CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022439Orig1s000

SUMMARY REVIEW

SUMMARY REVIEW FOR REGULATORY ACTION

Date	June 8, 2011
From	Lydia Gilbert-McClain, MD Deputy Division Director Division of Pulmonary, Allergy, and Rheumatology Products
Subject	Summary Review
NDA#	22439
Applicant Name	Cypress Pharmaceutical, Inc.
Date of Submission	December 8, 2010
PDUFA Goal Date	June 8, 2011
Proprietary Name/Established (USAN) Name	Zutripro/hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride
Dosage forms/Strength	Oral Solution/5 mg/4 mg/ 60 mg in each 5 ml
Proposed Indication (s)	(b) (4)
Recommended Action	Approval

Materials Reviewed/Consulted OND Action Package, including:	Names of Discipline reviewers
Medical Officer Review	Xu Wang, MD, PhD
Cross Discipline Team Leader Review	Anthony Durmowicz, MD
Pharmacology Toxicology Review	Grace Lee, PhD
CMC Review	Xiaobin Shen, PhD; Prasad Peri, PhD
Clinical Pharmacology review	Elizabeth Shang, PhD, R. Ph; Suresh Doddapaneni, PhD
DDMAC	Roberta Szydlo
DSI	Sripal R Mada, PhD
OSE/DMEPA	Richard Abate, R. Ph, MS

DDMAC – Division of drug Marketing, Advertising and Communication

DSI = Division of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
CDTL = Cross Discipline Team Leader

1. Introduction

This is the third review cycle for this new drug application from Cypress Pharmaceutical, Inc (Cypress). Cypress originally submitted this new drug application NDA 22-439 under section 505(b)(2) of the FD& C Act on November 6, 2008, for use of a combination oral solution comprised of hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride (b) (4) The clinical support for the application was based entirely on a clinical pharmacology program.

The original clinical pharmacology program failed to demonstrate the bioequivalence requirements to support approval of the application and the application was given a complete response on September 18, 2009. Cypress submitted a complete response on December 10, 2009 in response to the Agency's first Complete Response letter. In this resubmission, Cypress submitted the results of a new clinical pharmacology study; however, the data from that study could not be used to support the NDA due to the findings from the inspections conducted by the Division of Scientific Investigations at the clinical pharmacology study sites. As a result, the application received another Complete Response action in the second review cycle on June 11, 2010. Cypress submitted a complete response to the FDA's Complete Response letter dated June 11, 2010, on December 8, 2010. The PDUFA Goal date for this Complete Response is June 8, 2011. This review will summarize the salient aspects of the application and the basis for the regulatory decision.

Comment [b1]: changed to FDA for consistency in the remaining section of the document

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 initially approved Hydrocodone for use as an antitussive on March 23, 1943 (NDA 05213, 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. Under the DESI review process, the FDA found Hycodan® to be effective for the symptomatic relief of cough and classified it as a new drug product, thus requiring an approved NDA prior to marketing [47 FR 23809, June 1, 1982]. Currently, 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, an approved generic equivalents, and a hydrocodone polistirex and chlorpheniramine polistirex combination extended-release suspension product that is marketed under NDA 19111 as Tussionex®. However, there have been hundreds of unapproved

hydrocodone-containing products marketed illegally as antitussives[1]. Such products include, but are not limited to, hydrocodone in combination with an expectorant (such as guaifenesin), or in combination with a decongestant (such as phenylephrine or pseudoephedrine).

Since FDA determined that hydrocodone bitartrate is a new drug, 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). According to the FR notice, the manufacturing of unapproved hydrocodone-containing products was to cease by December 31, 2007, and shipment of currently marketed and listed unapproved hydrocodone-containing products was to halt by March 31, 2008.

This application is for a combination product containing hydrocodone bitartrate (HC), chlorpheniramine maleate (CPM), and pseudoephedrine hydrochloride (PSE), as an immediate release oral solution containing 5 mg, 4 mg, and 60 mg of HC, CPM, and PSE, per 5 mL respectively. Chlorpheniramine is an antihistamine, and pseudoephedrine is a sympathomimetic amine used for nasal decongestion. Both CPM and PSE are listed in the OTC monograph as permitted combinations (21 CFR 341.40).

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). However, because of the prior regulatory precedent of approving Tussionex Pennkinetic® (the combination of hydrocodone and chlorpheniramine) with clinical only pharmacology data, combination products containing hydrocodone and other monograph active ingredients that are permitted monograph combinations can be developed using a clinical pharmacology program. Therefore, clinical efficacy and safety studies may not be necessary to support this combination product provided that the applicant conducts a satisfactory clinical pharmacology program.

