oral ingestion. The product contains methylparaben and propylparaben at target concentrations of (b) (4) respectively which are found to be adequate for (b) (4). There are no outstanding microbiology issues with the formulation.

7. Clinical/Statistical-Efficacy

The application relies on a comparison of the bioavailability of the proposed drug product to that of approved reference products Hycodan and the OTC monograph products pseudoephedrine, and chlorpheniramine. No clinical studies were conducted.

8. Safety

The safety of the product is based on establishing bioequivalence of the product compared to approved reference products. In addition, the applicant conducted a review of the literature, and a search of the AERS database for post-marketing safety information for the individual ingredients and any combination thereof, for the period from October 2007 through March 2008. These searches did not reveal any new safety signals.

9. Advisory Committee Meeting

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

During the initial review cycle, a CDER regulatory briefing was held (June 12th, 2009) to discuss the need for abuse potential studies for hydrocodone-containing combination products because of the concern raised by the Controlled Substances Staff (CSS) that the other active ingredients could potentiate the abuse potential of hydrocodone. The CSS had recommended that this abuse potential be studied with animal and/or human studies.

The consensus from the regulatory briefing was that abuse potential assessment was not required for these combination products prior to approval. These combinations would remain in Schedule III by virtue of the hydrocodone component and would have abuse potential class labeling and it is not clear that the information from abuse potential studies will impact scheduling. Further, these types of combinations have been on the market for several years and there has been no safety concern raised regarding an increase in the abuse potential of these combinations. The recommendation from the regulatory briefing was that a post-marketing signal could trigger the need for abuse potential studies for these products in the future. The CSS staff subsequently wrote an addendum to the consultation noting that the sponsors of these products could conduct active surveillance and monitoring for signals of abuse, misuse, overdose and addiction and provide periodic summaries post approval.

10. Pediatrics

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

The request for waiver for children under 6 years of age is based on the fact that the proposed product contains hydrocodone which is contraindicated for use in children less than 6 years of age (because of the risk of respiratory depression). It would be appropriate to waive studies for pediatric patients less than 6 years of age because of this safety concern. However, although hydrocodone is currently labeled for use in children down to 6 years of age, safety concerns regarding dose-related respiratory depression identified over the last few years raises the issue of the need to be assured of the most appropriate dose for the pediatric population. Dose-related respiratory depression including fatalities due to respiratory failure has been reported with the use of hydrocodone in children. Several of these cases were associated with overdose, and led to the revised labeling currently in the single-ingredient and combination hydrocodone products; i.e. that hydrocodone is contraindicated in children less than 6 years of age and that the dose should be administered with an accurate measuring device. In view of this dose-related safety concern, it is appropriate to require the sponsor to establish the appropriate dose of hydrocodone for the pediatric (less than 18 years) population. Hydrocodone was approved under Drug Efficacy Study Implementation (DESI) review and the basis for the dose selection for the pediatric population is unclear. The dose of pseudoephedrine in the proposed combination product is the same as the doses in the Agency's approved OTC cough/cold monograph. Since the Agency is not aware of any new safety concerns with this ingredient at the current monograph dose and the current monograph is still in effect, the proposed dose for pseudoephedrine in this combination solution should be acceptable; however pharmacokinetic (PK) data for adequate dose selection and additional safety data should be required for the hydrocodone component. The need for additional PK and safety data for the pediatric (under 18 years of age) population was discussed with the Applicant during the review cycle and they submitted a plan to conduct a pharmacokinetic study and a safety study in the pediatric (6 to 17 years of age) population in the future.

The Applicant's proposed pediatric plan and the division's PREA assessment were presented to PERC on May 26th, 2010. The PERC agreed with the waiver of studies in children less than 6 years of age and a deferral for patients 6 to 17 years of age, with recommendations to incorporate efficacy assessments and population PK in the proposed safety study.

11. Other Relevant Regulatory Issues

A DSI audit was conducted for the 2 clinical pharmacology studies that were performed to support the application. The inspection of the clinical portions of the study S08-0179 was conducted at (b) (4) and the audit of the analytical portion of the study was at (b) (4). The inspection of the clinical portion of the study SAM 09-1010 was conducted at (b) (4) and the audit of the analytical site was conducted at (b) (4). During the inspections the DSI inspectors found several deficiencies. Specifically, at the

(b) (4) site, the inspectors noted that source documentation was missing for all the stability experiments and therefore the experiments conducted as part of pre-study method validations cannot be assured and the data for study SAM 09-1010 are questionable. The DSI inspection for study S08-0179 (b) (4) found that the records for the extraction of subject samples were falsified, and validation documentation was incomplete. Based on the DSI findings, the data from these clinical pharmacology studies are not acceptable to support the NDA

12. Labeling

Proprietary name

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

Physician labeling

The applicant submitted a label in the Physician's Labeling Rule Format. The labeling was extensively revised to comply with the PLR format. The indication covered by this two-ingredient combination product is essentially (b) (4) relief in common cold (i.e. cough and nasal congestion) and the indication was revised to reflect that. (b) (4)

(b) (4). A marked up label was sent to the applicant during the review cycle and the Applicant submitted revised labeling incorporating the Division's comments and edits. Additional labeling changes to the package insert have been made primarily to section 6 (Adverse Reactions) based on feedback from the PLR reviewers, and to section 12.3 (Pharmacokinetics) given that the pharmacokinetic data are not acceptable. A marked up label will be sent to the Applicant in the action letter.

Carton and Immediate Container Labels

A detailed review of the carton and immediate container labels was conducted in consultation with DMEPA and preliminary carton and container labeling comments were conveyed to the applicant during the review cycle.

Patient Labeling and Medication Guide

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

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Based on the findings of the DSI audit, the data submitted in this application cannot be used to support the NDA. The regulatory action on this application will be a complete response.

The comments below can be used for the complete response letter

- 1) An audit performed by the Agency of the bioequivalence studies S08-0179 and SAM 09-1010 designed to establish bioequivalence of the active ingredients hydrocodone, and pseudoephedrine in your drug product to the reference products

identified deficiencies both in the conduct of the study and in the methods used at the analytical sites. Because of these deficiencies, the bioequivalence studies cannot be relied upon to establish bioequivalence of your proposed drug product.

This deficiency may be addressed by doing the following:

- 1) Conduct another single-dose clinical pharmacology study to establish the bioequivalence of your proposed hydrocodone 5 mg/pseudoephedrine 60 mg/ per 5 mL oral solution to the reference products.

OR

- 2) Conduct a clinical development program with clinical efficacy and safety studies to support your combination product.

- Risk Benefit Assessment

The overall risk and benefit assessment of the individual ingredients hydrocodone and pseudoephedrine does not suggest an unfavorable risk benefit for these individual ingredients for the adult (18 years and older) population. However, the data are inadequate (due to the DSI findings) to establish the bioequivalence of their proposed combination product to the reference products, and a complete risk/benefit assessment cannot be made at this time. Since dose-related respiratory depression associated with fatalities from the use of hydrocodone has been reported for they younger population (patients under 18 years of age), additional PK and safety data to support the appropriate dose in the pediatric population would be necessary.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

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

- Recommendation for other Postmarketing Requirements and Commitments

Since this application is not going to be approved, there are no recommended postmarketing study commitments at this time. However, because of the safety concerns for the pediatric population, the sponsor will need to conduct PK and safety studies to evaluate the appropriate dose for patients under 18 years of age. These studies will be required studies under PREA and as such will be postmarketing requirements. Since the application is not going to be approved in this cycle a timeline for post marketing studies does not need to be agreed upon in this review cycle.

When the application is ready to be approved we will also be asking the sponsor to conduct active surveillance and monitoring for signals of abuse/misuse, overdose, and addiction and to provide periodic analysis and summary of surveillance and monitoring activities for

abuse/misuse, overdose and addiction. Depending on the outcome of this active surveillance, additional studies may be warranted.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22442	ORIG-1	CYPRESS PHARMACEUTICA L INC	REZIRA (hydrocodone bitartrate and PSEU)

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/s/

LYDIA I GILBERT MCCLAIN
06/11/2010

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-442
Submission Code	SN009
Letter Date	12/10/2009
Stamp Date	12/10/2009
PDUFA Goal Date	06/10/2010
Reviewer Name	Xu Wang, M.D., Ph.D.
Review Completion Date	05/26/2010
Established Name	Hydrocodone and pseudoephedrine
(Proposed) Trade Name	Rezira™ Oral Solution
Therapeutic Class	Antitussive/decongestant
Applicant	Cypress Pharmaceutical, Inc.
Priority Designation	S
Formulation	Oral solution
Dosing Regimen	For adults 18 years of age and over: (b) (4) (5 ml) every 4-6 hours as needed, not to exceed 4 doses (20 ml) in 24 hours
	(b) (4)
Indication	(b) (4) relief of cough and the (b) (4) relief of nasal congestion due to the common cold
Intended Population	Adults (b) (4)

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend a “Complete Response” action for this NDA application. The development program for the proposed drug product is a clinical pharmacology program. The proposed drug product Rezira™ Oral Solution depends on the bioequivalence to the reference drug Hycodan for hydrocodone and to OTC monograph ingredient pseudoephedrine to support its efficacy and safety. No clinical efficacy studies were submitted to support this application. 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.” 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.”

Rezira™ Oral Solution is an immediate release oral solution, containing 5 mg hydrocodone bitartrate and 60 mg pseudoephedrine hydrochloride per 5 mL. It is proposed as a fixed dose combination product containing an antitussive and nasal decongestant. The proposed indication is (b) (4) relief of cough and the (b) (4) relief of nasal congestion due to the common cold.

This is a complete response submission. In the original NDA submission, the results of a clinical pharmacology study showed that the hydrocodone component was not bioequivalent to the reference drug in that the 90% CI of the geometric mean ratio of C_{max} for hydrocodone in Rezira™ Oral Solution was outside of the 80–125% goal post for bioequivalence. The pseudoephedrine in Rezira™ Oral Solution was bioequivalent to the OTC monograph ingredient 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 Rezira™ Oral Solution to RLD, or conducting a clinical development program with clinical efficacy and safety studies to support the proposed drug product.

In the present complete response submission, the Applicant submitted data from a clinical pharmacology study, demonstrated that the hydrocodone component in Rezira™ Oral Solution was bioequivalent to the RLD. However, the deficiencies identified in the analytical site inspections lead to the conclusion that the clinical pharmacology study data submitted in the NDA are not acceptable. Therefore, a “Complete Response” action is recommended for the proposed drug product Rezira™ Oral Solution.

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. A routine post-marketing surveillance is recommended to monitor the adverse events associated with the use of Rezira™ 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

In the present NDA submission, the intended patient population for the proposed drug product is “adults (b) (4) (b) (4)

(b) (4)

The proposed dose for pseudoephedrine is the same as the dose in the Agency’s approved OTC monograph pseudoephedrine products. Since there are no new safety signals with these ingredients, and the doses that are proposed in the combination product are the doses that were declared by the agency to be safe and effective for OTC use, no additional PK data is necessary to support these doses. 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 be requested to conduct PK and safety studies in the pediatric population from 6 to under 18 years of age.

1.2.3 Other Phase 4 Requests

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 Rezira™ Oral Solution. If a signal of abuse, misuse, overdose and addiction is identified, further abuse liability assessment may need to be conducted.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This is a complete response submission, in which the Applicant included results of one clinical pharmacology study. The clinical pharmacology study SAM-09-1010 is an open-label bioavailability and drug-drug interaction study to evaluate the bioequivalence of hydrocodone between the proposed drug product, Rezira™ Oral Solution, and hydrocodone contained in Hi-Tech Pharma's Hydrocodone Bitartrate /Homatropine Methylbromide Syrup. In the original NDA submission, the Applicant submitted the clinical pharmacology study S09-0179 that showed that the pseudoephedrine in Rezira™ Oral Solution was bioequivalent to the OTC monograph ingredient pseudoephedrine.

The Applicant submitted a Summary of Clinical Safety including the safety data from the clinical pharmacology study SAM-09-1010 and a literature survey to provide support for the safety of the proposed drug product. In the original NDA submission, the Applicant provided the AERS database search results for post-marketing spontaneous adverse events associated with hydrocodone and pseudoephedrine.

1.3.2 Efficacy

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

1.3.3 Safety

The Applicant provided a Summary of Clinical Safety including the safety data from the clinical pharmacology study SAM-09-1010 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 pseudoephedrine. Safety was assessed through adverse events in the study SAM-09-1010 conducted in 152 adult subjects. There were no deaths or other serious adverse events in the clinical pharmacology study SAM-09-1010. There were 43 (29.1%) and 52 (34.4%) subjects who reported adverse events for the proposed drug and the hydrocodone syrup product,

respectively. In subjects taking the proposed drug, dizziness was the most common adverse event (16), followed by catheter site pain or reaction (13), nausea (4), and fatigue (3). The hydrocodone syrup product has similar spectrum of adverse events as that of the proposed drug product. The safety data from the clinical pharmacology study SAM-09-1010 did not identify a 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 acetaminophen (HC/ACT), hydrocodone plus other ingredients, pseudoephedrine (PSE), pseudoephedrine plus other ingredients. There were no new safety signals revealed through the search of AERS database for post-marketing adverse events.

The Applicant compiled five literature references for information relevant to safety of hydrocodone 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 hydrocodone and pseudoephedrine. The literature survey revealed no new safety signals for hydrocodone and pseudoephedrine. 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), a 120-day safety update including data from clinical studies, animal studies, and other sources is required for a NDA submission. However, there are no animal studies and clinical safety studies conducted for the test drug and the test drug has not been manufactured and marketed. The Applicant did not submit a safety update. This reviewer does not expect new safety information for the test drug product.

