Center for Drug Evaluation and Research

APPLICATION NUMBER:
21-369

MEDICAL REVIEW

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 21-369	TRADE NAME:	Codeprex™ Pennkinetic® Extended-Release Suspension
APPLICANT/SPONSOR:	Celltech Pharmaceuticals, Inc.	USAN NAME:	Codeine/chlorpheniramine maleate
MEDICAL OFFICER:	Charles E. Lee, M.D.		
TEAM LEADER:	Lydia Gilbert-McClain, M.D.	CATEGORY:	Antitussive/antihistamine
DATE:	6/2/04	ROUTE:	Oral

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
12/19/03	12/22/03	NDA 21-369, N000 BZ	Response to approvable letter, 37 volumes

RELATED APPLICATIONS

Document Date	Application Type	Comments
4/13/01	NDA 21-369, N000	Original NDA submission, 51 volumes
12/22/97	IND 54,892, N000	Opening IND submission

REVIEW SUMMARY:

Celltech Pharmaceuticals, Inc. has developed an extended-release suspension of codeine and chlorpheniramine maleate. The proposed trade name is Codeprex™ Pennkinetic® Extended-Release Suspension. Each 5 mL of the proposed product contains 20 mg of codeine and 4 mg of chlorpheniramine maleate as active ingredients bound to a polistirex resin. The proposed indication is the 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 or throat, and itchy watery eyes due to hay fever, other upper respiratory allergies, or allergic rhinitis. The applicant's application was submitted under Section 505(b)(2) of the FD&C Act. This application relies on the Agency's previous findings of safety of the active drugs as described in the appropriate over-the-counter monographs. The original NDA was submitted on April 13, 2001. An approvable action was taken because of CMC issues, including stability and dissolution specifications. The applicant chose to change the coating of the product to address these deficiencies and has conducted three new clinical pharmacology studies. Safety data from the applicant's new clinical pharmacology studies, including adverse events, vital signs, physical examination, laboratory studies, and ECGs, did not reveal any safety signal. The applicant's summary of the literature in the original NDA suggested that the elderly and pediatric populations may be at higher risk for AEs, particularly from overdose or respiratory depression. The literature review in this submission identified four cases of neonatal narcotic withdrawal associated with codeine use by the mother. None of the mothers were codeine abusers, but all used codeine at much higher doses than required for antitussive activity. The applicant's proposed labeling warns that neonatal codeine withdrawal has occurred in infants born to addicted and non-addicted mothers who had been taking codeine-containing medications in the days prior to delivery. The label describes symptoms associated with neonatal narcotic withdrawal and implies that symptoms are self-limited and do not require treatment. Labeling should be changed to note that specific treatment for neonatal opiate withdrawal may be necessary. The applicant's safety data identifies no other new safety information and supports the safety of the applicant's product. ——— which has a "structural alert", was discovered to be present in the applicant's product at higher than acceptable levels. The applicant will be asked to tighten their specification for ——— to a lower level, and to make a Phase 4 commitment to conduct pharmacology/toxicology safety studies within six months of approval.

OUTSTANDING ISSUES: There are no outstanding clinical issues. The applicant will be asked to make a Phase 4 commitment to perform non-clinical studies to address the presence of ——— in the product.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	___ APPROVAL—X	___ APPROVABLE	NOT APPROVABLE
OTHER ACTION:	COMMENTS FOR THE APPLICANT—X		

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1. EXECUTIVE SUMMARY

1.1. Recommendations on approvability

The applicant's safety data from pivotal clinical pharmacology studies and their review of the literature support the safety of their product. From the clinical perspective, this reviewer recommends an approval action.

1.2. Recommendations on Phase 4 studies and risk management steps

———— was identified as a degradant in the applicant's product. It possesses a "structural alert." The proposed specification of———— is not acceptable to the pharmacology/toxicology review team.

The applicant will be asked to tighten the specification to a lower level and to make a Phase 4 commitment to conduct pharmacology/toxicology safety studies within six months. The applicant will be asked to perform either a 28-day in vivo toxicology study to detect in vivo metabolism of codeine to ——— or two in vivo genotoxicity studies. If codeine is found to be genotoxic, levels of ————in the product should be less than ———

The applicant should make changes to proposed labeling regarding use of the product in children and the elderly. Labeling should be changed to note that specific treatment for neonatal opiate withdrawal may be necessary. Recommended text for the Geriatric Use subsection and ADVERSE REACTIONS and DRUG ABUSE AND DEPENDENCE sections of the label should be provided for the applicant.

