Acting Division Director Review

NDA:	21,369
Product:	Codeprex™ Extended Release Suspension Codeine polistirex/chlorpheniramine polistirex extended release suspension
Sponsor:	Celltech Pharmaceuticals
Route:	Oral
Claim:	Monograph claim for treatment of cough and upper respiratory symptoms associated with allergy or a cold
Date:	1/30/02
Reviewer:	Marianne Mann, Acting Director, DPADP

This is an Acting Division Director's summary of the review of NDA 21,369.

Overview

This NDA is for a combination product containing 40 mg/10 ml codeine and 8 mg/10ml chlorpheniramine provided as an extended release suspension and intended for twice a day use in patients age 6 and older. There are no clinical trials required to establish safety and efficacy for this indication since these ingredients are available as immediate release products under the Tentative Monograph for OTC Cold, Cough, Allergy, Bronchodilator, and Antihistaminic Combination Drug Products and are generally recognized as safe and effective. The sponsor therefore submitted an NDA that relies mainly on chemistry information to establish the quality of the drug product and on biopharmaceutical trials to establish bioequivalence of the extended release product product to the monograph immediate release products. An additional critical aspect of this application is the establishment of in vitro/in vivo correlation so that dissolution specifications can be accurately determined and so that bioequivalence will be assured as drug is released over time to the public. The clinical review of this NDA was limited to a safety overview of the adverse events noted in the bioequivalence trial and a food effect trial, and no specific safety concerns were elicited. Significant concerns are raised, however, in both the chemistry and biopharmaceutical reviews. These concerns will be summarized.

Clinical Pharmacology and Biopharmaceutics

The reviewer noted that the bioequivalence studies performed adequately establish bioequivalence for chlorpheniramine in the new extended release suspension compared to the monograph immediate release product. The reviewer noted that while bioequivalence was established for codeine for AUC, it was not met for Cmax, being somewhat low. Failure to demonstrate bioequivalence for Cmax for codeine, however, was not a major concern regarding the overall safety and efficacy profile of the drug. Furthermore, the food effect study did not show any significant effects on the systemic exposure of both chlorpheniramine and codeine. Thus, these trials, taken alone, would support approval.

There are significant concerns raised otherwise, however, which preclude such an action. The biopharmaceutic reviewer noted with some concern that a Level A in vitro/in vivo

correlation (IVIVC) had not been established clearly for either chlorpheniramine or codeine. For chlorpheniramine, the problem was more modest in that while a reasonable IVIVC modeling was proposed, validation of that modeling had not been obtained. Thus, the reviewer recommended that the sponsor use their food effect study data for external validation of the Level A IVIVC. If validated, the sponsor could then apply the IVIVC to determine dissolution specifications for chlorpheniramine.

For codeine, the reviewer felt the sponsor failed to establish IVIVC, indicating that the in vitro dissolution data cannot accurately predict the in vivo performance. Therefore, the reviewer could not apply IVIVC data to determine dissolution specifications. The reviewer therefore relied on dissolution data of the biobatch immediately after it was produced to determine appropriate specifications, and these were signficantly tighter than those proposed by the sponsor. Furthermore, based on stability data that show significantly decreased release rates of both chlopheniramine and codeine over time, it is clear that these tighter specifications would result in failed batches and an unmarketable drug product.

A very significant issue raised in both the biopharmaceutical review and the chemistry review was a stability concern. Substantial reductions in release rate of both bio- and stability batches for codeine and chlorpheniramine (e.g. ——— reductions in dissolution at 3 hours and 6 hours noted after ———RH). The reviewer felt that it was possible that if the sponsor could establish level A IVIVC for chlorpheniramine (i.e. by validating their proposed model), then this may allow a reasonable determination for in vitro dissolution specifications. The reviewer expressed that for codeine, however, there was no data to assure the in vivo performance of any batch that had a significantly reduced release profile for codeine. Thus, the reviewer felt a shelf-life would clearly need to be ——— depending on storage conditions, which is not feasible for marketing.

Chemistry

An extensive number of CMC deficiencies were noted by Dr. Shah in his review. One of the more serious concerns he notes is that the data demonstrate a rather significantly decreased release rate for both chlorpheniramine and codeine over time as drug is stored at various conditions. The sponsor's proposed specifications for codeine and chlorpheniramine release rates for the final drug product were quite broad and were not supported. Dr. Shah therefore asks the sponsor to provide appropriate IVIVC data for all lots beyond their release and through the proposed shelf-life of the drug product to demonstrate that the product will remain bioequivalent over time ——— and at various conditions of storage (——— . In the absence of IVIVC data, he proposes the sponsor use the release ranges that are observed for codeine and chlorphenriamine at release as acceptable dissolution criteria. It is clear that if the sponsor were to use the latter data, they would fail to have a marketable drug product as the shelf life would be too limited. Therefore, in the absence of IVIVC data that supports broader specifications, it is very possible that the sponsor may need to reformulate their drug product in order to address these significant issues.