1.3.4 Dosing Regimen and Administration

The application is for Rezira™ Oral Solution. The proposed drug product contains 5 mg hydrocodone bitartrate and 60 mg pseudoephedrine hydrochloride per 5 mL. It is proposed as a prescription drug combination of antitussive and nasal decongestant. The indication is for relief of cough and nasal congestion associated with common cold. The proposed dosage is (b) (4) (5 mL) every 4 to 6 hours as needed, not to exceed (NTE) 4 doses (20 mL) in 24 hours for adults (b) (4)

1.3.5 Drug-Drug Interactions

There is no drug-drug interaction study conducted in this NDA submission. The result of the clinical pharmacology study S08-0179 in the original NDA submission (NDA 22-439/NDA 22-442 N-000) showed that the subjects' exposure for hydrocodone in the 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 SAM-09-1010 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 pseudoephedrine exposure between the hydrocodone, chlorpheniramine, and pseudoephedrine oral solution and the OTC monograph pseudoephedrine solution. More information regarding possible drug-drug interaction affecting the hydrocodone exposure in the proposed drug product may be found in the Clinical Pharmacology Review [NDA 22-439/NDA 22-442, Clinical Pharmacology Review, Elizabeth Shang, 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 Special Populations

There were no studies in special populations for Rezira™ 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 Rezira™ 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 when it is considered for approval.

Reviewer 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 pseudoephedrine. The drug product contains 5 mg hydrocodone bitartrate and 60 mg pseudoephedrine hydrochloride per 5 mL. It is proposed as a prescription drug combination of antitussive and decongestant. The indication is for relief of cough and nasal congestion associated with common cold. The sponsor's proposed name is Rezira™ Oral Solution. 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) Codeprex Extended-Release Suspension (NDA 21-369, UCB, Inc.), 4) Advil Allergy/Sinus Tablets (NDA 21441, Wyeth Consumer Products), 5) Mucinex D Tablets (NDA 21-585, Adams Respiratory Therapeutics), 6) Tavist Allergy/Sinus/Headache Tablets (NDA 21-082, Novartis), and 7) 21 CFR 341.20 for pseudoephedrine hydrochloride. Of note, reliance on Tussionex or Codeprex is not necessary to determine safety or efficacy of this application, as the information that the sponsor cites from these labels to support their labeling, is information that comes from the published literature. Subsequent to the complete response action for the original NDA application, the Hycodan syrup manufactured by Endo Pharmaceuticals was discontinued from the market (not for reasons of safety or efficacy). The Applicant needed to conduct another bioavailability study and used the hydrocodone bitartrate/homatropine methylbromide syrup developed by HI-TECH Pharma as the reference for the bioavailability study. 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). Hydrocodone 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

- Children less than 6 years of age: The administration of hydrocodone in children less than 6 years of age is contraindicated due to the risk of respiratory depression [Reference to NDA 19-111, Tussionex Pennkinetic product labeling].

Pseudoephedrine (PSE) is considered to be GRASE as an oral nasal decongestant [21 CFR 341.20] in the following age groups at the following oral doses [21 CFR 341.80(d)]:

- Adults and children 12 years of age and over: 60 mg every 4 to 6 hours, NTE 240 mg in 24 hours
- Children 6 to under 12 years of age: 30 mg every 4 to 6 hours, NTE 120 mg in 24 hours
- Children 2 to under 6 years of age: 15 mg every 4 to 6 hours, NTE 60 mg in 24 hours
- Children under 2 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 nasal decongestant to be a permitted combination [21 CFR 341.40].

Reviewer comment:

Hydrocodone, a schedule II controlled substance and a prescription drug, is not an OTC monograph antitussive. Therefore, the proposed combinations of (b) (4) 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) M-001, MR, Charles E. Lee, M.D., 9/25/2006. 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). There are other generic Hydrocodone products as antitussive drugs on the market. These are Hydrocodone Compound (ANDA 88-017), Tussicaps (ANDA 77-273), Tussigon ((b) (4)) and Homatropine Methylbromide and Hydrocodone Bitartrate Tablet and Syrup (ANDA 40295, ANDA 40-613, ANDA 88-008).

Pseudoephedrine is readily available non-prescription monograph drug, being considered to be generally recognized as safe and effective (GRASE) at OTC monograph doses for the temporary relief of nasal congestion. In addition to pseudoephedrine, phenylephrine is another available non-prescription nasal decongestant. Nasal decongestants 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 for cough (Tussionex Pennkinetic, NDA 19-111) 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 (b) (4) 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].

Pseudoephedrine is currently approved in the United States in tablets (Afrinol, NDA 18191), in combination with chlorpheniramine (Chlor-Trimeton, NDA 18397), with ibuprofen and chlorpheniramine (Advil Allergy Sinus Caplet, NDA 21441), and with guaifenesin (Mucinex™ D, NDA 21585). These products are extended release formulations. Pseudoephedrine 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).

Pseudoephedrine is an OTC monograph drug of oral nasal decongestant [21 CFR 341.20]. Pseudoephedrine can be unlawfully used to make the illicit drug methamphetamine. The

Combat Methamphetamine Act restricts the access of pseudoephedrine by requiring retailers to place OTC drug products with pseudoephedrine behind the counter, limiting a person's daily and monthly purchases, and requiring buyers' identification and signature for each purchase.

2.5 Presubmission Regulatory Activity

The Applicant had a pre-IND meeting on January 14, 2008 with the Division (b) (4)

The Division's comments in the pre-IND meeting which relate to this application are summarized as follows [Pre-IND (b) (4) 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 (b) (4), and subsequently submitted a 505(b)(2) NDA for the proposed Rezira (hydrocodone and pseudoephedrine) Oral Solution on November 06, 2008. During the original NDA review cycle, 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 c pseudoephedrine component was bioequivalent to the OTC monograph reference product 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 Rezira™ Oral Solution to RLD, or conducting a clinical development program with clinical efficacy and safety studies to support the proposed drug product. The Applicant filed the present complete response on December 12, 2009.

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 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 (b) (4). 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)

(b) (4) The in-process tests used are pH, appearance, density, and viscosity. A detailed review of the CMC portion of the application may be found in the ONDQA review [NDA 22-439/NDA 22-442 N-000, ONDQA Review, Xiaobin Shen, Ph.D., July 8, 2009].

Hydrocodone bitartrate dihydrate 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)

Pseudoephedrine hydrochloride USP used in the test formulation is manufactured by

(b) (4)

The proposed drug product Rezira™ is a non-sterile oral solution.

(b) (4)

(b) (4)

The product quality microbiology reviewer recommends an approval from a quality microbiology standpoint [NDA 22-439/NDA 22-442 N-000, Product Quality Microbiology Review, Denise Miller, Microbiologist, March 16, 2009].

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 product pseudoephedrine. The Applicant's drug development program for Rezira™ 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 pseudoephedrine. This complete response submission includes to one new clinical pharmacology study SAM-09-1010. 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 SAM-09-1010, a single-dose bioavailability study, to characterize the exposure of hydrocodone immediate release solution in fasted, healthy, adult subjects. In the original NDA submission, the Applicant presented one clinical pharmacology study S08-0179, which is not included in this review because it has been reviewed in the original NDA review cycle. Table 1 summarizes 2 clinical pharmacology studies.

Table 1. Summary of Clinical Pharmacology Studies

Study number	Treatment	Study design	Diagnosis, subjects' age	Materials submitted
SAM-09-1010	Test drug: 5 ml (b) (4) (5 mg HC/ 4 mg CPM/ 60 mg PSE) Reference drug: 5 mL Hi-Tech Syrup (5 mg HC/ 1.5 mg Homatropine)	Randomized, single dose, 2-period cross over with a 7-day washout period between dosing	Healthy males and females, 18-62 yrs	Study report
S08-0179*	Test drug: 5 ml (b) (4) (HC/CPM/PSE solution 5/4/60 mg) Reference drugs: 5 mL PSE solution (60 mg) 5 mL CPM solution (4 mg) 5 mL HC/homatropine solution (5/1.5 mg)	Randomized, single dose, 4-period cross over with a 7-day washout period between dosing	Healthy males and females, 18-54 yrs	Study report

* Study S08-0179 has been submitted and reviewed in the original NDA review cycle.

4.3 Review Strategy

This is a review of the safety data from Study SAM-09-1010, and of the data from AERS database for post-marketing and spontaneous adverse event reports and the literature review for hydrocodone and pseudoephedrine.

4.4 Data Quality and Integrity

This is a clinical pharmacology program. The clinical pharmacology team requested DSI audit for clinical pharmacology studies SAM-09-1010 included in this complete response submission, and S08-0179 submitted and reviewed in the original NDA submission.

The Division of Scientific Investigation (DSI) issued a Memorandum on May 5, 2010, which cited deficiencies in the analytical site inspection for the clinical pharmacology study SAM-09-1010. DSI concluded that “the bioequivalence data for study SAM-09-1010 submitted in the NDA are questionable due to the absence of source documentation at [REDACTED] (b) (4), the experiments conducted as part of pre-study method validations cannot be assured.” [Memorandum, DSI Report on an Audit of Study SAM-09-1010, Martin K. Yau, Ph. D. 5/05/2010]

DSI issued a Memorandum on May 20, 2010 regarding the audit result for study S-08-0179. Based on the deficiencies found in the analytical site inspection, DSI recommended that “Study S-08-0179 should not be accepted for review at this time due to record falsification and incomplete investigation of complaint allegations.” [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]

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 14].

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 the complete response submission. A summary of data from the Applicant’s clinical pharmacology study follows below. Detailed information can be found in the Clinical Pharmacology Review [NDA 22-439/NDA 22-442, Clinical Pharmacology Review, Elizabeth Shang, Ph. D.].

The formulation of Hydrocodone/Chlorpheniramine/Pseudoephedrine Oral Solution is displayed in Table 2. The experimental formulation is manufactured and supplied by [REDACTED] (b) (4)

Table 2 Formulation of Hydrocodone/Chlorpheniramine/Pseudoephedrine Oral Solution

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

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

Study SAM-09-1010 was a single center, single dose, 2-period crossover, relative bioavailability study. Two study arms were: 1) Hydrocodone, chlorpheniramine and pseudoephedrine Oral Solution (5 mg/4 mg/60 mg) and 2) Hi-Tech Pharma's Hydrocodone Bitartrate /Homatropine Methylbromide Syrup (5 mg/1.5 mg per 5 mL, ANDA 40-613). The study was performed under a fasted condition. A total of 152 healthy volunteers were enrolled, and 147 subjects completed the study. The following pharmacokinetic variables were calculated for each treatment: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, Kel, and T_{1/2}.

Table 3 shows the PK measurements of the study SAM-09-1010. The Applicant compared the PK of hydrocodone between Hydrocodone, Chlorpheniramine and Pseudoephedrine Oral Solution and the reference drug (Table 3). The comparison shows that the 90% CI of ratios of AUC and C_{max} for hydrocodone between Hydrocodone, Chlorpheniramine and Pseudoephedrine Oral Solution and the reference drug are within the 80 - 125% goal post for bioequivalence.

Table 3 Pharmacokinetics results, Study SAM-09-1010

PK parameters	AUC _{0-inf} (pg·hr/mL) Mean (SD)	C _{max} (pg/mL) Mean (SD)	T _{max} (hr) Mean (SD)	t _{1/2} (hr) Mean (SD)
Rezira 5mL (N=144) Hydrocodone	(b) (4)			
Reference d* 5 mL (N=144) Hydrocodone				
Ratio of Test drug/Reference (90% confidence interval)				

* The reference used in this study is Hi-Tech Pharma's Hydrocodone Bitartrate /Homatropine Methylbromide Syrup(5 mg/1.5 mg per 5 mL), ANDA 40-612, approved February 8, 2008.
 (Source: m2, Section 2.7.1, page 4-6)

Reviewer comment: The original NDA was submitted on November 6, 2008 (NDA 22-439 N-000). In the original NDA, Hycodan (NDA 5-213, approved March 23, 1953) was used as the RLD for hydrocodone in the bioavailability study. Subsequent to the complete response action on the application, the manufacture of Hycodan syrup (Endo) discontinued marketing of Hycodan

syrup, therefore, the sponsor used Hi-Tech Pharma’s Hydrocodone Bitartrate /Homatropine Methylbromide Syrup as the reference for hydrocodone in their bioavailability study.. In the original NDA, the Applicant submitted the results of a pharmaceutical study (S08-0179) showing that the hydrocodone component in the proposed drug product was not bioequivalent to the reference drug, because the ratio of C_{max} between the test drug and Hycodan was outside of the bioequivalence range of 80 - 125% (see Table 4 and 5 below). Since the pseudoephedrine in the proposed drug product has been bioequivalent to the RLD, as demonstrated in the study S08-0179 in the original NDA submission, the Applicant evaluated only the BE of hydrocodone component in the current complete response submission. Since Hycodan has since been discontinued, the Applicant used the hydrocodone syrup product by HI-TECH Pharma (a generic product) to determine the bioavailability of the hydrocodone component in the the Applicant’s combination product.

Table 4 Pharmacokinetics results, Study S08-0179

PK parameters	AUC_{0-inf} (ng·hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Test drug 5mL (N=25) Hydrocodone Chlorpheniramine Pseudoephedrine	(b) (4)			
Hycodan 5 mL (N=25) Hydrocodone				
Chlorpheniramine 4 mg/5 mL (N=25)				
Pseudoephedrine 60 mg/5 mL (N=25)				

(Source: NDA 22-439 N-000, m2, Section 2.7, page 5-6)

Table 5 Comparison of PK, Study S08-0179

Comparison	Ratio between test and reference drugs (%)	
	Point estimate (mean)	90% confidence interval
Test drug/Hycodan AUC_{0-inf} C_{max}	(b) (4)	
Test drug /chlorpheniramine AUC_{0-inf} C_{max}		
Test drug/pseudoephedrine AUC_{0-inf} C_{max}		

(Source: NDA 22-439 N-000, m2, Section 2.7, page 8)

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 and pseudoephedrine. No clinical efficacy studies were conducted to support this application.

6.1 Indication

The proposed indication for this product follows below:

Rezira™ Oral Solution is for relief of cough and nasal congestion associated with common cold.

7 INTEGRATED REVIEW OF SAFETY

The Applicant submitted a Summary of Clinical Safety including the safety data from the clinical pharmacology study SAM-09-1010 and a literature survey. The safety was assessed through adverse events in the study SAM-09-1010. The safety data from this clinical pharmacology study in adult subjects did not identify a safety signal. Study SAM09-1010 was conducted in 152 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 and pseudoephedrine [m2, Section 2.7.4, pages 26 - 32].]