1.3. Summary of Clinical Findings

Celltech Pharmaceuticals, Inc. has developed an extended-release suspension of codeine and chlorpheniramine maleate. The proposed trade name is Codeprex™ Pennkinetic® Extended-Release Suspension. Each 5 mL of the proposed product contains 20 mg of codeine and 4 mg of chlorpheniramine maleate as active ingredients bound to a polistirex resin. The proposed indication is the 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 or throat, and itchy watery eyes due to hay fever, other upper respiratory allergies, or allergic rhinitis.

The applicant's application was submitted under Section 505(b)(2) of the FD&C Act. This application relies on the Agency's previous findings of safety of the active drugs as described in the appropriate over-the-counter monographs. The original NDA was submitted on April 13, 2001. An approvable action was taken because of CMC issues, including stability and dissolution specifications. The applicant chose to change the coating of the product to address these deficiencies and has conducted three new clinical pharmacology studies.

The frequency of adverse events (AEs) in the applicant's new clinical pharmacology studies was similar for the extended-release suspension (64.2%) and the immediate-release (65.9%) solution. Somnolence, headache, constipation, fatigue, dysmenorrhea, nausea, pruritus-generalized, pharyngitis, and increased sweating occurred more frequently in the extended-release group. Dizziness, abdominal distention, dyspepsia, and dry throat occurred more frequently in the immediate-release group. Although many of these AEs are known to be associated with codeine (e.g. somnolence, constipation, pruritus) and chlorpheniramine (e.g., somnolence, headache, nausea, dizziness) it is difficult to draw strong conclusions based on these data because of the small number of AEs. There were no deaths or SAEs in these studies. Vital signs, physical examination, laboratory studies, and ECGs did not reveal any safety signal.

The applicant's summary of the literature in the original NDA suggested that the elderly and pediatric populations may be at higher risk for AEs, particularly from overdose or respiratory depression. The literature review in this submission identified four cases of neonatal narcotic withdrawal associated with codeine use by the mother. None of the mothers were codeine abusers, but all used codeine at much higher doses than required for antitussive activity. The applicant's proposed labeling warns that neonatal codeine withdrawal has occurred in infants born to addicted and non-addicted mothers who had been taking codeine-containing medications in the days prior to delivery. The label describes symptoms associated with neonatal narcotic withdrawal and implies that symptoms are self-limited and do not require treatment. Labeling should be changed to note that specific treatment for neonatal opiate withdrawal may be necessary. The applicant's safety data identifies no other new safety information and supports the safety of the applicant's product.

2. BACKGROUND

Celltech Pharmaceuticals, Inc. has developed an extended-release suspension of codeine and chlorpheniramine maleate. The proposed trade name is Codeprex™ Pennkinetic® Extended-Release Suspension. Each 5 mL of the proposed product contains 20 mg of codeine and 4 mg of chlorpheniramine maleate as active ingredients bound to a polistirex resin [Volume 1.1, Page 2.4].

The proposed indication is the 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 or throat, and itchy watery eyes due to hay fever, other respiratory allergies, or allergic rhinitis [Volume 1.1, Page 2.7].

The proposed dose for adults and adolescents ages 12 years and older is two teaspoonfuls (10 mL, 40 mg codeine/8 mg chlorpheniramine) every 12 hours, not to exceed four teaspoonfuls in 24 hours. The proposed dose for children ages 6 years to less than 12 years is one teaspoonful (5 mL, 20 mg codeine/4 mg chlorpheniramine) every 12 hours, not to exceed two teaspoonfuls in 24 hours. The product is not indicated for children under the age of 6 years [Volume 1.1, page 2.16].

Codeine is an opiate that is marketed in various forms as an antitussive and analgesic. Chlorpheniramine maleate is marketed in various forms as an antihistamine. The proposed product contains the above active drugs in an extended-release suspension containing polystirex resin. There are no currently marketed products containing codeine or chlorpheniramine maleate alone or in combination in such a formulation. Fisons previously marketed Penntuss (NDA 18-928), containing 10 mg/5 mL of codeine and 4 mg/5mL of chlorpheniramine maleate. This product has since been discontinued. The applicant, Celltech Pharmaceuticals, Inc. markets Tussionex (NDA 19-111), 10 mg/5mL of hydrocodone bitartrate and 8 mg/5mL of chlorpheniramine maleate in an extended-release suspension containing polystirex resin.