Summary and Conclusions

In summary, the critical deficiency in this review is that we cannot assure that the drug product to be marketed will provide a safe and effective profile when used clinically. Additional work, possibly involving reformulation of the drug product, may be necessary to address these deficiencies. Finally, if reformulation of the drug product is significant, we may require repetition of the clinical studies to again demonstrate bioequivalence and/or lack of food effect.

Marianne Mann, M.D.
Acting Director, DPADP

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/s/

Marianne Mann
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MEDICAL OFFICER

DIVISION DIRECTOR'S MEMORANDUM

Date: June 21, 2004

To: NDA 21-369

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Drug products, HFD-570

Product: Codeprex Pennkinetic (codeine polistirex and chlorpheniramine polistirex) Extended-Release Suspension

Applicant: Celltech Pharmaceuticals, Inc.

Administrative and Introduction

Celltech Pharmaceuticals, Inc., submitted NDA 21-369 for Codeprex Pennkinetic (codeine polistirex and chlorpheniramine polistirex) Extended-Release Suspension as a 505(b)(2) application on April 13, 2001. An approvable action was taken on the application on February 13, 2002, because of various problems with the formulation, particularly because the product failed to demonstrate consistent dissolution and release profile over the shelf life, and in vitro/in vivo correlation (IVIVC) could not be established for the formulation. To address the problems the applicant changed the target coating range of the product, and conducted three new clinical pharmacology studies to support the product. On December 19, 2003, the applicant submitted a complete response, which is the subject of this action. The formulation problems are resolved and the new data support approval of this application.

Each teaspoonful (5 mL) of Codeprex Extended-Release Suspension contains codeine polistirex equivalent to 20 mg of codeine and chlorpheniramine polistirex equivalent to 4 mg chlorpheniramine. The product is proposed to be sold as a prescription drug for use in patients 6 years of age and older for temporary relief of cough, as may occur with the common cold or inhaled irritants, and for the temporary relief of runny nose, sneezing, itching of the nose and throat, and itchy watery eyes due to hay fever, other upper respiratory allergies, or allergic rhinitis. The indication language conforms to the monograph language of the two active components – codeine and chlorpheniramine. Immediate release formulations of codeine and chlorpheniramine are listed in the monograph for cold, cough, allergy, bronchodilator, and antiasthmatic drug products for over-the-counter human use (21 CFR 341). Codeprex will be a prescription product because the concentration of codeine 4 mg/mL in the formulation is greater than the 2.2 ng/mL limit for exemption of codeine from prescription requirements (21 CFR 290.2). The product will be classified as a Schedule C-III prescription product in accordance with 21 CFR 1308.13(e)(2).

Chemistry, Manufacturing, and Controls, and Establishment Evaluation
Codeprex Extended-Release Suspension is a pink to purple-pink colored, cherry-cream flavored, aqueous oral suspension containing codeine polistirex, chlorpheniramine polistirex, and excipients. The CMC issues that precluded approval during the previous cycle are resolved with implementation of several changes in the manufacturing process including a narrower target coating range that originally proposed for the coating of PEG-treated codeine polistirex with ethyl cellulose to produce a stable, reproducible, and predictable suspension that does not change significantly over time. The DMFs associated with the manufacture of drug substances are adequate. All manufacturing sites related to this application have acceptable evaluation status. The CMC team has recommended an approval action on this application, and I concur with that recommendation.

One major CMC review issue was the presence of the degradant ——— in the Codeprex drug product. ——— has a structural alert and is a common degradant in many opiate drug products. This issue has been resolved by limiting the amount of ——— in Codeprex, the drug product, to the lowest level that is technically feasible, at or below —— (the LOQ of the assay). Celltech has committed to conduct genetic toxicity tests with ——— as a Post Marketing Study Commitment and further limit the level of ——— if the genetic toxicity test results are positive. There are also some minor CMC issues that will not impact the safety or efficacy of the drug product, which the applicant has agreed to resolve post-approval. These are discussed in detail in Dr. Shah's review and are also listed in the action letter.