The AERS database search used terms of hydrocodone (HC), hydrocodone plus acetaminophen (HC/ACT), pseudoephedrine (PSE), 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 five literature references for information relevant to safety of hydrocodone 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 pseudoephedrine. 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), a 120-day safety update including data from clinical studies, animal studies, and other sources is required for a NDA submission. However, there are no animal studies and clinical safety studies conducted for the test drug and the test drug has not been manufactured and marketed. The Applicant did not submit a safety update. This reviewer does not expect new safety information for the test drug.

7.1 Methods and Findings

7.1.1 Deaths

There was no death in the clinical pharmacology study SAM-09-1010 in this application.

7.1.2 Other Serious Adverse Events

There was no serious adverse event occurred in the clinical pharmacology study SAM-09-1010 in this application.

7.1.3 Dropouts and Other Significant Adverse Events

A total of 152 healthy volunteers were enrolled into the clinical pharmacology study SAM-09-1010, 148 subjects dosed with the proposed drug product, and 151 subjects dosed with the RLD. The total number of subjects who completed the whole study was 147. There were 3 subjects discontinued the study due to adverse events (one vomiting and one dizziness after taking the RLD, and one ear pain and bleeding reported before dosing). One subject withdrew the consent, and one subject was lost the follow-up before crossing-over to take the RLD. 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 SAM-09-1010, there were 43 (29.1%) and 52 (34.4%) subjects reported adverse events for the proposed drug and RLD, respectively (see Table 6). In subjects taking the proposed drug product, dizziness was the most common adverse event (16), followed by catheter site pain or reaction (13), nausea (4), and fatigue (3). The RLD has similar spectrum of adverse events as that of the proposed drug product. 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. Four adverse events received not-specified drug treatment, and 22 adverse events received not-specified non-drug therapy. The adverse events occurred in the clinical pharmacology study SAM-09-1010 did not reveal a new safety signal.

Table 6 Adverse events in study SAM-09-1010

Adverse event*	Number (%) of subjects	
	Test drug, N=148	RLD, N=151
Subject with any AE	43 (29.1)	52 (34.4)
Ear and labyrinth disorder		
Tympenic membrane perforation	1 (0.7)	--
Eye disorder		
Eyelid oedema	1 (0.7)	--
Visual disturbance	1 (0.7)	--
GI disorder		
Epigastric discomfort	1 (0.7)	--
Nausea	4 (2.7)	16 (10.6)
Paraesthesia oral	--	1 (0.7)
Vomiting	2 (1.4)	7 (4.6)
General & administration site disorder		
Catheter site (bruise, pain, & reaction)#	13 (9.9)	10 (6.7)
Fatigue	3 (2.0)	1 (0.7)

Feeling cold or hot	--	3 (2.0)
Musculoskeletal & connective tissue dis. Arthralgia	1 (0.7)	--
Nervous system disorder Dizziness	16 (10.8)	19 (12.6)

* MedDRA preferred term version 11

Vessel punctured in collecting blood sample
 (Source: m2, Section 2.7.4, page 11)

Reviewer 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 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 hydrocodone¹. 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 2005². Although hydrocodone dosages as an antitussive are much lower than that of analgesics and illicit drugs, hydrocodone-containing medications should be prescribed and administered with caution.

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

Pseudoephedrine is a sympathomimetic amine used as an oral nasal decongestant. It can be unlawfully used to make illicit drug methamphetamine³. The Combat Methamphetamine Act, signed into law by President Bush on March 9, 2005, restricts the access of pseudoephedrine by requiring retailers to place drug products with pseudoephedrine behind the counter, limiting a person's daily and monthly purchases, and requiring buyers' identification and signature for each purchase. The potential of unlawfully using pseudoephedrine in the proposed drug to make methamphetamine is addressed by the access restriction required in the Combat Methamphetamine Act.

The proposed Rezira™ (hydrocodone and pseudoephedrine) 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 milk⁴. 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 Rezira™ with caution.

7.1.16 Overdose Experience

There is no overdose experience reported in the clinical pharmacological study SAM-09-1010. 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 frequently reported as adverse events associated with hydrocodone and pseudoephedrine 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 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

³ www.streetdrugs.org, accessed on March 5, 2009

⁴ Anderson PO, Sauberan JB, Lane JR, et al. Breastfeeding Med March 2007;2(1):10-14

proposed combination drug. In a consult for another hydrocodone containing combination drug product (NDA (b) (4) (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 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 Rezira™ 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 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), pseudoephedrine (PSE), and pseudoephedrine plus other ingredients. Table 7 summarizes the results of the AERS search covering the period from October 2007 through March 2008.

Table 7 Post-marketing adverse events (AERS database, Oct. 2007 to March, 2008)

Adverse event	HC	HC/CPM	HC/ACT	CPM/PSE	PSE	PSE/other
Total adverse events	37	2	160	6	40	19
<6 years	1	0	1	1	15	7
6-<12 years	0	1	0	2	0	5
≥12 years	28	1	88	1	21	5
Age unknown	8	0	71	2	4	2
Misuse/overdose/error	8	0	11	0	12	3
Death	29	0	123	0	33	6
Suicide	12	0	94	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. There were 33 and 6 death reports for pseudoephedrine and pseudoephedrine plus other ingredients, respectively. The data also reflect suicide cases in pseudoephedrine use.

Reviewer 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 a new safety signal for hydrocodone and pseudoephedrine.

7.2 Adequacy of Patient Exposure and Safety Assessments

In the clinical pharmacology study SAM-09-1010, a total of 148 healthy, adult subjects aged 18 to 62 years received a single dose of 5 mL Test drug (HC 5mg/CPM 4 mg/PSE 60 mg) and 151 subjects received a single dose of RLD (Hi-Tech Pharma’s Hydrocodone Bitartrate /Homatropine Methylbromide Syrup 5 mg/1.5 mg per 5 mL). The demographic characteristics of the subjects are shown in Table 8.

In the clinical pharmacology study SAM-09-1010, there were 43 (29.1%) and 52 (34.4%) subjects reported adverse events for the proposed drug and RLD, respectively. There were no death or other serious adverse events occurred during the clinical pharmacology study SAM-09-1010. There were 43 (29.1%) and 52 (34.4%) subjects reported adverse events for the proposed drug and RLD, respectively. In subjects taking the test drug, dizziness was the most common adverse event (16), followed by catheter site pain or reaction (13), nausea (4), and fatigue (3). The RLD has similar spectrum of adverse events as that of the proposed drug product. There were 3 subjects discontinued the study due to adverse events (one vomiting, one ear pain and bleeding, and one dizziness) after taking the RLD. One subject withdrew the consent, and one subject was lost the follow-up before crossing-over to take the RLD. The adverse events occurred in the clinical pharmacology study SAM-09-1010 did not reveal a new safety signal.

Table 8 Demographic characteristics of subjects in study SAM-09-1010

	All subjects, N=152	Female, N=86	Male, N=66
Race Caucasian	122 (80.3%)	73 (84.9%)	49 (74.2%)
Black	30 (19.7%)	13 (15.1%)	17 (25.8%)
Age Mean	33.1	35.0	30.7
Min, Max	18, 62	18, 62	18, 60
BMI* Mean	24.9	24.3	25.6
Min, Max	19, 29.9	19, 29.8	19.1, 29.9

*Body Mass Index (kg/m²)

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, pseudoephedrine and chlorpheniramine. 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 pseudoephedrine. The AERS database and literature search revealed no new safety signals for hydrocodone and pseudoephedrine at proposed doses. Given the extensive experience with use of hydrocodone as an antitussive and pseudoephedrine as a nasal decongestant, this reviewer concludes that the overall clinical exposure to the proposed drug is adequate.

7.2.9 Additional Submissions, Including Safety Update

There are no additional submissions including safety update received for this application.

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), a 120-day safety update including data from clinical studies, animal studies, and other sources is required for a NDA submission. However, there are no animal studies and clinical safety studies conducted for the proposed drug and the proposed drug has not been manufactured and marketed. The Applicant did not submit a safety update. This reviewer does not expect new safety information for the proposed drug.

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 Rezira™ Oral Solution. The proposed drug product contains 5 mg hydrocodone bitartrate and 60 mg pseudoephedrine hydrochloride per 5 mL. It is proposed as a

prescription combination drug product of antitussive and decongestant. The proposed indication is “(b) (4) relief of cough and the (b) (4) relief of nasal congestion due to the common cold.” The proposed dosage is (b) (4) (b) (4) (5 mL) every 4 to 6 hours as needed, not to exceed (NTE) 4 doses (20 mL) in 24 hours for adults (b) (4)

8.2 Drug-Drug Interactions

There is no drug-drug interaction study conducted in this NDA submission. The result of the clinical pharmacology study S08-0179 in the original NDA submission (NDA 22-439 N-000) 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 SAM-09-1010 in current complete response submission, the exposure of hydrocodone is within the bioequivalence range compared to the RLD. There were no differences in pseudoephedrine exposure between the test drug and the OTC monograph pseudoephedrine solution. More information regarding possible drug-drug interaction affecting the hydrocodone exposure in the Rezira™ Oral Solution may be found in the Clinical Pharmacology Review [NDA 22-439/NDA 22-442, Clinical Pharmacology Review, Elizabeth Shang, Ph. D.].

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.

8.3 Special Populations

There were no studies in special populations for Rezira™ 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 Rezira™ 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 when it is considered for approval.

8.4 Pediatrics

The clinical pharmacology study SAM-09-1010 included no pediatric subjects. In the original NDA submission, the Applicant conducted the post-marketing adverse event search in AERS for hydrocodone and pseudoephedrine 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 frequently reported in pediatric age groups of under 6 and 6 to 12 years of age pseudoephedrine drugs, because it 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 pseudoephedrine 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. FDA has received reports of life-threatening adverse events and death in patients, including children, who have received 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>].

(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 pseudoephedrine is the same as the dose in the Agency's approved OTC monograph pseudoephedrine products. Since there are no new safety signals with these ingredients, and the doses that are proposed in the combination product are the doses that were declared by the agency to be safe and effective for OTC use, no additional PK data is necessary to support these doses. 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 be requested to conduct PK and safety studies in the pediatric population from 6 to under 18 years of age.

Reviewer comment:

The Division had a telephone-conference with the Applicant conveying the concerns of lacking PK and safety data 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, including timelines of the planned pediatric studies, was submitted on May 6, 2010. The partial pediatric waiver request and the pediatric study plan have been submitted to the Pediatric Review Committee (PeRC) meeting scheduled for May 26, 2010.

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)^{1,2} 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 patients³. OTC monograph, Cochran reviews, and controlled trials have demonstrated that pseudoephedrine^{4,5} is safe and effective as a decongestant in treatment of symptoms of common cold.

Reference

1. Endo Pharmaceuticals. HYCODAN (Hydrocodone Bitartrate and Homatropine Methylbromide) Tablet and Syrup Prescribing Information. 2003.
2. Eddy NB, Halbach H, Braenden OJ. Synthetic substances with morphine-like effect: clinical experience; potency, side-effects, addiction liability. Bull World Health Organ 1957; 17(4- 5):569-863.
3. Homsy J, Walsh D, Nelson KA, Sarhill N, Rybicki L, Legrand SB et al. A phase II study of hydrocodone for cough in advanced cancer. Am J Hosp Palliat Care 2002; 19(1):49-56.
4. Taverner D, Latte J. Nasal decongestants for the common cold. Cochrane Database Syst Rev 2007;(1):CD001953.
5. Facts and Comparisons 4.0. Oral Monograph: Pseudoephedrine HCl. Available at: http://online.factsandcomparisons.com/MonoDisp.aspx?monoID_fandc-hcp12309&#monoTab. 2007.

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 (b) (4) 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) (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 (b) (4) Oral Solution. If a signal of abuse, misuse, overdose and addiction is identified, further abuse liability assessment should be conducted.

9 OVERALL ASSESSMENT

9.1 Conclusions

The Applicant seeks the approval of Rezira™ Oral Solution based on a clinical pharmacology program to demonstrate the bioequivalence to the reference drug and to OTC monograph products. No clinical efficacy and safety studies were submitted to support this application. The results of bioequivalence studies submitted in the original NDA and the present complete response show that the proposed combination drug product is bioequivalent to the reference drug for hydrocodone and OTC monograph product for pseudoephedrine. However, the deficiencies identified in the analytical site inspections lead to the conclusion that the clinical pharmacology study data submitted in the NDA are not acceptable.

The proposed indication for Rezira™ Oral Solution, “(b) (4) relief of cough and the (b) (4) relief of nasal congestion due to the common cold,” is the same as the indication of the reference drug Hycodan and OTC monograph indication of pseudoephedrine. To be consistent with the indication of another prescription cough, cold and allergy combination product (b) (4) NDA 22-439), the product labeling indication is revised to be “Relief of cough and nasal congestion associated with common cold.”

The clinical pharmacology studies to support this NDA were conducted in adults 18 years of age and older. In the NDA submission, the intended patient population for the proposed drug product is “adults (b) (4)

(b) (4) 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. The proposed dose for pseudoephedrine is the same as the dose in the Agency’s approved OTC monograph pseudoephedrine products. Since there are no new safety signals with these ingredients, and the doses that are proposed in the combination product are the doses that were declared by the agency to be safe and effective for OTC use, no additional PK data is necessary to support these doses. 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 be requested to conduct PK and safety studies in the pediatric population from 6 to under 18 years of age t (b) (4)

9.2 Recommendation on Regulatory Action

I recommend a “Complete Response” action for this NDA application. The development program for the proposed drug product is a clinical pharmacology program. However, the deficiencies identified in the analytical site during the DSI inspection lead to the conclusion that “the results of bioequivalence studies from studies S-08-0179 and SAM-09-1010 are not acceptable.” Therefore, a “Complete Response” action is recommended for the proposed drug product Rezira™ Oral Solution.

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 (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.