The initial clinical pharmacology studies for this application were conducted using Hycodan® (Endo Pharmaceuticals) as the reference for hydrocodone. Subsequent to the completion and submission of the initial clinical pharmacology studies the manufacturer of Hycodan® discontinued marketing Hycodan® Tablets on Jan 4, 2008 and Oral Solution on May 14, 2008. However, the discontinuation was not 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, and this RLD was used in subsequent clinical pharmacology

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

studies for comparative purposes. The other individual active ingredients CPM and PSE, are monograph products. Since the dose and dosing frequency proposed for these ingredients are consistent with the monograph, we can rely on the monograph to make an assessment of efficacy and safety of these ingredients.

The clinical pharmacology program for this triple combination product also supports the two-ingredient oral solution product (hydrocodone/pseudoephedrine) also under development by Cypress and submitted under NDA 22442. The original NDA for the two-ingredient combination product was submitted on November 7, 2008. Since the two formulations proposed for marketing are exactly the same, except that one product contains chlorpheniramine (NDA 22439) and the other does not (NDA 22442), it is acceptable to use the same clinical pharmacology program to support both NDAs

3. CMC

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

There are no outstanding CMC issues regarding the drug substance or drug product that will affect approvability. All inspections sites are acceptable and the stability data support a 24 month expiry.

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 (Study 11058503) in 112 adult healthy volunteers to evaluate the rate and extent of exposure of hydrocodone bitartrate (HC), chlorpheniramine maleate (CPM), and pseudoephedrine hydrochloride (PSE) compared to the reference product hydrocodone bitartrate syrup (Hi-Tech Pharma). This was an open-label, single-dose, randomized, four period cross-over study under fasted conditions. The results showed that each of the three active ingredients in the formulation was bioequivalent to the reference. The table below summarizes these results (*data source Clinical study report page 36 – 41*).

Table 1: Summary statistics on bioequivalence of hydrocodone, chlorpheniramine, and pseudoephedrine following single dose administration of 5 mL Zutripro (TEST) and individual reference products: Study 11058503

Results for Hydrocodone (n = 98)			
Parameter	TEST	Hydrocodone reference	Ratio of Test/reference (90% CI)
AUC_{0-t} (pg.h/mL)	67540.16	69723.40	0.9687 (0.95, 0.99)
$AUC_{0-\infty}$ (pg h/mL)	69747.27	72063.25	0.9679 (0.94, 0.99)
Cmax (pg/mL)	10290.79	11364.25	0.9055 (0.88, 0.93)
Results for chlorpheniramine (n = 97)			
	TEST	CPM reference	Ratio of test/ref (90% CI)
AUC_{0-t} (pg.h/mL)	159719.12	155681.52	1.02 (0.99, 1.05)
$AUC_{0-\infty}$ (pg h/mL)	181409.61	174224.49	1.04 (1.01, 1.06)
Cmax (pg/mL)	6923.48	6789.48	1.01 (0.99, 1.04)
Results for pseudoephedrine (n = 100)			
	TEST	Pseudoephedrine reference	Ration of test/ref (90% CI)
AUC_{0-t} (pg.h/mL)	1824.27	1813.41	1.006 (0.98, 1.03)
$AUC_{0-\infty}$ (pg h/mL)	1943.05	1926.70	1.008 (0.98, 1.03)
Cmax (pg/mL)	207.17	204.90	1.011 (0.99, 1.01)

Hydrocodone reference: Hi-Tech Pharma's hydrocodone bitartrate/homatropine methylbromide syrup (5 mg/1.5 mg per 5 mL [ANDA 40-613]
Chlorpheniramine reference: Chlorpheniramine maleate oral solution 4 mg/5 mL manufactured by (b) (4) , manufactured for Cypress Pharmaceutical Inc
Pseudoephedrine reference: Pseudoephedrine hydrochloride oral solution, 60 mg/5 mL (manufactured by (b) (4) for Cypress Pharmaceuticals, Inc.)

6. Clinical Microbiology

This is a non-sterile solution product for oral ingestion. The product contains methylparaben and propylparaben (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. 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.

During the first review cycle, a CDER regulatory briefing was held on June 12, 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 regulatory panel concluded that abuse potential assessment was not required for these combination products. These combinations would remain in Schedule III by virtue of the hydrocodone component and would have abuse potential class labeling. Moreover, it is not clear that the information from abuse potential studies will impact scheduling. Additionally, a combination product of hydrocodone and chlorpheniramine (Tussionex Pennkinetic ®) has been on the market for over 20 years and no safety concern has been raised regarding an increase in the abuse potential with this product. However, the regulatory panel noted that a post-marketing signal with these new products could trigger the need for abuse potential studies in the future.