The applicant seeks to develop this product to meet a clinical need for patients ages 6 years and older for a combination of codeine and chlorpheniramine in a single product with a twice daily dosing frequency for relief of symptoms that occur with allergies, the common cold, or from exposure to airborne irritants.

A single dose of the extended-release codeine and chlorpheniramine product given every 12 hours is equivalent to that from the highest monograph-specified dose every 6 hours if given twice in an immediate-release form [21 CFR 341.72, 21 CFR 341.74, 21 CFR 341.90]. Therefore the amount of the proposed product given over 12-hour and 24-hour periods is in concordance with the amount of the immediate-release products specified by the monograph over these same periods. The concentration of codeine in the formulation is greater than the limit for exemption of codeine for prescription products, therefore the product will be classified as a Schedule C-III prescription product, in accordance with 21 CFR 1308.13(e)(2).

The applicant's application was submitted under Section 505(b)(2) of the FD&C Act. This application relies on the Agency's previous findings of safety of the active drugs as described in the appropriate monographs. The relevant monographs for the constituent drugs are:

- Final Monograph for Antitussive Drug Products, for codeine as a narcotic antitussive [21 CFR 341.74]
- Final Monograph for OTC Antihistamine Drug Products, for chlorpheniramine maleate as an antihistamine [21 CFR 341.72]
- Final Monograph for Combination Cough, Cold and Bronchodilator Drug Products, for the combination of codeine and chlorpheniramine maleate [21 CFR 341.40]

The original NDA was submitted on April 13, 2001. Bioequivalence data supported the applicant's conclusion that the extended-release product was likely to have a similar degree of effectiveness as codeine and chlorpheniramine antitussive and antihistamine products specified in the OTC monograph. Although the application could have been approved from the purely clinical perspective, an approvable action was taken because of CMC issues, including stability and dissolution specifications. The applicant chose to change the coating of the product to address these deficiencies and has conducted three new clinical pharmacology studies.

The applicant's response to the approval letter was submitted on December 19, 2003 and received by the Agency on December 22, 2003. Clinical materials included in the response to approvable letter include reports for the three clinical pharmacology studies, an Integrated Summary of Safety, and proposed labeling. This review briefly summarizes the applicant's revised drug development program and clinical pharmacology studies. The review focuses on the Integrated Summary of Safety. Comments on the proposed labeling are provided.

3. DRUG DEVELOPMENT PROGRAM

As noted above, bioequivalence data in the clinical pharmacology studies in the original NDA supported the applicant's conclusion that the extended-release product was likely to have a similar degree of effectiveness as codeine and chlorpheniramine antitussive and antihistamine products specified in the OTC monograph. Although the application could have been approved from the purely clinical perspective, an approvable action was taken because of CMC issues, including stability and dissolution specifications. The applicant chose to change the coating of the product to address these deficiencies and has conducted three new clinical pharmacology studies to support the product. The three new clinical pharmacology studies are listed below, and are summarized in Table 1.

- Study COD03-01, a bioequivalence study comparing 10 mL of extended-release suspension of codeine 40 mg and chlorpheniramine (CPM) 8 mg and 5 mL of immediate-release solution of codeine 20 mg and CPM 4 mg
- Study CD00900, a multiple dose bioequivalence study comparing the steady-state bioavailability of 10 mL of an extended-release suspension of codeine 40 mg and CPM 8 mg given twice daily and 5 mL of an immediate-release solution of codeine 20 mg and CPM 4 mg given four times daily
- Study CD00800, a single dose food effect study to confirm that extended-release performance is maintained in a fed and fasted state

Table 1. Summary of studies, revised drug development program, NDA 21-369 [Volume 1.24, page 8.215; Volume 1.29, pages 8.1555, 8.1560; Volume 1.33, page 8.3237].