A routine post-marketing surveillance is recommended to monitor the adverse events associated with the use of (b) (4) 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 pseudoephedrine 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 pseudoephedrine is the same as the dose in the Agency’s approved OTC monograph pseudoephedrine products. Since there are no new safety signals with these ingredients, and the doses that are proposed in the combination product are the doses that were declared by the agency to be safe and effective for OTC use, no additional PK data is necessary to support these doses. 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 be requested to conduct PK and safety studies in the pediatric population from 6 to under 18 years of age.

9.4 Labeling Review

The proposed package insert was submitted in Physician's Labeling Rule (PLR) format. The Division of Medication Error Prevention and Analysis at the Office of Surveillance and Epidemiology (DMEPA/OSE) has been consulted regarding the product labeling and the proposed trade name Rezira™ Oral Solution.

Detailed labeling review has been conducted as appended below.

(b) (4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22442	ORIG-1	CYPRESS PHARMACEUTICA L INC	REZIRA ^(b) ₍₄₎ (HYDROCODONE BITARTRATE AND PSEU

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

/s/

XU WANG
05/26/2010

LYDIA I GILBERT MCCLAIN
06/01/2010

DIVISION DIRECTOR SUMMARY REVIEW

Date: September 18th, 2009

From: Lydia I. Gilbert-McClain, MD, Deputy Director, DPAP

Through: Badrul A. Chowdhury, MD, PhD, Division Director, DPAP

Subject: Division Director Summary Review

NDA Number: 22-442

Applicant Name: Cypress

Date of Submission: November 4th, 2008

PDUFA Goal Date: September 4th, 2009

Proprietary Name: Rezira (b) (4)

Established Name: Hydrocodone bitartrate, and Pseudoephedrine hydrochloride

Dosage form: Oral Solution

Strength: 5 mg/60 mg/5 mL

Proposed Indications: For the (b) (4) relief of cough, and the (b) (4) relief of nasal congestion due to the common cold

Action: Complete Response

1. Introduction

Cypress Pharmaceuticals Inc. submitted a 505 (b)(2) new drug application (NDA 22-442) on November 4th, 2008 (received on November 7th, 2008, CDER stamp date) for use of a combination oral solution comprised of hydrocodone bitartrate, and pseudoephedrine hydrochloride oral solution for (b) (4) relief of cough, and nasal congestion in adults (b) (4). The product is to be marketed by Hawthorne Pharmaceuticals a subsidiary of Cypress Pharma. The application was reviewed under a standard review timeline and the PDUFA action date is September 4th, 2009. Because of ongoing discussions with the Controlled Substances Staff regarding the need for abuse potential studies, the PDUFA action on this application was delayed pending clarification of CSS consult recommendations. The recommendations were finalized on September 11, 2009, and an action on this application will be taken on September 18th, 2009.

To support this NDA the Applicant cross-references the clinical pharmacology data for NDA 22-439 the triple combination product containing hydrocodone, chlorpheniramine, and pseudoephedrine. The clinical pharmacology program under NDA 22-439 failed to demonstrate the bioequivalence requirements to support approval of that application, and as such this NDA 22-442 does not have support for approval. In addition there are several outstanding CMC issues that need to be addressed before the application can be approved. This review will summarize the salient aspects of the program.

2. Background

Hydrocodone is an opioid derived from codeine that has antitussive and analgesic effects. Hydrocodone is a Schedule II narcotic under the Controlled Substance Act (21 U.S.C. 801 *et seq*) and combination products with hydrocodone and non-narcotic active ingredients are Schedule III. FDA first approved Hydrocodone for use as an antitussive on March 23, 1943 (NDA 05-213, HYCODAN, submitted by ENDO Laboratories Inc.). A subtherapeutic amount of homatropine methylbromide was later added to this product to help prevent abuse or intentional overdose. HYCODAN was reviewed under the DESI program and was found to be effective for the symptomatic relief of cough, and was classified as a new drug product for which an approved NDA was required prior to marketing [47 FR 23809, June 1, 1982]. Hydrocodone products are prescription only products [21 CFR 1306.21, 21 CFR 1308.13].

Approved applications for antitussive formulations of hydrocodone include HYCODAN syrup and tablets and their approved generic equivalents and a hydrocodone polistirex and chlorpheniramine polistirex combination suspension extended-release product (NDA 19-111), marketed as TUSSIONEX. However, there have been hundreds of unapproved hydrocodone-containing products marketed illegally as antitussives¹. Such products include, but are not limited to, hydrocodone in combination with an expectorant, such as guaifenesin, or a decongestant, such as phenylephrine or pseudoephedrine.

Under the DESI review, FDA determined that hydrocodone bitartrate is a new drug. Therefore, manufacturers must have an approved application before marketing any drug product that contains hydrocodone bitartrate, or any other salt or ester of hydrocodone. In June 2006, the Agency published a final guidance for FDA staff and Industry: *Marketed Unapproved Drugs-Compliance Policy Guide* in which the Agency outlined its plan to address marketed new drugs without NDAs or ANDAs. The compliance policy guide describes how the Agency intends to exercise enforcement discretion with regard to drugs marketed in the United States that do not have the required FDA approval for marketing. To this end, FDA published a Federal Register (FR) notice of its intention to take enforcement action against illegally marketed drug products containing hydrocodone on October 1, 2007 [Docket No. 2007N-0353]. Manufacturers who wish to market a drug containing hydrocodone must obtain FDA approval of a new drug application (NDA) or an abbreviated new drug application (ANDA). Based on the FR notice, manufacturing of unapproved hydrocodone-containing products should have ceased by December 31, 2007, and shipment of currently marketed and listed unapproved hydrocodone-containing products should have ceased by March 31, 2008.

¹ Federal Register Notice October 1, 2007 Docket No. 2007N-0353

The Agency has encouraged manufacturers of these and other unapproved products to obtain approval for marketing in the United States. This NDA is one of these applications submitted to obtain marketing approval of a combination product containing hydrocodone for a cough/cold indication.

The current application is to market a combination product containing hydrocodone bitartrate (HC), and pseudoephedrine hydrochloride (PSE), as an immediate release oral solution containing 5 mg HC and 60 mg of PSE, per 5 mL respectively. Pseudoephedrine is a well known sympathomimetic amine used for nasal decongestion. Pseudoephedrine is listed in the OTC monograph and permitted to be combined with an antitussive (21 CFR 341.40). However, since HC is not a monograph product, clinical studies would normally be required to support a combination product containing hydrocodone and other active ingredients in order to demonstrate the contribution of each component to the combination product as required by regulation (21CFR 300.50). Because of the prior regulatory precedent of approving Tussionex Pennkinetic (the combination of hydrocodone and chlorpheniramine) with clinical pharmacology data only, combination products containing hydrocodone and other monograph active ingredients that are permitted monograph combination drug classes can be developed under a clinical pharmacology program only. Therefore, clinical efficacy and safety studies may not be necessary to support this combination product provided that the applicant carries out a satisfactory clinical pharmacology program.

The applicant cites NDA 19-111 (Tussionex, UCB Inc), NDA 05-213 (Hycodan Tablets and Syrup, ENDO Pharma), Advil Allergy Sinus Tablets (NDA 021-441, Wyeth Consumer Products Whitehall-Robbins Healthcare), Mucinex D tablets (NDA021-585, Adams Respiratory Therapeutics (now Reckitt Benckiser Inc.)), Tavist Allergy Sinus/Headache Tablets (NDA 021-082, Novartis), and 21 CFR 341.20 for pseudoephedrine hydrochloride as references for this 505 (b) (2) application.

Of the numerous products listed as reference products for this application, we are relying on the Hycodan product (NDA 005213) by Endo Pharmaceuticals Inc to make the assessment of bioequivalence for hydrocodone. Hycodan was the reference used in the clinical pharmacology study. The other ingredients CPM and PSE are monograph products and since the dose and dosing frequency proposed for these other ingredients are consistent with the monograph, we can rely on the monograph to make an assessment of efficacy and safety. For the labeling we need to also rely on Tussionex and Codeprex because there are statements related to hydrocodone that are not in the Hycodan label and we are relying on the Tussionex label (NDA 19-111) for that, and statements regarding chlorpheniramine for which we need to reference Codeprex (NDA 021-369). Of note during the review cycle, the manufacturer of Hycodan discontinued marketing the product; however, we have no data to suggest that the discontinuation was for reasons of safety or efficacy. The Orange Book now lists the hydrocodone product from Hi Tech Pharma (ANDA 040613) as the RLD for hydrocodone bitartrate syrup.

The development program for this combination product, (b) (4) was discussed at a pre-IND meeting in January 2008 (preIND (b) (4)) and the Division agreed that a clinical pharmacology program to determine the bioequivalence of hydrocodone (reference product Hycodan), and to determine the drug-drug interaction of the individual ingredients in the combination product was necessary. The clinical pharmacology study for this combination product was done under IND 102,177.

The applicant submitted (b) (4) in November 2008 as follows: NDA 22-439 (b) (4) (Hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride) submitted November 10th, 2008)

The two (b) (4) NDAs share the same clinical pharmacology program and this summary review will be cross-referenced to both NDAs.

3. CMC

The proposed product in this NDA is for an aqueous oral solution containing hydrocodone bitartrate (HC) 5 mg, and pseudoephedrine hydrochloride (PSE) 60 mg, per 5 mL. Inactive ingredients (excipients) include citric acid, sodium citrate, sodium saccharine, sucrose, glycerin, propylene glycol, and methylparaben and propylparaben (b) (4). The product is grape flavor and will be available in 16 oz white HDPE bottles as commercial product and (b) (4) bottles as physicians' samples. The two active substances are USP ingredients that have been previously assessed to support other NDA applications in the past. There are several outstanding CMC issues that will affect approvability, related to the need to reduce the total impurity level of the drug product, and the analytical test methods. The EES evaluations are acceptable for all facilities.

4. Nonclinical Pharmacology/Toxicology

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

5. Clinical Pharmacology/Biopharmaceutics

The applicant conducted one clinical pharmacology study S08-0179 in 25 adult healthy volunteers to evaluate the rate and extent of exposure of hydrocodone compared to the reference product Hycodan® Syrup, and to evaluate the drug-drug interaction of the three

active ingredients HC, CPM, and PSE in the formulation. This study was conducted to support both NDAs 22-439 and NDA 22-442. This was an open-label, single-dose, randomized, four period cross-over study under fasted conditions. The results showed that hydrocodone was not bioequivalent to the reference product Hycodan syrup (Endo Pharmaceuticals Inc). The clinical pharmacology team was able to reproduce the Applicant's study results. The Cmax for hydrocodone was (b) (4) which is outside of the accepted 80% - 125 % bioequivalence range. The other ingredients in the solution CPM, and PSE are bioequivalent to their respective test products. A summary of the results for hydrocodone bitartrate are shown in the table below. The failure to establish bioequivalence of to the Hydrocodone is an approvability issue. Since there are no clinical studies to support the product, and the PK/PD response relationship of hydrocodone is not known, the applicant must establish bioequivalence of hydrocodone to the reference product in order to support the efficacy and safety of the product. Because the oral solution formulation does not contain (b) (4) excipients know to affect the bioavailability of the active ingredients, the 4-period cross-over study conducted in the fasted state should be adequate to address the drug-drug interaction of the ingredients once bioequivalence has been established. In this case, the study results did not establish bioequivalence of the hydrocodone component. General comments about the clinical pharmacology requirements for hydrocodone combination solution products were conveyed to the Applicant during the review cycle on June 9th, 2009, and some of these comments will be used in the Complete Response letter.

Table 1: Pharmacokinetic results for hydrocodone bitartrate (study S08-0179)
(n = 25)

PK Parameters	HC/CPM/PSE	Hycodan® Oral solution	Ratio of Test/reference (90% CI)
AUC _{0-∞} (ng.h/mL)	(b) (4)		
AUC _{0-t} (ng.h/mL)			
Cmax (ng/mL)			

6. Clinical Microbiology

This is a non-sterile solution product for oral ingestion. The product contains methylparaben and propylparaben at target concentrations of (b) (4). There are no outstanding microbiology issues with the formulation.

7. Clinical/Statistical- Efficacy

The application relies on a comparison of the bioavailability of the proposed drug product to that of approved reference products Hycodan and the OTC monograph products pseudoephedrine, and chlorpheniramine. No clinical studies were required to support the application as discussed in Section 2 (Background).

8. Safety

The safety of the product is based on establishing bioequivalence of the product compared to approved reference products. In addition, the applicant conducted a review of the literature, and a search of the AERS database for post-marketing safety information for the individual ingredients and any combination thereof, for the period from October 2007 through March 2008. These searches did not reveal any new safety signals.

9. Advisory Committee Meeting

An advisory committee meeting was not necessary for this application. The three active ingredients present in this product are well known molecules, and as previously discussed the combination of products of these classes are accepted for the proposed indications.

(b) (4)

A CDER regulatory briefing was held on June 12th, 2009 to discuss the need for abuse potential studies for hydrocodone-containing combination products because of the concern raised by the Controlled Substances Staff (CSS) that the other active ingredients could potentiate the abuse potential of hydrocodone. The CSS had recommended that this potential be studied with animal and/or human studies.

The consensus from the panel was that abuse potential assessment was not required for these combination products prior to approval. These combinations would remain in Schedule III by virtue of the hydrocodone component and would have abuse potential class labeling and it is not clear that the information from abuse potential studies will impact scheduling. Further, these types of combinations have been on the market for several years and there has been no safety concern raised regarding an increase in the abuse potential of these combinations. The panel recommended that a post-marketing signal could trigger the need for abuse potential studies for these products in the future.

The Control Substances Staff consulted the Office of Surveillance and Epidemiology regarding the hydrocodone combination products. In the consult response, OSE incorrectly stated that the recommendation from the regulatory briefing was for abuse potential studies for these combination products, and that these studies could be done post approval. In the consult they (OSE) state that they agree with the regulatory briefing recommendation. The OSE primary reviewer was contacted regarding this error in the OSE consult but to date the Division has not received a response. The minutes of the regulatory briefing accurately reflect the recommendations from the briefing.