In follow up discussions between Dr. Michael Klein, Director of the CSS, and the DPARP team during the first review cycle, Dr. Klein agreed that signals of abuse, misuse, overdose, and addiction that may arise from post-marketing surveillance could trigger the need to conduct dedicated abuse potential studies post approval; however these studies were not necessary prior to approval.

10. Pediatrics

Cypress' original proposal was (b) (4) a waiver of studies in children less than 6 years of age because of the risk of fatal respiratory depression associated with hydrocodone in children less than 6 years of age. Because of this safety concern, a waiver for pediatric assessment in children 0 to 5 years of age is appropriate and will be granted. Although hydrocodone is currently labeled for use in adults and 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 (6 to 17 years) population. Dose-related respiratory depression including fatalities due to respiratory failure had 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 hydrocodone combination products[2]. In view of this dose-related safety

[2] The use of HYCODAN is not recommended for use in children less than 6 years of age because of the risk of fatal respiratory depression (see **ADVERSE REACTIONS** –**Respiratory Depression**). HYCODAN produces dose-related respiratory depression by directly acting on brain stem respiratory centers: Hycodan® label [Endo Pharmaceuticals; August 28, 2008]

concern, it is appropriate to require the sponsor to establish the appropriate dose of hydrocodone for the pediatric (6 to 17 years) population.

Hydrocodone was approved under DESI review and the dose selection for the pediatric population is not based on PK data in children. The dose of PSE and CPM in the proposed combination product is the same as the dose in the Agency's approved OTC cough/cold monograph. Since the current monograph is still in effect and the proposed doses for the CPM and PSE in the combination solution are the same as the monograph doses, the main concern with the combination product is regarding the appropriate dose of the hydrocodone for the pediatric population. The need for additional PK and safety data for the pediatric (6 to 17 years of age) population was discussed with the applicant and at the Agency's Pediatric Review Committee (PERC) during the second review cycle. The PERC agreed with the waiver of studies in children 0 – 5 years of age and a deferral for pediatric assessment in patients 6 to 17 years of age with the recommendation to incorporate efficacy assessments and population PK in the proposed safety study.

11. Other Relevant Regulatory Issues

Data Quality, Integrity, and Financial Disclosure
There are no outstanding Division of Scientific Investigation (DSI) issues with this application. The DSI conducted an audit for both the clinical study and the bioanalytic sites. Some irregularities were found to which the Applicant provided an acceptable response, and the DSI has concluded that the data from study 11058503 can be used to support the NDA. There is no data integrity, study conduct, or financial disclosure issues with the application.

12. Labeling

Proprietary name

The proposed proprietary name Zutripro has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and found to be acceptable.

Physician labeling

The applicant submitted a label in the Physician's Labeling Rule Format. The label was extensively reviewed in the second review cycle. The applicant submitted labeling in this complete response incorporating all the Division's labeling recommendations. There are no outstanding labeling issues.

Carton and Immediate Container Labels

The carton and immediate container labels were reviewed in consultation with DMEPA and DDMAC and there are no outstanding issues.

Patient Labeling and Medication Guide

The use of Tussionex Pennkinetic Extended-Release Suspension is contraindicated in children les than 6 years of age due to the risk of fatal respiratory depression: Tussionex® label [UCB, Inc. 01/2008]

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

13. Action and Risk Benefit Assessment

Regulatory action

The submitted data from the clinical pharmacology study has established the bioequivalence of Zutripro to the individual reference products. In establishing bioequivalence, the Agency is able to rely on previous determinations of efficacy and safety of hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride for the proposed indications for relief of cough/cold symptoms and upper respiratory allergies. The regulatory action for the application is approval. The wording of the indications has been slightly revised to more accurately reflect the contribution of the individual ingredients in the combination product.

The applicant's initially proposed indications were:

(b) (4)

The indications have been re-worded as follows:

1. Relief of cough and nasal congestion associated with common cold

2. Relief of symptoms including nasal congestion associated with upper respiratory allergies

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.

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. At this time, the abuse potential can be managed by appropriate labeling and routine post-marketing surveillance.

Postmarketing Study Commitments/Requirements

Because of the safety concerns for the pediatric population, Cypress will need to conduct PK and safety studies to evaluate the appropriate dose for patients less than 18 years of age. Cypress will conduct 2 studies: a PK study to assess the pharmacokinetics of each of the active ingredients in Zutripro (HC, CPM, and PSE) in approximately 25 – 35 children 6 to 17 years of age with symptoms of the common cold. The results of this PK study will be used to guide dose selection for the combination product to be evaluated in a second study to assess the safety of Zutripro when used in children ages 6 to 17 years of age. Cypress has agreed to the following post marketing requirements to:

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

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

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

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

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/s/

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06/08/2011
Deputy Division Director