Study Number	Study Type	Treatment Groups	Duration of treatment	Design	Number of subjects	Diagnosis, age of subjects,
COD03-01	Single dose PK	Extended-release 40 mg COD[1]/8 mg CPM[2] Immediate-release 20 mg COD/4 mg CPM	Single dose[3]	Single center, randomized, active-controlled, fasting, two-way crossover	20	Healthy males, 21-40 years
CD00900	Multiple dose PK	Extended-release 40 mg COD/8 mg CPM Q12h Immediate-release 20 mg COD/4 mg CPM Q 6h	6.5 days	Single center, randomized, open-label, two-way crossover	26	Healthy females and males, 21-40 years
CD00800	Fed and fasted bioavailability	Extended-release 40 mg COD/8 mg CPM fed Extended-release 40 mg COD/8 mg CPM fasted	Single dose	Single center, randomized, open-labeled, fed and fasting, two-way crossover	36	Healthy females and males, 21-40 years

[1]COD: codeine
[2]CPM: chlorpheniramine maleate
[3]Immediate-release product dosed as two separate doses 6 hours apart

4. CHEMISTRY, MANUFACTURING, AND CONTROLS

As noted earlier in this review, the original NDA received an approvable action largely because of CMC issues, including stability and dissolution specifications. The applicant chose to change the coating of the product to address these deficiencies. The applicant has addressed these deficiencies in this submission. More details may be found in the reviews of Dr. Vibhakar Shah and Dr. Shinja Kim [CMC Review, V. Shah, Ph.D., NDA 21-369, N000 BZ 12/19/03 and Clinical Pharmacology and Biopharmaceutics Review, S. Kim, Ph.D., NDA 21-369, N000 BZ 12/19/03].

5. PHARMACOLOGY/TOXICOLOGY

——— was identified as a degradant in the applicant's product. It possesses a "structural alert" and may react with DNA. The applicant proposed an acceptance criterion of ——————. However, testing of the drug batches under accelerated conditions found a gradual accumulation of ——————. Furthermore, accumulation of ——— in drug batches produced with the prior manufacturing process was observed to reach levels ——————— under recommended storage conditions (i.e., ——— relative humidity) [Pharmacology/Toxicology Consultation, T. Robison, Ph.D., NDA 21-369, N000 BZ 12/19/03].

The proposed specification of ——————— is not acceptable to the pharmacology/toxicology review team. The applicant will be asked to tighten the specification to a lower level and to make a Phase 4 commitment to conduct pharmacology/toxicology safety studies within six months. The applicant will be asked to perform either a 28-day in vivo toxicology study to detect in vivo metabolism of codeine to ——— or two in vivo genotoxicity studies. If codeine is found to be genotoxic, levels of ——— in the product should be ——————— [Pharmacology/Toxicology Consultation, T. Robison, Ph.D., NDA 21-369, N000 BZ 12/19/03].

6. CLINICAL PHARMACOLOGY STUDIES

A brief summary of data from the applicant's clinical pharmacology studies follows below. Details may be found in Dr. Shinja Kim's review [Clinical Pharmacology and Biopharmaceutics Review, S. Kim, Ph.D., NDA 21-369, N000 BZ 12/19/03].

6.1. Study COD03-01

This was a randomized, open-label, two-way crossover, Phase 1 clinical pharmacology study designed to compare the oral bioavailability of a single dose of 10 mL of extended-release (ER) suspension of codeine 40 mg and chlorpheniramine (CPM) 8 mg relative to 5 mL of immediate-release (IR) solution of codeine 20 mg and CPM 4 mg administered every 6 hours for 2 consecutive doses under fasting conditions. Twenty subjects were enrolled, and 19 completed the study [Volume 1.23, page 8.8].

Statistical comparisons were performed to determine if the test ER suspension was bioequivalent to the reference IR solution in this single dose study. The results are summarized in Table 2. The test ER suspension met 80-125% bioequivalence criteria for $lnAUC_{0\text{-}inf}$ for codeine and CPM. Mean lnC_{max} values were lower for the test ER suspension than for the IR solution for both codeine and CPM, and fell below 80-125% bioequivalence criteria [Volume 1.23, pages 8.9, 8.23].

Table 2. Pharmacokinetics results, Study COD03-01 [Volume 1.23, page 8.23].