Of note, an approved hydrocodone combination product TUSSIONEX (hydrocodone and chlopheniramine) has been on the market for several years with no safety signal for increased potential for abuse, and given this history, it seems acceptable to not request specific abuse potential studies for these hydrocodone combination products pre-approval.

A follow up meeting was held with Dr. Michael Klein the director of the CSS and DPAP where we discussed the consult recommendations from CSS and OSE, and the discussions and recommendations from the regulatory briefing. Dr. Klein agreed that the sponsors of these

products could conduct active surveillance and monitoring for signals of abuse, misuse, overdose and addiction and provide periodic summaries and analysis of these surveillance and monitoring activities for a period of time (e.g. 5 years) post approval and provided these recommendations in a subsequent memo to the NDAs dated 9/11/2009. I concur with the revised recommendations from CSS. Since the NDA is not going to be approved, and this is a recommendation that will be carried out post approval, there is no need to include this in the Complete Response letter.

10. Pediatrics

The applicant is requesting a

(b) (4)

(b) (4)

the applicant requested a *partial* waiver for pediatric assessment (i.e. for patients under 6 years of age). Since the proposed product contains hydrocodone which is contraindicated for use in children under 6 years of age (because of the risk of respiratory depression) it would be appropriate to waive studies for pediatric patients less than 6 years of age. The application was presented to PERC on July 29th, 2009. The PERC discussed the lack of pharmacokinetic and clinical efficacy and safety studies with hydrocodone in the pediatric population and commented on the limitations of the current Cough/Cold OTC monograph to inform about safety and efficacy of the currently classified as GRAS and GRAE ingredients. The PERC felt that further discussion was needed with our legal colleagues to assess whether under the current system we could request clinical studies in pediatric patients. Based on this discussion, the PERC decided to not make a determination about PREA at this time since this application was not going to be approved.

11. Other Relevant Regulatory Issues

Data Quality, Integrity, and Financial Disclosure

A DSI audit was not conducted because from the outset it is evident that the study results cannot support approval of the NDA. There are no ethical issues present, and the study that was performed was done in accordance with accepted clinical standards. The applicant submitted acceptable financial disclosure statements.

12. Labeling

Proprietary name

The applicant proposed initially proposed the name (b)(4) but this name was not found to be acceptable. The Applicant subsequently proposed the name REZIRA, and this name was found to be acceptable by the agency. However, the Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Surveillance and epidemiology (OSE) would not recommend the use of the root name REZIRA for future product (b)(4)

Physician labeling

The applicant submitted a label in the Physician's Labeling Rule Format. Since the product will not be approved, the Division did not discuss detailed labeling language with the applicant.

Carton and Immediate Container Labels

As with physician labeling, detailed review of the carton and immediate container label was not done. Preliminary carton and container labeling comments were conveyed to the applicant in a Chemistry IR during the review cycle.

Patient Labeling and Medication Guide

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

13. Action and Risk Benefit Assessment

Regulatory action

The submitted data do not support approval of the fixed dose combination oral solution of Hydrocodone, and Pseudoephedrine, oral solution for use as an antitussive and decongestant medication [REDACTED] ^{(b) (4)}. The results of bioavailability study conducted showed that the hydrocodone bitartrate in the oral solution was not bioequivalent to the reference product Hycodan. Since the Applicant has not submitted any clinical studies to support the efficacy and safety of the proposed triple combination oral solution product, the action on this application will be Complete Response due to failure to establish bioequivalence for the hydrocodone bitartrate component.

The comments below can be used for the Complete Response action letter

- 1) The clinical pharmacology study submitted to support this application show that the hydrocodone component of your oral solution product is not bioequivalent to the reference Hycodan® oral solution. The C_{max} for hydrocodone bitartrate in your product is outside of the 80 -125% goal post for bioequivalence.

This deficiency may be addressed by doing the following:

- 1) Conduct a single-dose clinical pharmacology study to establish the bioequivalence of your proposed REZIRA (Hydrocodone 5 mg pseudoephedrine 60 mg/ per 5 mL) oral solution to the reference products.

OR

- 2) Conduct a clinical development program with clinical efficacy and safety studies to support your combination product.

Risk Benefit Assessment

The overall risk and benefit assessment of the individual ingredients hydrocodone, chlorpheniramine, and pseudoephedrine does not suggest an unfavorable risk benefit for these individual ingredients. However, for this combination product, a risk benefit assessment cannot be fully made because the applicant has not established the bioequivalence of their proposed combination product (hydrocodone component) to the reference product. These data are lacking and as such the product cannot be approved at this time.

Postmarketing Risk Management Activities

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

Postmarketing Study Commitments

Since this application is not going to be approved, there are no recommended postmarketing study commitments at this time. When this product is ready for approval, we will be asking the sponsor to conduct active surveillance and monitoring for signals of abuse/misuse, overdose, and addiction and to provide periodic analysis and summary of surveillance and monitoring activities for abuse/misuse, overdose and addiction for a period of 5 years. Depending on the outcome of this active surveillance, additional studies may be warranted.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22442	ORIG-1	CYPRESS PHARMACEUTICA L INC	REZIRA ^(b) ₍₄₎ (HYDROCODONE BITARTRATE AND PSEU

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

/s/

LYDIA I GILBERT MCCLAIN
09/18/2009

BADRUL A CHOWDHURY
09/18/2009
I concur

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-442
Submission Code	N-000
Letter Date	11/07/08
Stamp Date	11/11/08
PDUFA Goal Date	09/11/09
Reviewer Name	Xu Wang, M.D., Ph.D.
Review Completion Date	07/23/09
Established Name	Hydrocodone and pseudoephedrine
(Proposed) Trade Name	Rezir ^(b) ₍₄₎ Oral Solution
Therapeutic Class	Antitussive/nasal decongestant
Applicant	Cypress Pharmaceutical, Inc.
Priority Designation	S
Formulation	Oral solution
Dosing Regimen	For adults ^(b) ₍₄₎ ^(b) ₍₄₎ (5 ml) every 4-6 hours as needed, not to exceed 4 doses (20 ml) in 24 hours ^(b) ₍₄₎
Indication	For ^(b) ₍₄₎ relief of cough and the ^(b) ₍₄₎ relief of nasal congestion due to the common cold
Intended Population	Adults ^(b) ₍₄₎

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The proposed drug product Rezira^(b)₍₄₎ Oral Solution is not ready for approval in the present NDA submission and I recommend that the application be given a Complete Response Action.

The development program for the proposed drug product is a clinical pharmacology program. No clinical efficacy studies were submitted to support this application. The proposed drug product Rezira^(b)₍₄₎ Oral Solution depends on the bioequivalence to the reference drug product Hycodan and the OTC monograph drug pseudoephedrine to support its efficacy and safety. The clinical pharmacology study submitted in this application showed that the hydrocodone component in the proposed combination drug product was not bioequivalent to the reference drug, because the ratio of C_{max} between the proposed combination drug product and Hycodan was outside of the bioequivalence range of 80 - 125%. Clinical efficacy and safety studies are necessary to support the proposed drug product Rezira^(b)₍₄₎ Oral Solution.

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. No special post-marketing risk management activities are recommended at this time since the recommended regulatory action is Complete Response.

1.2.2 Required Phase 4 Commitments

Hydrocodone is a controlled substance that is known to have a certain level of abuse potential. The risk associated with Rezira^(b)₍₄₎ 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 ^(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.

No special Phase 4 commitments are recommended at this time since the recommended regulatory action is Complete Response.

1.2.3 Other Phase 4 Requests

There are no Phase 4 requests for this application.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This is a clinical pharmacology program. The Applicant included one clinical pharmacology study in the NDA submission. The clinical pharmacology study S08-0179 is an open-label bioavailability and drug-drug interaction study to evaluate the BA/BE of hydrocodone and pseudoephedrine from a single dose of 5 mL immediate release oral solution containing 5 mg hydrocodone bitartrate, 4 mg chlorpheniramine maleate, and 60 mg pseudoephedrine hydrochloride under fasting condition in 28 healthy adult subjects compared to the reference drug Hycodan and OTC monograph drug pseudoephedrine.

The Applicant submitted an Overview of Safety including the safety data from the clinical pharmacology study S08-0179, a search of the AERS database for post-marketing spontaneous adverse events, and a literature survey to provide support for the safety of the proposed drug product.

1.3.2 Efficacy

No clinical efficacy studies were submitted to support this application. This is a 505(b)(2) application using clinical pharmacology studies to support approval. The Agency's previous findings of efficacy and safety of approved hydrocodone products (Hycodan, NDA 5-213) and the OTC monograph for pseudoephedrine are being used to substantiate the efficacy and safety of this combination product.

1.3.3 Safety

The Applicant submitted an Overview of Safety including the safety data from the clinical pharmacology study S08-0179, post-marketing spontaneous adverse events report, and a literature survey.

Safety was assessed through adverse events in the study S08-0179 conducted in 28 adult subjects. Eight subjects reported 27 adverse events over the course of the study. There was no death or serious adverse event occurred in this study. Dizziness was the most common adverse event (8), followed by headache (5), nausea (4), and puncture site pain (4). The proposed drug product only had one case of dry mouth reported as the adverse event. Most adverse events (16 out of 27 AEs) were reported from subjects received the reference drug Hycodan. The safety data from the clinical pharmacology study S08-0179 did not identify a 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 acetaminophen (HC/ACT), hydrocodone plus other ingredients, pseudoephedrine (PSE), and pseudoephedrine plus other ingredients. There were no new safety signals revealed through the search of AERS database for post-marketing adverse events.

The Applicant compiled 5 literature references for information relevant to safety of hydrocodone 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 hydrocodone and pseudoephedrine. The literature survey revealed no new safety signals for hydrocodone and pseudoephedrine. 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), a 120-day safety update including data from clinical studies, animal studies, and other sources is required for a NDA submission. However, there are no animal studies and clinical safety studies conducted for the test drug and the test drug has not been manufactured and marketed. The Applicant did not submit a safety update. This reviewer does not expect new safety information for the test drug.

1.3.4 Dosing Regimen and Administration

The application is for Rezir^(b)₍₄₎ Oral Solution. The proposed drug product contains 5 mg hydrocodone bitartrate and 60 mg pseudoephedrine hydrochloride per 5 mL. It is proposed as a prescription drug combination of antitussive and decongestant. The proposed indications are “for ^(b)₍₄₎ relief of cough and the ^(b)₍₄₎ relief of nasal congestion due to the common cold.” The proposed dosage is ^(b)₍₄₎ (5 mL) every 4 to 6 hours as needed, not to exceed (NTE) 4 doses (20 mL) in 24 hours for adults ^(b)₍₄₎

1.3.5 Drug-Drug Interactions

The result of clinical pharmacology study S08-0179 showed that the subjects’ exposure for hydrocodone in the proposed combination drug product was lower than that in the reference drug Hycodan. This suggests that there may be drug-drug interaction between hydrocodone and pseudoephedrine, hydrocodone and other ingredients in the proposed drug formulation. There were no differences in the pseudoephedrine exposure between the proposed combination drug product and the OTC monograph pseudoephedrine solution. More information regarding possible drug-drug interaction affecting the hydrocodone exposure in the proposed drug product can be found in the Clinical Pharmacology Review [NDA 22-439/NDA 22-442, Clinical Pharmacology Review, Sheetal Agarwal, 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 for these drug-drug interactions.

1.3.6 Special Populations

There were no studies in special populations for Rezira^(b)₍₄₎ 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₎

^(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 Rezira^(b)₍₄₎ 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 when it is considered for approval.

Reviewer 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 pseudoephedrine. The drug product contains 5 mg hydrocodone bitartrate and 60 mg pseudoephedrine hydrochloride per 5 mL. It is proposed as a prescription drug combination of antitussive and decongestant. The proposed indication is for ^(b)₍₄₎ relief of cough and the ^(b)₍₄₎ relief of nasal congestion due to the common cold. The sponsor's proposed name is Rezira^(b)₍₄₎ Oral Solution. 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 cites the following reference listed drugs (RLDs) and OTC monograph: 1) Hycodan Tablets and Syrup (NDA 05213, Endo Pharmaceuticals), 2) Tussionex Extended-Release Suspension (NDA 19111, UCB, Inc.), 3) Codeprex Extended-Release Suspension (NDA 21369, UCB, Inc.), 4) Advil Allergy/Sinus Tablets (NDA 21441, Wyeth Consumer Products), 5) Tavist Allergy/Sinus/Headache Tablets (NDA 21082, Novartis), and 6) 21 CFR 341.20 for pseudoephedrine hydrochloride.

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 2 controlled substance as a single ingredient (21 CFR 1308.12), a schedule 3 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 1306.21).

Hycodan Tablets and Syrup (HC 5 mg plus homatropine methylbromide (HTM) 1.5 mg, and HC 5 mg plus HTM 1.5 mg per 5 mL, NDA 5-213) was classified in the DESI review as safe and effective for prescription drug for the symptomatic relief of cough (DESI Notice #5123). The approved dosages are:

- Adults: One tablet or one teaspoonful of the syrup (5 mg HC) every 4 to 6 hours as needed; not to exceed (NTE) 6 tablets or 6 teaspoonfuls (30 mg HC) in 24 hours
- Children 6 to 12 years of age: One-half (1/2) tablet or one-half (1/2) teaspoonful of the syrup (2.5 mg HC) every 4 to 6 hours as needed; NTE 3 tablets or 3 teaspoonfuls (15 mg HC) in 24 hours
- Children less than 6 years of age: The administration of hydrocodone in children less than 6 years of age is contraindicated due to the risk of respiratory depression [Reference to NDA 19-111, Tussionex Pennkinetic product labeling].

Pseudoephedrine (PSE) is considered to be GRASE as an oral nasal decongestant [21 CFR 341.20] in the following age groups at the following oral doses [21 CFR 341.80(d)]:

- Adults and children 12 years of age and over: 60 mg every 4 to 6 hours, NTE 240 mg in 24 hours
- Children 6 to under 12 years of age: 30 mg every 4 to 6 hours, NTE 120 mg in 24 hours
- Children 2 to under 6 years of age: 15 mg every 4 to 6 hours, NTE 60 mg in 24 hours
- Children under 2 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 nasal decongestant (such as pseudoephedrine) and any single antihistamine (such as chlorpheniramine) to be a permitted combination [21 CFR 341.40].