Clinical Pharmacology and Biopharmaceutics, and Clinical
The applicant submitted results of three new clinical pharmacology studies with this submission, as well as a summary of safety data with the original submission and later updates. The three clinical pharmacology studies were conducted in healthy adult volunteers. The studies were designed to show bioequivalence of Codeprex Extended-Release Suspension to reference immediate-release solution after a single dose (Study COD03-01) and at steady state (Study CD00900), and to assess the effect of high fat high calorie diet on the absorption of codeine and chlorpheniramine from Codeprex Extended-Release Suspension (Study 00800). The Cmax and AUC data from the three studies are shown in Table 1. For all three studies the 90% CI were within the accepted 80% to 125% bioequivalence limit for the AUC data, which is relevant for comparison between immediate-release and extended-release formulations. The clinical pharmacology studies were reviewed in depth by the Office of Clinical Pharmacology and Biopharmaceutics (OCBP) Reviewer Dr. Kim, and all submitted studies and additional safety data were reviewed by Medical Officer Dr. Lee. The OCBP team concluded that the pharmacokinetic profiles are sufficient to support approval of Codeprex Extended-Release Suspension, and I concur with that conclusion. Dr. Lee also concluded that the overall safety data are sufficient to support approval, and I concur with that conclusion.

Controlled Substance Staff (HFD-009) was consulted to review the drug abuse related sections of the proposed labeling. All recommendation from the Controlled Substance Staff Consultation was incorporated in the label.

Table 1. Ratio between test and reference products (test/reference) for arithmetic mean values of codeine and chlorpheniramine from various studies

		Codeine		Chlorpheniramine	
	PK parameter	Point estimate	90% CI	Point estimate	90% CI
Study COD03-01 (Single dose) *					
	Cmax	[redacted]	73.0-85.5	[redacted]	61.9-67.7
	AUC inf	0.89	82.5-95.0	0.85	81.0-89.8
Study CD00900 (Steady state) *					
	Cmax	[redacted]	87.7-98.2	[redacted]	85.6-93.8
	AUC 0-12hr,ss	1.04	99.2-108.9	0.92	88.7-95.9
Study CD00800 (Food effect)					
	Cmax	[redacted]	108.4-124.2	[redacted]	95.4-104.0
	AUC inf	1.12	107.4-117.4	1.01	95.8-105.8

* Reference drugs: codeine 20 mg / chlorpheniramine 4 mg / 5 mL immediate release solution every 6 hours for 2 doses

† Reference drugs: codeine 20 mg / chlorpheniramine 4 mg / 5 mL immediate release solution every 6 hours for 26 doses

Pharmacology and Toxicology

The applicant did not conduct any new preclinical studies for this application because the active components of Codeprex Extended-Release Suspension are listed in the monographs.

Data Quality, Integrity, and Financial Disclosure

The Division of Scientific Investigation (DSI) conducted inspection of one study center that conducted Study COD-02002, which was part of the original submission, and the center that conducted the analysis of the study. The study center was [redacted], and the analysis center was [redacted] No serious deficiencies were noted in either of the centers, and DSI recommended acceptance of the data. None of the centers that conducted the three subsequent studies that were submitted with this complete response was inspected by DSI. During review of these studies no issues with data quality and integrity were noted. All studies were conducted in accordance with accepted ethical standards. No financial disclosure issues were present.

Pediatric Considerations

The applicant is proposing use of Codeprex Extended-Release Suspension in patients 6 years of age and older and has not submitted a development program for patients below 6 years of age. The product is likely to be used by children below 6 years of age because the dosage form is suitable for administration to younger children and the disease exists below 6 years of age. Therefore, the applicant will be asked to submit pediatric studies in children below 6 years of age within the next three years.

Product Name
The product name Codeprex Pennkinetic Extended-Release Suspension was found to acceptable by the review teams of this Division, and the Division of Medication Errors and Technical Support (DMETS) of the Office of Drug Safety. The word "Pennkinetic" has been used by the same company as a part of the drug product name for a similar product, Tussionex Pennkinetic (hydrocodone polistirex and chlorpheniramine polistirex) Extended-Release Suspension.

Labeling
The label submitted by Celltech Pharmaceuticals has been reviewed by all relevant disciplines of this Division, the Division of Medical Errors and Technical Support, of the Office of Drug Safety, Controlled Substance Staff, and the Division of Drug Marketing, Advertising, and Communications. The Division and Celltech Pharmaceuticals have agreed on a final labeling text.

Action
The clinical pharmacology data and clinical safety data are sufficient to support approval of Pennkinetic Extended-Release Suspension for use in patients 6 years of age and older for temporary relief of cough and for temporary relief of symptoms of allergic rhinitis. Therefore, the action on this application will be APPROVAL.

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/s/

Badrul Chowdhury
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MEDICAL OFFICER