Codeine		
Parameter	**90% CI**	**% Mean ratio***
lnC_{max}	[illegible]	79.0
$lnAUC_{0\text{-}inf}$	82.5 – 95.0	88.5
Chlorpheniramine		
Parameter	**90% CI**	**% Mean ratio***
lnC_{max}	[illegible]	64.7
$lnAUC_{0\text{-}inf}$	81.0 – 89.9	85.4

* Ratio of values for test ER suspension/reference IR suspension

6.2. Study CD00900

This was a multiple dose, randomized, open-label, two-way crossover, Phase 1 clinical pharmacology study designed to assess the steady-state bioavailability of 10 mL of an ER suspension of codeine 40 mg and CPM 8 mg given twice daily relative to 5 mL of an IR solution of codeine 20 mg and CPM 4 mg given four times daily. A total of 26 subjects were enrolled, and 24 subjects completed the study [Volume 1.23, page 8.11].

Statistical comparisons were performed to determine if the test ER suspension was bioequivalent to the reference IR solution in this multiple dose study. The results are summarized in Table 3. The test ER suspension met 80-125% bioequivalence criteria for lnC_{max} for codeine and CPM in this multiple dose study. Values for lnC_{min} for the test ER suspension exceeded 80-125% bioequivalence criteria for lnC_{min} for codeine ([illegible] . The test ER suspension met 80-125% bioequivalence criteria for lnC_{min} for CPM ([illegible] [Volume 1.23, pages 8.9, 8.23].

Table 3. Pharmacokinetics results, Study CD00900 [Volume 1.23, page 8.23].

Codeine		
Parameter	**90% CI**	**% Mean ratio***
lnC_{max}	[illegible]	92.7
$lnAUC_{144\text{-}456}$	99.2 – 108.9	103.9
lnC_{min}	[illegible]	116.6
Chlorpheniramine		
Parameter	**90% CI**	**% Mean ratio***
lnC_{max}	[illegible]	89.6
$lnAUC_{144\text{-}456}$	88.7 – 95.9	92.2
lnC_{min}	[illegible]	94.8

* Ratio of values for test ER suspension/reference IR suspension

6.3. Study CD00800

This was a randomized, open-label, two-way crossover, Phase 1 clinical pharmacology study designed to evaluate the oral bioavailability of a single dose of 10 mL of an ER suspension of codeine 40 mg and CPM 8 mg given after a high-fat breakfast and under fasting conditions. A total of 36 subjects were enrolled, and 35 subjects completed the study [Volume 1.23, page 8.14].

Statistical comparisons were performed to determine the bioavailability of the ER suspension in the fasted and fed states. The results are summarized in Table 4. The lnC_{max} and $lnAUC_{0\text{-}inf}$ values for codeine were slightly higher for the ER suspension in the fed state than in the fasted state. The lnC_{max} and $lnAUC_{0\text{-}inf}$ values for CPM were similar in the fed and in the fasted states [Volume 1.23, pages 8.9, 8.23].

Table 4. Pharmacokinetics results, Study COD00800 [Volume 1.23, page 8.23].

Codeine		
Parameter	**90% CI**	**% Mean ratio***
lnC_{max}		116
$lnAUC_{0\text{-}inf}$	107.4 – 117.4	112.3
Chlorpheniramine		
Parameter	**90% CI**	**% Mean ratio***
lnC_{max}		99.6
$lnAUC_{0\text{-}inf}$	95.8 – 105.8	100.7

* Ratio of values for ER suspension, fed conditions/ER suspension, fasted conditions

Reviewer comment:

At first glance, data from Study COD03-01 suggest a potential for decreased antitussive efficacy of the extended-release product because of the low C_{max} as compared with the reference product. However, this is an extended-release preparation, and one would expect a lower C_{max} than for an immediate-release solution. $AUC_{0\text{-}inf}$ in both COD03-01 and the multiple dose study CD00900 met bioequivalence criteria. It is also important to note that the dose of codeine delivered by the proposed dose in both children and adults is twice the minimum dose specified in the monograph. Even though in COD03-01, the C_{max} for the proposed dose of the extended-release product is low compared with the reference product, a margin of efficacy is provided, as one-half of the proposed dose of the proposed product would be within specifications of the monograph for the lowest nominal dose. This would also provide for an increased safety margin because of the lower C_{max} for codeine as compared with the immediate-release products. The experimental product and OTC monograph specifications are compared below in Table 5 [Medical Officer Review, Charles E. Lee, M.D. NDA 21-369 N000, 4/13/01].