Reviewer comment:

Hydrocodone, a schedule controlled substance and a prescription drug, is not an OTC monograph antitussive. Therefore, the proposed combinations of ^(b)₍₄₎ 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₎ M-001, MR, Charles E. Lee, M.D., 9/25/2006. 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 plan 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, and that approval can be based on establishment of bioequivalence.

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 5213, 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. Hydrocodone is also approved in combination with chlorpheniramine in an extended release suspension for cough (Tussionex Pennkinetic, NDA 19111). There are other generic Hydrocodone products as antitussive drugs on the market. These are Hydrocodone Compound (ANDA 88017), Tussicaps (ANDA 77273), Tussigon (ANDA 88506), and Homatropine Methylbromide and Hydrocodone Bitartrate Tablet and Syrup (ANDA 40295, ANDA 40613, ANDA 88008).

Pseudoephedrine is a readily available OTC monograph drug, being considered to be generally recognized as safe and effective (GRASE) at OTC monograph dose for the temporary relief of nasal congestion. In addition to pseudoephedrine, phenylephrine is another readily available OTC nasal decongestant. Oral nasal decongestants 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 for cough (Tussionex Pennkinetic, NDA 19111) and generic antitussive drugs Hydrocodone Compound (ANDA 88017), Tussicaps (ANDA 77273), Tussiongon (ANDA ^(b)⁽⁴⁾), and Homatropine Methylbromide and Hydrocodone Bitartrate Tablet and Syrup (ANDA 40295, ANDA 40613, ANDA 88008). 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 20716), Vicodin and Vicodin HP (ANDA 88058, ANDA 40117), Lortab (ANDA 40100, ANDA 87722), and Anexsia (ANDA 40405, ANDA 40409, ANDA ^(b)⁽⁴⁾ ANDA 40686, ANDA 89160). 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].

Pseudoephedrine is currently approved in the United States in tablets (Afrinol, NDA 18191), in combination with chlorpheniramine (Chlor-Trimeton, NDA 18397), with ibuprofen and chlorpheniramine (Advil Allergy Sinus Caplet, NDA 21441), and with guaifenesin (MucinexTM D, NDA 21585). These products are extended release formulations. Pseudoephedrine 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 1306.21).

Pseudoephedrine is an OTC monograph drug of oral nasal decongestant [21 CFR 341.20]. Pseudoephedrine can be unlawfully used to make the illicit drug methamphetamine. The Combat Methamphetamine Act restricts the access of pseudoephedrine by requiring retailers to place OTC drug products with pseudoephedrine behind the counter, limiting a person's daily and monthly purchases, and requiring buyers' identification and signature for each purchase.

2.5 Presubmission Regulatory Activity

The Applicant had a pre-IND meeting on January 14, 2008 with the Division ^{(b) (4)}

^{(b) (4)} The Division's comments in the pre-IND meeting which relate to this application are summarized as follows [Pre-IND ^{(b) (4)} Meeting Minutes, February 6, 2008]:

- A 505(b)(2) pathway would be an acceptable approach for the planned combination drug products.
- The bioequivalence (BE) should be demonstrated between hydrocodone in the proposed products and an approved hydrocodone antitussive drug product (e.g. Hycodan) by conducting bioequivalence studies.
- A BE study for an active ingredient in one of the combination solutions (^{(b) (4)} ^{(b) (4)}) may be used to support the BE of the same ingredient in other combination solutions, provided that there were no major differences between the formulations.
- 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 ^{(b) (4)}

^{(b) (4)} The opening IND study was a single-dose bioavailability study that was determined safe to proceed. The Applicant filed a 505(b)(2) NDA for the proposed Rezira^{(b) (4)} (hydrocodone and pseudoephedrine) Oral Solution on November 7, 2008. During the 45-day filing review period, 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/NDA 22-442, 74-day Letter, January 23, 2009].

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 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 ^{(b) (4)}. 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). The in-process tests used are pH, appearance, density, and viscosity. A detailed review of the CMC portion of the application may be found in the ONDQA review [NDA 22-442 N-000, ONDQA Review, Xiaobin Shen, Ph.D., July 13, 2009].

Hydrocodone bitartrate dihydrate 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)

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

The proposed drug product Rezira^(b)₍₄₎ is a non-sterile oral solution. (b) (4)

The product quality microbiology reviewer recommends an approval from a quality microbiology standpoint [NDA 22-439/NDA 22-442 N-000, Product Quality Microbiology Review, Denise Miller, Microbiologist, March 16, 2009].

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 bioequivalence of the proposed drug product to the reference drug Hycodan and the monograph drug pseudoephedrine. The Applicant's drug development program for Rezira^(b)₍₄₎ Oral Solution is based on establishing that their combination product produces exposures that are equivalent to

that of an approved and marketed product for hydrocodone and to that of OTC monograph dose of pseudoephedrine. There were no clinical efficacy or safety studies in this application.

This application refers to one clinical pharmacology study S08-0179 which was conducted to support the Applicant's another combination drug product ^{(b) (4)} Oral Solution (NDA 22-439, hydrocodone, chlorpheniramine, and pseudoephedrine). In a pre-IND meeting discussion, the Agency agreed that a BE study for an active ingredient in one of the combination solutions ^{(b) (4)} may be used to support the BE of the same ingredient in other combination solutions, provided that there were no major differences between the formulations [Pre-IND ^{(b) (4)} Meeting Minutes, February 6, 2008]. The proposed Rezira^{(b) (4)} Oral Solution formulation is exactly the same as that of the ^{(b) (4)} Oral Solution except that Rezira^{(b) (4)} contains no chlorpheniramine.

4.2 Table of Clinical Studies

The Applicant has submitted the results from Study S08-0179, a single-dose bioavailability study, to characterize the exposure of hydrocodone, chlorpheniramine, and pseudoephedrine immediate release solution in fasted, healthy, adult subjects. The study in this application is summarized below in Table 1.

Table 1. Summary of Study S08-0179

Study number	Study type	Treatment group	Treatment duration	Study design	Number of subjects	Diagnosis, age of subjects	Materials submitted
S08-0179	BA/BE	5 ml ^{(b) (4)} (HC/CPM/PSE solution 5/4/60 mg) 5 mL PSE solution (60 mg) 5 mL CPM solution (4 mg) 5 mL HC/homatropine solution (5/1.5 mg)	Single dose	Open label, single dose, randomized, 4-period cross over	28	Healthy males and females, 18-54 yrs	Study report

4.3 Review Strategy

This is a review of the safety data from Study S08-0179, and of the data from AERS database for post-marketing and spontaneous adverse event reports and the literature review for hydrocodone, chlorpheniramine, and pseudoephedrine.

4.4 Data Quality and Integrity

This drug development program is a clinical pharmacology program. The clinical pharmacology team is not requesting DSI audit because the clinical pharmacology study failed to demonstrate

the bioequivalence of the hydrocodone component of ^{(b) (4)} Oral Solution and the reference drug Hycodan.

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 8].

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 the submission. A summary of data from the Applicant's clinical pharmacology study follows below. Detailed information can be found in the Clinical Pharmacology Review [NDA 22-442, Clinical Pharmacology Review, Sheetal Agarwal, Ph. D.].

The formulation of ^{(b) (4)} Oral Solution is displayed in Table 2. The proposed Rezira^{(b) (4)} formulation is exactly the same as that of the ^{(b) (4)} formulation except that Rezira^{(b) (4)} contains no chlorpheniramine. The experimental formulation is manufactured and supplied by ^{(b) (4)}

Table 2 Study S08-0179, formulation of ^{(b) (4)} Oral Solution

Ingredient	% w/v	mg/5 mL	Mg/480 mL
Hydrocodone bitartrate USP	^{(b) (4)}	5.0	480
*Chlorpheniramine maleate USP		4.0	384
Pseudoephedrine hydrochloride USP		60	5,760
Sucrose NF			^{(b) (4)}
Glycerin 99.7% USP			^{(b) (4)}
Polyethylene glycol USP			^{(b) (4)}
Methylparaben NF			^{(b) (4)}
Propylparaben NF			^{(b) (4)}
Citric acid anhydrate USP			^{(b) (4)}
Sodium citrate USP			^{(b) (4)}
Sodium saccharin USP			^{(b) (4)}
Grape flavor #6175			^{(b) (4)}
^{(b) (4)} water USP			^{(b) (4)}

* Rezira^{(b) (4)} is the same formulation as ^{(b) (4)} without chlorpheniramine component. (Source: m2, Section 2.3, page 5)

Study S08-0179 was a single center, single dose, 4-period crossover, relative bioavailability and drug-drug interaction study. Four study arms were: 1) ^{(b) (4)} Oral Solution (hydrocodone, pseudoephedrine, and chlorpheniramine oral solution 5 mg/60 mg/4 mg), 2) pseudoephedrine oral solution (60 mg/5 ml), 3) chlorpheniramine oral solution (4 mg/5 ml), and 4) Hycodan Syrup (5 mg hydrocodone bitartrate/1.5 mg homatropine methylbromide per 5 ml). The study was performed under fasted conditions. A total of 28 healthy volunteers were enrolled, and 25 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 $T_{1/2}$.

Table 3 shows the PK measurements of the study S08-0179. The Applicant compared the PK of ^{(b) (4)} to that of the reference drugs (Table 4). The comparison shows that the C_{max} of the hydrocodone component in ^{(b) (4)} was lower than that of the reference drug Hycodan, and the ratio of C_{max} between ^{(b) (4)} and Hycodan was outside of the bioequivalence range of 80 - 125%. The ratio of AUC for hydrocodone between ^{(b) (4)} and Hycodan was within the BE range. The ratios of AUC and C_{max} for chlorpheniramine and pseudoephedrine were all within the BE range.

Table 3 Pharmacokinetics results, Study S08-0179

PK parameters	AUC_{0-inf}	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
	(ng·hr/mL) Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
^{(b) (4)} 5mL (N=25) Hydrocodone Chlorpheniramine Pseudoephedrine	^{(b) (4)}			
Hycodan 5 mL (N=25) Hydrocodone				
Chlorpheniramine 4 mg/5 mL (N=25)				
Pseudoephedrine 60 mg/5 mL (N=25)				

(Source: m2, Section 2.7, page 5-6)

Table 4 Comparison of PK, Study S08-0179

Comparison	Ratio between ^{(b) (4)} and reference drugs (%)	
	Point estimate (mean)	90% confidence interval
^{(b) (4)} Hycodan AUC_{0-inf} C_{max}	^{(b) (4)}	
^{(b) (4)} chlorpheniramine AUC_{0-inf} C_{max}		
^{(b) (4)} pseudoephedrine AUC_{0-inf} C_{max}		

(Source: m2, Section 2.7, page 8)

Reviewer comment:

This drug development program is a clinical pharmacology program. The proposed drug product Rezira^{(b) (4)} depends on the bioequivalence to the reference drug product Hycodan and to OTC monograph drug pseudoephedrine to support its efficacy and safety. In a pre-IND meeting discussion, the Agency agreed that the clinical pharmacology requirements for the proposed hydrocodone and pseudoephedrine oral solution (Rezira^{(b) (4)}) can be supported by the study conducted for the hydrocodone, chlorpheniramine, and pseudoephedrine oral solution (^{(b) (4)}) provided that there were no major differences between two formulations [Pre-IND Meeting Minutes, February 6, 2008]. The proposed Rezira^{(b) (4)} formulation is exactly the same as that of the ^{(b) (4)} formulation except that Rezira-^{(b) (4)} contains no chlorpheniramine.

The results of study S08-0179 shows that the hydrocodone component in ^{(b) (4)} is not bioequivalent to the reference drug Hycodan, because the ratio of C_{max} between ^{(b) (4)} and Hycodan was outside of the bioequivalence range of 80 - 125%. In a communication the Applicant stated that “no well defined therapeutic range or C_{max} concentration threshold has been established for the hydrocodone therapeutic effect” and the lower confidence interval of C_{max} in ^{(b) (4)} “reduces the possibility of any safety concerns.” [NDA 22-439, Facsimile, June, 9, 2009]. The Applicant’s statement is true in that the exposure-response relationship for hydrocodone has not been well established. But this fact only further emphasizes the importance that the proposed drug product should be bioequivalent to the reference drug Hycodan. Clinical studies are necessary to support the efficacy and safety of the proposed drug product.

6 INTEGRATED REVIEW OF EFFICACY

This application is supported by the bioequivalence of the proposed drug product and the approved hydrocodone product (Hycodan Syrup) and OTC monograph drug pseudoephedrine. No clinical efficacy studies were conducted to support this application.

6.1 Indication

The proposed indication for this product follows below:

Rezira^{(b) (4)} Oral Solution is for ^{(b) (4)} relief of cough and for the ^{(b) (4)} relief of nasal congestion due to the common cold.

7 INTEGRATED REVIEW OF SAFETY

The Applicant submitted an Overview of Safety including the safety data from the clinical pharmacology study S08-0179, post-marketing spontaneous adverse events report, and literature survey. The safety was assessed through adverse events in Study S08-0179. The safety data from this clinical pharmacology study in adult subjects did not identify a safety signal. Study S08-0179 was conducted in only 28 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 and pseudoephedrine [m2, Section 2.7.4, pages 19 - 25].

The AERS database search used terms of hydrocodone (HC), hydrocodone plus acetaminophen (HC/ACT), hydrocodone plus other ingredients, pseudoephedrine (PSE), and pseudoephedrine plus other ingredients. 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.

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), a 120-day safety update including data from clinical studies, animal studies, and other sources is required for a NDA submission. However, there are no animal studies and clinical safety studies conducted for the test drug and the test drug has not been manufactured and marketed. The Applicant did not submit a safety update. This reviewer does not expect new safety information for the test drug.

7.1 Methods and Findings

7.1.1 Deaths

There was no death in the clinical pharmacology study S08-0179 in this application. The Applicant searched the AERS database for the terms of hydrocodone (HC), hydrocodone plus acetaminophen (HC/ACT), hydrocodone plus other ingredients, pseudoephedrine (PSE), and pseudoephedrine plus other ingredients. Table 5 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/ACT	HC/other	PSE	PSE/other
Total adverse events	37	160	6	40	29
<6 years	1	1	0	15	9
6-<12 years	0	0	1	0	7
≥12 years	28	88	4	21	6
Age unknown	8	71	1	4	7
Death	29	123	1	33	7
Suicide	12	94	1	6	0
Misuse/overdose/error	8	11	0	12	3

(Source: m2, Section 2.7.4, page 21)

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. There were 33 and 7 death reports for pseudoephedrine and pseudoephedrine plus other ingredients, respectively. The data also reflect a large portion of suicide cases in pseudoephedrine use.

Reviewer 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 safety signals.

7.1.2 Other Serious Adverse Events

There was no serious adverse event occurred in the clinical pharmacology study S08-0179 in this application.

The search of the AERS database covering the period from October, 2007 through March, 2008 did not identify new safety signals for hydrocodone, chlorpheniramine, and pseudoephedrine.

7.1.3 Dropouts and Other Significant Adverse Events

A total of 28 healthy volunteers were enrolled into the clinical pharmacology study S08-0179, and 25 subjects completed the study. One subject withdrew from the study due to work schedule. Two subjects dropped out due to a positive drug screen test and missing the blood collection. There was no dropout or withdrawal due to adverse events. 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 S08-0179, there were 8 subjects reported 27 adverse events over the course of the study (Table 6). One adverse event (headache) occurred before the subject received any treatment. The Hycodan group had the highest incidence (16 out of 27 AEs) of adverse events and the ^(b)₍₄₎ group had only one adverse event. Dizziness was the most

common adverse event (8), followed by headache (5), nausea (4), and puncture site pain (4). All adverse events were mild or moderate in nature. Eighteen adverse events spontaneously resolved without special treatment, and 9 adverse events received symptomatic treatments and resolved.

The case report review revealed that there were 4 males and 4 females aged from 19 to 46 years old reported adverse event in the study. In terms of race/ethnicity, there were 7 whites and one Native American. Noticeably, 13 of the 27 reported adverse events in study S08-0179 were from one subject who was a 38 years female Native American. This subject received all 4 treatment drugs in 4 crossover periods and had 13 adverse events, including multiple reports of dizziness, vessel punctation pain, headache, nausea, tremor, and hyperhidrosis. Eight of the 13 adverse events were occurred while this subject received the reference drug Hycodan.

Table 6 Adverse events in study S08-0179

Adverse event*	^(b) ₍₄₎ (N=26)	Pseudoephedrine (N=26)	Chlorpheniramine (N=27)	Hycodan (N=27)	Total (N=28)
Subjects with AEs	1	2	3	5	8
Somnolence			1		1
Puncture site pain#			4		4
Headache [^]		1	2	2	6
Nausea				4	4
Dizziness		1		7	8
Hyperhidrosis				1	1
Dry mouth	1			1	2
Tremor				1	1
Total	1	2	7	16	27

* MedDRA preferred term version 11

Vessel punctured in collecting blood sample

[^] One subject reported headache before receiving any treatment

(Source: m2, Section 2.7.4, page 11)

Reviewer 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 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 hydrocodone¹. 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 2005². Although hydrocodone dosages as an antitussive are much lower than that of analgesics and illicit drugs, hydrocodone-containing medications should be prescribed and administered with caution.

Pseudoephedrine is a sympathomimetic amine used as an oral nasal decongestant. It can be unlawfully used to make illicit drug methamphetamine³. The Combat Methamphetamine Act, signed into law by President Bush on March 9, 2005, restricts the access of pseudoephedrine by requiring retailers to place drug products with pseudoephedrine behind the counter, limiting a person's daily and monthly purchases, and requiring buyers' identification and signature for each purchase. The potential of unlawfully using pseudoephedrine in the proposed drug to make methamphetamine is addressed by the access restriction required in the Combat Methamphetamine Act.

The proposed ^(b) ⁽⁴⁾ (hydrocodone, chlorpheniramine and pseudoephedrine) 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 milk⁴. 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

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 www.streetdrugs.org, accessed on March 5, 2009

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

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 ^(b)₍₄₎ with caution.

7.1.16 Overdose Experience

There is no overdose experience reported in the clinical pharmacological study S08-0179. The Applicant searched the AERS database covering the period from October 2007 through March 2008 and the result showed that overdose/misuse/error were frequently reported as adverse events associated with hydrocodone and pseudoephedrine 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 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 ^(b)₍₄₎ ^(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 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 Rezira^(b)₍₄₎ 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 and hydrocodone drug products, including approved and unapproved drug products containing hydrocodone as antitussives and analgesics.

Reviewer comment:

The post-marketing adverse event data search from AERS did not identify a new safety signal for hydrocodone, pseudoephedrine, and chlorpheniramine.

7.2 Adequacy of Patient Exposure and Safety Assessments

In the clinical pharmacology study S08-0179, a total of 28 healthy, adult subjects aged 18 to 54 years received a single dose of 5 mL ^(b) Oral Solution (HC 5mg/CPM 4 mg/PSE 60 mg), 5 mL PSE solution (60 mg), 5 mL CPM solution (4 mg), or 5 mL Hycodan (HC 5 mg/homatropine 1.5 mg). There were 8 subjects who reported 27 adverse events in the study. These adverse events were mild or moderate in nature and majority of the adverse events resolved spontaneously without special treatment.

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 [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, pseudoephedrine and chlorpheniramine. 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 in 28 healthy subjects. The study was small in size and 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 pseudoephedrine. The AERS database and literature search revealed no new safety signals for hydrocodone and pseudoephedrine at proposed doses. Given the extensive experience with use of hydrocodone as an antitussive and pseudoephedrine as a nasal decongestant, this reviewer concludes that the overall clinical exposure to the proposed drug is adequate.

7.2.9 Additional Submissions, Including Safety Update

There are no additional submissions including safety update received for this application.

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), a 120-day safety update including data from clinical studies, animal studies, and other sources is required for a NDA submission. However, there are no animal studies and clinical safety studies conducted for the proposed drug and the proposed drug has not been manufactured and marketed. The Applicant did not submit a safety update. This reviewer does not expect new safety information for the proposed drug.

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 Rezira^(b)₍₄₎ Oral Solution. The proposed drug product contains 5 mg hydrocodone bitartrate and 60 mg pseudoephedrine hydrochloride per 5 mL. It is proposed as a prescription drug combination of antitussive and decongestant. The proposed indications are “for ^(b)₍₄₎ relief of cough and the ^(b)₍₄₎ relief of nasal congestion due to the common cold.” The proposed dosage is ^(b)₍₄₎ (5 mL) every 4 to 6 hours as needed, not to exceed (NTE) 4 doses (20 mL) in 24 hours for adult ^(b)₍₄₎

8.2 Drug-Drug Interactions

The result of clinical pharmacology study S08-0179 showed that the subjects’ exposure for hydrocodone in the proposed drug hydrocodone 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 pseudoephedrine, hydrocodone and other ingredients in the proposed drug formulation. There were no differences in pseudoephedrine exposure between ^(b)₍₄₎ Oral Solution and the OTC monograph pseudoephedrine solution. More information regarding possible drug-drug interaction affecting the hydrocodone exposure in the ^(b)₍₄₎ Oral Solution may be found in the Clinical Pharmacology Review [NDA 22-439/NDA 22-442, Clinical Pharmacology Review, Sheetal Agarwal, Ph. D.].

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.

8.3 Special Populations

There were no studies in special populations for Rezira^(b)₍₄₎ 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₎

^(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 Rezira^(b)₍₄₎ 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 when it is considered for approval.

8.4 Pediatrics

The clinical pharmacology study S08-0179 included no pediatric subjects. The Applicant conducted the post-marketing adverse event search in AERS for hydrocodone, chlorpheniramine, and pseudoephedrine 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 frequently reported in pediatric age groups of under 6 and 6 to 12 years of age for pseudoephedrine drugs, because pseudoephedrine 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 pseudoephedrine 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. FDA has received reports of life-threatening adverse events and death in patients, including children, who have received 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>].

The Applicant is requesting a ^(b)₍₄₎

^(b)₍₄₎

^(b)₍₄₎

The prescription only status and the labeling indications of this drug will limit the exposure of the drug in pediatric population. The safety of hydrocodone in patients 6 years of age and older is established by DESI review. The safety of pseudoephedrine in patients down to age 2 is established by OTC monograph.

(b) (4)

8.6 Literature Review

Hydrocodone has been approved as an antitussive for more than 50 years. The proposed drug product is relying on the reference drug Hycodan (NDA 5-213, approved on March 23, 1943) to support the efficacy and safety of hydrocodone^{1,2}. Clinical studies have demonstrated the effectiveness and safety of hydrocodone in treatment of cough symptom in cancer patients³. OTC monographs, Cochran reviews, and controlled trials have demonstrated that pseudoephedrine^{4,5} are safe and effective as a decongestant in treatment of symptoms of common cold and allergic rhinitis.

Reference

1. Endo Pharmaceuticals. HYCODAN (Hydrocodone Bitartrate and Homatropine Methylbromide) Tablet and Syrup Prescribing Information. 2003.
2. Eddy NB, Halbach H, Braenden OJ. Synthetic substances with morphine-like effect: clinical experience; potency, side-effects, addiction liability. Bull World Health Organ 1957; 17(4- 5):569-863.
3. Homsy J, Walsh D, Nelson KA, Sarhill N, Rybicki L, Legrand SB et al. A phase II study of hydrocodone for cough in advanced cancer. Am J Hosp Palliat Care 2002; 19(1):49-56.
4. Taverner D, Latte J. Nasal decongestants for the common cold. Cochrane Database Syst Rev 2007;(1):CD001953.
5. Facts and Comparisons 4.0. Oral Monograph: Pseudoephedrine HCl. Available at: http://online.factsandcomparisons.com/MonoDisp.aspx?monoID_fandc-hcp12309&#monoTab. 2007.

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 Rezira^(b)₍₄₎ Oral Solution is expected being similar to the risks of other hydrocodone-containing antitussives. In a consult for another hydrocodone containing drug product ^(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 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.

No special post-marketing risk management plan is recommended at this time since the recommended regulatory action is Complete Response.

9 OVERALL ASSESSMENT

9.1 Conclusions

The Applicant seeks the approval of Rezira^(b)₍₄₎ Oral Solution. The proposed drug product is an immediate release oral solution, containing 5 mg hydrocodone bitartrate and 60 mg pseudoephedrine hydrochloride per 5 mL. It is proposed as a prescription drug combination of antitussive and decongestant. The proposed dosage is ^(b)₍₄₎ (5 mL) every 4 to 6 hours, not to exceed (NTE) 4 doses (20 mL) in 24 hours for adults ^(b)₍₄₎

Pseudoephedrine is an OTC monograph drug, being considered to be generally recognized as safe and effective (GRASE) in specified dose as an oral nasal decongestant. The monograph considers the combination of any single monograph oral antitussive drug (such as codeine phosphate) with any single nasal decongestant (such as pseudoephedrine) to be a permitted combination [21 CFR 341.40].

Hydrocodone, a schedule controlled substance and a prescription drug, is not an OTC monograph antitussive. Therefore, the proposed combination of hydrocodone/pseudoephedrine 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 hydrocodone with an OTC monograph product. The FDA has previously determined that clinical studies are not necessary for the combination of hydrocodone and a permitted OTC monograph ingredient. Based on this policy, the Division has approved drug development programs for hydrocodone and OTC monograph product combinations, concluding that a drug development plan does not need to establish the efficacy, safety, or the contribution of hydrocodone or an OTC monograph ingredient to the efficacy and safety of the combination product.

The development program for the proposed drug product is a clinical pharmacology program. No clinical efficacy studies were submitted to support this application. The proposed drug product Rezira^(b)₍₄₎ Oral Solution depends on the bioequivalence to the reference drug product Hycodan and to OTC monograph drug pseudoephedrine to support its efficacy and safety. The clinical pharmacology study submitted in this application showed that the hydrocodone component in the proposed combination drug product is not bioequivalent to the reference drug Hycodan, because the ratio of C_{max} between the proposed combination drug and Hycodan was

outside of the bioequivalence range of 80 - 125%. Clinical efficacy and safety studies are necessary to support the proposed drug product.

The safety data from the clinical pharmacology study in adult subjects did not identify a safety signal. Because of the small number of the subjects, there was no meaningful information in differences of adverse events in gender, age, and race/ethnicity. The Applicant's search of the AERS database for adverse events related to hydrocodone and pseudoephedrine identified no new safety signals.

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 ^(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 to place such abuse potential studies as a post-marketing requirement after the proposed hydrocodone containing drug product obtained the approval.

9.2 Recommendation on Regulatory Action

The proposed drug product Rezira^(b)₍₄₎ Oral Solution is not ready for approval in the present NDA submission and I recommend that the application be given a Complete Response Action.

The development program for the proposed drug product is a clinical pharmacology program. No clinical efficacy studies were submitted to support this application. The proposed drug product Rezira^(b)₍₄₎ Oral Solution depends on the bioequivalence to the reference drug product Hycodan and to OTC monograph drug pseudoephedrine to support its efficacy and safety. The clinical pharmacology study submitted in this application showed that the hydrocodone component in the proposed combination drug product was not bioequivalent to the reference drug Hycodan, because the ratio of C_{max} between the proposed combination drug product and Hycodan was outside of the bioequivalence range of 80 - 125%. Clinical efficacy and safety studies are necessary to support the proposed drug product.

9.3 Recommendation on Postmarketing Actions

No special post-marketing risk management activities are recommended at this time since the recommended regulatory action is Complete Response.

9.4 Labeling Review

The proposed package insert was submitted in Physician's Labeling Rule (PLR) format. The Division of Medication Error Prevention and Analysis at the Office of Surveillance and Epidemiology (DMEPA/OSE) has been consulted regarding the product labeling and the

Clinical Review, Xu Wang, M.D., Ph.D.