C_{max} values for chlorpheniramine in Study COD03-01 were also were lower for the ER suspension than for the IR solution. However, as with codeine, $AUC_{0\text{-}inf}$ met bioequivalence criteria. Chlorpheniramine is likely to be effective for the proposed indication at lower doses than specified by the OTC monograph, which provides an additional margin of efficacy. Advil Allergy Sinus demonstrated efficacy in a clinical study at half the monograph dose of chlorpheniramine and was approved on December 19, 2002 [Medical Officer Consultation, Charles E. Lee, M.D., NDA 21-441, N000, 2/28/02].

In study COD0900, for codeine, values for C_{min} for the test ER suspension exceeded bioequivalence criteria. This however, does not represent a safety issue, as the C_{min} (——— ———) is well below the C_{max} (———————) and the C_{max} and AUC values for codeine met bioequivalence criteria [Volume 1.29, page 8.1539].

Table 5. Comparison of experimental and OTC monograph products [Volume 1.1, page 2.4-2.16; 21 CFR 341.72; 21 CFR 341.74; Medical Officer Review, Charles E. Lee, M.D. NDA 21-369 N000, 4/13/01].

Product	Formulation	Dosage Regimen	Total Daily Dose
Adults and Adolescents ≥12 years			
Proposed Product: Extended-release	40 mg COD/8 mg CPM/10 mL	40 mg COD/8 mg CPM Q12H	80 mg COD/16 mg CPM
Reference Product Immediate-release	40 mg COD/8 mg CPM/10 mL	20 mg COD/4 mg CPM Q6H	80 mg COD/16 mg CPM
Codeine OTC Monograph 21 CFR 341.74	Per monograph	10 to 20 mg Q4-6H	40 to 120 mg
Chlorpheniramine OTC Monograph 21 CFR 341.72	Per monograph	4 mg Q4-6H	16 to 24 mg
Children ≥6 to <12 years			
Proposed Product: Extended-release	40 mg COD/8 mg CPM/10 mL	20 mg COD/4 mg CPM Q12H	40 mg COD/8 mg CPM
Reference Product Immediate-release	40 mg COD/8 mg CPM/10 mL	10 mg COD/2 mg CPM Q6H	40 mg COD/8 mg CPM
Codeine OTC Monograph 21 CFR 341.74	Per monograph	5 to 10 mg Q4-6H	20 to 60 mg
Chlorpheniramine OTC Monograph 21 CFR 341.72	Per monograph	2 mg Q4-6H	8 to 12 mg

7. INTEGRATED SUMMARY OF SAFETY

Integrated review of safety data supporting this application follows below.

7.1. Summary and conclusions

The frequency of AEs in the clinical pharmacology studies was similar for the extended-release suspension (64.2%) and the immediate-release (65.9%) solution. Somnolence, headache, constipation, fatigue, dysmenorrhea, nausea, pruritus-generalized, pharyngitis, and increased sweating occurred more frequently in the extended-release group. Dizziness, abdominal distention, dyspepsia, and dry throat occurred more frequently in the immediate-release group. Although many of these AEs are known to be associated with codeine (e.g. somnolence, constipation, pruritus) and chlorpheniramine (e.g., somnolence, headache, nausea, dizziness) it is difficult to draw strong conclusions based on these data because of the small number of AEs. There were no deaths or SAEs in these studies. Vital signs, physical examination, laboratory studies, and ECGs did not reveal any safety signal.

The applicant's summary of the literature in the original NDA suggested that the elderly and pediatric populations may be at higher risk for AEs, particularly from overdose or respiratory depression. The literature review in this submission identified four cases of neonatal narcotic withdrawal associated with codeine use by the mother. None of the mothers were codeine abusers, but all used codeine at much higher doses than required for antitussive activity. The applicant's proposed labeling warns that neonatal codeine withdrawal has occurred in infants born to addicted and non-addicted mothers who had been taking codeine-containing medications in the days prior to delivery. The label describes symptoms associated with neonatal narcotic withdrawal and implies that

symptoms are self-limited and do not require treatment. Labeling should be changed to note that specific treatment for neonatal opiate withdrawal may be necessary.

The applicant's Integrated Summary of Safety identifies no other new safety information and supports the safety of the applicant's product.