NDA 22-442, N-000, Rezira^(b)₍₄₎ Oral Solution (hydrocodone bitartrate and pseudoephedrine hydrochloride)

proposed trade name ^(b)₍₄₎ Oral Solution. The Applicant withdrew the request for the proprietary name review of ^(b)₍₄₎ in a letter dated January 29, 2009.

Brief labeling review revealed the following sections need to be revised. Additions are shown underlined, and deletions are shown in strikeout. These will need to be addressed at the time the application is considered for approval.

- Revise the INDICATIONS AND USAGE section as follows:

^(b)₍₄₎

9.5 Comments to Applicant

Deficiency comments will be sent to the applicant in the complete response letter.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22442	ORIG 1	CYPRESS PHARMACEUTICA L INC	REZIRA ^(b) ₍₄₎ (HYDROCODONE BITARTRATE AND PSEU

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

/s/

XU WANG
07/29/2009

LYDIA I GILBERT MCCLAIN
07/29/2009

1. GENERAL INFORMATION

This is a 505(b)(2) application for an immediate release oral solution combination product containing hydrocodone bitartrate and pseudoephedrine hydrochloride (5 and 60 mg, respectively, per 5 ml). The sponsor is Cypress Pharmaceutical Inc. The proposed name for the product is Rezira^{(b) (4)} Oral Solution. The proposed indication is for ^{(b) (4)} relief of cough and the ^{(b) (4)} relief of nasal congestion due to the common cold. This NDA references NDA 22-439 for ^{(b) (4)} Oral Solution. ^{(b) (4)} contains hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride (5, 4, and 60 mg, respectively, per 5 ml).

As a basis for the 505(b)(2) submission route, the applicant cites the following reference listed drugs (RLDs) and OTC monographs: 1) Hycodan Tablets and Syrup (NDA 005-213, Endo Pharmaceuticals), 2) Tussionex Extended-Release Suspension (NDA 019-111, UCB, Inc.), 3) Advil Allergy/Sinus Tablets (NDA 021-441, Wyeth Consumer Products), 4) Mucinex D Tablets (NDA 021-585, Adams Respiratory Therapeutics), 5) Tavist Allergy/Sinus/Headache Tablets (NDA 021-082, Novartis), and 6) 21 CFR 341.20 for pseudoephedrine hydrochloride.

The intended holder of this NDA is Cypress; however, the approved product will be marketed by Hawthorn Pharmaceuticals, Inc. Hawthorn is a wholly owned subsidiary of Cypress.

Cypress is requesting a priority review of the application in order to fulfill the market need for an approved hydrocodone/decongestant combination product.

The application is provided electronically.

Reviewer comment:

This application does not qualify for a priority review. Products regulated by CDER are eligible for priority review if they provide a significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease (Draft Guidance for Industry on Available Therapy, Feb 2002). Hydrocodone and pseudoephedrine are currently marketed cough and cold products. In addition, all proposed products provide symptomatic relief only and do not treat the underlying disease process.

1. CLINICAL DEVELOPMENT PROGRAM

Based on a pre-IND meeting with DPAP, the applicant conducted a single pharmacokinetic study (S08-0179) with ^{(b) (4)} in healthy adult volunteers that was intended to support both of the NDAs for ^{(b) (4)} and for Rezira^{(b) (4)}. The objectives of the study were: 1) to determine bioequivalence of hydrocodone in ^{(b) (4)} with Hycodan, 2) to determine the drug-drug interaction of pseudoephedrine with hydrocodone and chlorpheniramine in ^{(b) (4)} and 3) to determine the drug-drug interaction of chlorpheniramine with hydrocodone and pseudoephedrine in ^{(b) (4)}.

Reviewer comment:

The submitted clinical trial (S08-0179) is also intended to support NDA 22-442 for ^{(b) (4)} Oral Solution. NDA 22-442 was submitted at the same time as NDA 22-439. Separate clinical reviews will be written for the two applications. However, because the applications are so closely related, regulatory review meetings for the two applications will be conducted in tandem.

2. FOREIGN MARKETING AND REGULATORY HISTORY

Cypress submitted the opening IND for Rezira on April 15, 2008 (IND 102,177). A pre-IND meeting for this application was held on January 14, 2008 as IND (b)(4) with the Division of Pulmonary and Allergy Products (DPAP). In the pre-IND meeting, the applicant proposed (b)(4) : 1) liquid solution products containing pseudoephedrine (b)(4), developed under IND 102,177, (b)(4)

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.
- A specific food effect study need not be conducted for this application provided that a food effect study is submitted for the (b)(4)

In 2007, FDA ordered companies making unapproved hydrocodone drug products to cease the manufacturing of such products on or before December 31, 2007, and for those companies marketing unapproved hydrocodone products labeled for use in children younger than 6 years of age to stop manufacturing and distributing the products by October 31, 2007.

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.

It is unclear if Rezira was ever marketed in the US as an unapproved product. If it was, the Applicant should provide safety information and marketing history.

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 (provided under NDA 22-439)
 - S08-0179 [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 (provided under NDA 22-439) [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 (provided under NDA 22-439) [m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study-report-s08-0179\crfs]
- Financial disclosure (provided under NDA 22-439) [m1\13-administrative-information\134-financial-certification-disclosure]

Reviewer comment:

The applicant has requested a (b) (4) (b) (4)

(b) (4) (b) (4)
Hycodan is approved in (b) (4)
children aged 6 and above, (b) (4). Further, on October 8, 2008, FDA released a statement supporting voluntary action of the Consumer Healthcare Products Association eliminating use of OTC cough and cold medications in children under the age of 4 years. Although the waiver does not specifically request it, the applicant is also seeking a waiver from pediatric studies (b) (4). The clinical study performed enrolled healthy volunteers aged 18-65 years. In the pre-IND meeting held for this product, DPAP agreed that submission of a waiver request was appropriate.

4. CLINICAL STUDIES

There was a single clinical bioavailability and drug-drug interaction study conducted for the drug development program of Rezira (b) (4). The study report is submitted under NDA 22-439 (b) (4) and is appropriately indexed to allow review. A summary of the study follows.

Study S08-1079

Study S08-1079 was a single center, single dose, 4-period crossover, relative bioavailability and drug-drug interaction study. Study arms included: 1) hydrocodone, pseudoephedrine, and chlorpheniramine oral solution (5 mg/60 mg/4 mg; (b) (4) 2) pseudoephedrine oral solution (60 mg/5 ml), 3) chlorpheniramine oral solution (4 mg/5 ml), and 4) Hycodan Syrup (5 mg hydrocodone bitartrate/1.5 mg homatropine methylbromide per 5 ml). The study was performed under fasted conditions. A total of 28 healthy volunteers were enrolled, and 25 completed. The following pharmacokinetic variables were calculated for each treatment: AUC_{0-t} , AUC_{0-inf} , C_{max} , T_{max} , Kel , and $T_{1/2}$. For the log-transformed hydrocodone data, the 90% confidence intervals about the ratio of the test geometric mean to reference geometric mean are within the 80-125% limits for AUC_{0-t} and AUC_{0-inf} , but not for C_{max} , which falls below the limit (lower bound of the CI (b) (4)). For the log-transformed pseudoephedrine and chlorpheniramine data, the sponsor reports that the 90% confidence intervals about the ratio of the test geometric mean to reference geometric mean are within the 80-125% limits for AUC_{0-t} , AUC_{0-inf} , and C_{max} . Nausea and headache were the most common adverse events reported in the study.

Reviewer comment:

The hydrocodone component of Rezira does not meet the 90% confidence interval of 80-125% for C_{max} versus Hycodan. This may represent a significant issue for approvability of this product.

In addition, no food effect study was submitted. In the pre-IND meeting, it was noted that a food effect study conducted (b) (4)

5. BRIEF REVIEW OF PROPOSED LABELING

Proposed package labeling has been included in this submission with annotation noting comparator products from which specific paragraphs were derived. A brief review of the proposed labeling was performed. The majority of the proposed label was taken from the following sources: 1) Hycodan, 2) pseudoephedrine monograph, 3) Tussionex Pennkinetic, and 4) Codeprex Pennkinetic. A brief description of the pharmacokinetic study performed with ^(b)₍₄₎ is included in Section 12.3 Pharmacokinetics, and specific drug and packaging information is provided in Section 11 Description and Section 16 Storage and Handling.

Reviewer comment:

A careful review of the labels from the comparator products will be required in order to assure that all pertinent information is included in the Rezira label. No particular labeling concerns are raised in this initial review. The carton/container labels contain a simple purple and blue design that does not interfere with the tradename.

6. DSI REVIEW AND AUDIT

The clinical team is not requesting DSI audit as part of this application. The clinical pharmacology team has requested a DSI audit of the sites for the clinical pharmacology study S08-0179 as part of NDA 22-439.

Cetero Research [clinical site]
400 Fountain Lakes Blvd.
St. Charles, MO 63301

^(b)₍₄₎

7. SUMMARY

This is a 505(b)(2) application for an immediate release oral solution combination product containing hydrocodone bitartrate and pseudoephedrine hydrochloride (5 and 60 mg, respectively, per 5 ml). The sponsor is Cypress Pharmaceutical Inc. The proposed name for the product is Rezira^(b)₍₄₎ Oral Solution. The proposed indication is for ^(b)₍₄₎ relief of cough and the ^(b)₍₄₎ relief of nasal congestion due to the common cold.

As a basis for the 505(b)(2) submission route, the applicant cites the following reference listed drugs (RLDs) and OTC monographs: 1) Hycodan Tablets and Syrup (NDA 005-213, Endo Pharmaceuticals), 2) Tussionex Extended-Release Suspension (NDA 019-111, UCB, Inc.), 3) Advil Allergy/Sinus Tablets (NDA 021-441, Wyeth Consumer Products), 4) Mucinex D Tablets (NDA 021-585, Adams Respiratory Therapeutics), 5) Tavist Allergy/Sinus/Headache Tablets (NDA 021-082, Novartis), and 6) 21 CFR 341.20 for pseudoephedrine hydrochloride.

There was a single clinical bioavailability and drug-drug interaction study conducted for the drug development program of Rezira^(b)₍₄₎. This study was submitted under NDA 21-439 (^(b)₍₄₎) and also supports this application. Study S08-1079 was a single center, single dose, 4-period

crossover, relative bioavailability and drug-drug interaction study. Study arms included: 1) hydrocodone, pseudoephedrine, and chlorpheniramine oral solution (5 mg/60 mg/4 mg; ^(b)₍₄₎ 2) pseudoephedrine oral solution (60 mg/5 ml), 3) chlorpheniramine oral solution (4 mg/5 ml), and 4) Hycodan Syrup (5 mg hydrocodone bitartrate/1.5 mg homatropine methylbromide per 5 ml). The study was performed under fasted conditions. The hydrocodone component of Rezira does not meet the 90% confidence interval of 80-125% for C_{max} versus Hycodan. In addition, a food effect was not determined as part of this study, which was conducted in the fasted state. These findings raise significant concerns regarding the approvability of this application.

Cypress requested a priority review for this application. The application does not qualify for priority review because all of the components of the proposed product are currently marketed cough and cold products. The submission is adequate to allow for clinical review. The submission is filable. Additional information regarding prior marketing status will be requested from the sponsor.

8. REVIEW TIMELINE

The schedule for review is provided in Table 1. Write-up will be concomitant with the review process. Clinical review will focus initially on the pivotal clinical pharmacology study, followed by the integrated summary of efficacy, integrated summary of safety, and any data provided in the 4-month safety update. 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 June 8, 2009, and the review will be finalized July 7, 2009, two months in advance of the action date.

Table 1: Review timeline for NDA 22-439

Milestone	Target date for completion
Filing and planning meeting	December 15, 2008
Clinical pharmacology study S08-0179	January 20, 2009
72-day letter	January 22, 2009
Integrated Summary of Efficacy	January 30, 2009
Integrated Summary of Safety	February 27, 2009
4 month safety update	March 15, 2009
Midcycle review meeting	March 31, 2009
Label	May 1, 2009
Initial draft review complete	June 8, 2009
Wrap-up meeting	June 29, 2009
Final draft review complete	June 30, 2009
Final review complete	July 7, 2009
Division goal date	July 10, 2009
Sponsor teleconference	August 5, 2009
PDUFA Action date (10 months)	September 10, 2009

9. COMMENTS FOR THE SPONSOR

The following comment is to be communicated to the sponsor.

Please supply the following information for utilization in the review process of your application:

- *Any information regarding previous marketing of your product, including safety information and marketing history.*

Additional comments regarding review issues of bioequivalence and food effect will be conveyed by the clinical pharmacology reviewer.

Reviewed by:

Theresa M. Michele, M.D.
Medical Officer, Division of Pulmonary and Allergy Products

Sally Seymour, M.D.
Medical Team Leader, Division of Pulmonary and Allergy Products

cc: Original NDA
HFD-570/Division File
HFD-570/Seymour/Medical Team Leader
HFD-570/Chowdhury/Director
HFD-570/Michele/Medical Reviewer
HFD-715/Li/Biometrics Reviewer
HFD-570/Whitehurst/Pharmacology-Toxicology Reviewer
ONDQA/Shen/CMC Reviewer
OCP/Suarez/Clinical Pharmacology Reviewer
HFD-570/Bowen/CS

	Content Parameter	Yes	No	NA	Comment
	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	
SAFETY					
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 ¹) 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 ² 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

¹ 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.

² 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).

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?		X		No food effect study; this is a review issue
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	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
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
DATASETS					
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			
CASE REPORT FORMS					
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			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
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.

The following comment is to be communicated to the sponsor.

Please supply the following information for utilization in the review process of your application:

- *Any information regarding previous marketing of your product, including safety information and marketing history.*

Additional comments regarding review issues of bioequivalence and food effect will be conveyed by the clinical pharmacology reviewer.

Reviewing Medical Officer

Date

Clinical Team Leader

Date

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

/s/

Theresa M Michele
12/19/2008 09:40:44 AM
MEDICAL OFFICER

Sally Seymour
12/19/2008 09:54:36 AM
MEDICAL OFFICER
I concur.