7.2. Content

The following data were reviewed in preparation of this review of safety:

- Applicant's integrated safety data from the following pivotal studies
  - COD03-01
  - CD00900
  - CD00800
  - Review of published literature on safety of codeine and chlorpheniramine

7.3. Integrated safety data, pivotal studies

7.3.1. Description of pivotal studies

Integrated safety data for this application included three pivotal studies:

- Study COD03-01, a bioequivalence study comparing 10 mL of extended-release (ER) suspension of codeine 40 mg and chlorpheniramine (CPM) 8 mg and 5 mL of immediate-release (IR) solution of codeine 20 mg and CPM 4 mg
- Study CD00900, a multiple dose bioequivalence study comparing the steady-state bioavailability of 10 mL of an ER suspension of codeine 40 mg and CPM 8 mg given twice daily and 5 mL of an IR solution of codeine 20 mg and CPM 4 mg given four times daily
- Study CD00800, a single dose food effect study to confirm that extended-release performance is maintained in a fed and fasted state

These studies are summarized earlier in this document in Table 1.

7.3.2. Demographics

Subjects in the pivotal studies were evenly divided between male and female genders. Mean age was 29 years, and ranged from 21 to 40 years. Patients of Hispanic race were represented most frequently, followed by patients of Caucasian, Black, and Asian races.

Table 6. Demographics, pivotal studies [Volume 1.23, page 8.106-8.107]

Characteristic	Extended-release Codeine/CPM N = 82		Immediate-release Codeine/CPM N = 46	
Gender	n	(%)	n	(%)
Female	41	(50.0)	23	(50.0)
Male	41	(50.0)	23	(50.0)

Characteristic	Extended-release Codeine/CPM N = 82		Immediate-release Codeine/CPM N = 46	
Age, years				
Mean age	29		29	
Range	21 – 40		21 – 40	
Race	**n**	**(%)**	**n**	**(%)**
Black	4	(4.9)	3	(6.5)
Hispanic	51	(62.2)	29	(63.0)
Asian	1	(1.2)	1	(2.2)
Caucasian	26	(31.7)	13	(28.3)

7.3.3. Disposition

Subject disposition is summarized in Table 7. A total of 82 subjects were randomized to the extended-release suspension, and 46 of these subjects were also exposed to the immediate-release solution. The frequency of withdrawals was similar for both study treatments.

Table 7. Disposition, pivotal studies [Volume 1.23, page 8.109]

	Extended-release Codeine/CPM N = 82		Immediate-release Codeine/CPM N = 46	
	n	**(%)**	**n**	**(%)**
Subjects randomized	82	(100)	46	(100)
Subjects completed	78	(95.1)	43	(93.5)
Withdrawals	4	(4.9)	3	(6.5)
AE	1	(1.2)	0	(0)
Noncompliance	1	(1.2)	1	(2.2)
Lost to follow-up	2	(2.4)	2	(4.3)

7.3.4. Exposure

Exposure to study medication is summarized in Table 8. Subjects were exposed a single dose of extended-release 40 mg codeine/8 mg chlorpheniramine up to 6.5 days of extended-release 40 mg codeine/8 mg chlorpheniramine given twice daily. There were a total of 81 subjects exposed to either study medication, 81 subjects exposed to the extended-release suspension, and 44 exposed to the immediate-release solution.

Table 8. Exposure, pivotal studies [Volume 1.23, page 8.110]

Characteristic	Drug tested	Subjects exposed	Daily dose, duration
Study COD03-01			
	ER 40 mg codeine/8 mg CPM	20	Single dose, one day
	IR 20 mg codeine/4 mg CPM	19	Two doses, one day
Study CD00900			
	ER 40 mg codeine /8 mg CPM	25	BID for 6.5 days
	IR 20 mg codeine/4 mg CPM	25	QID for 6.5 days
Study CD00800			
	ER 40 mg codeine /8 mg CPM, high fat	36	Single dose, one day
	ER 40 mg codeine /8 mg CPM, fasted	35	Single dose, one day

7.3.5. Adverse events

AEs occurring in more than one patient are summarized in Table 9. The frequency of AEs was similar for the extended-release suspension (64.2%) and the immediate-release

(65.9%) solution. Somnolence, headache, constipation, fatigue, dysmenorrhea, nausea, pruritus-generalized, pharyngitis, and increased sweating occurred more frequently in the extended-release group. Dizziness, abdominal distention, dyspepsia, and dry throat occurred more frequently in the immediate-release group. Although many of these AEs are known to be associated with codeine (e.g. somnolence, constipation, pruritus) and chlorpheniramine (e.g., somnolence, headache, nausea, dizziness) it is difficult to draw strong conclusions based on these data because of the small number of AEs.

Table 9. AEs occurring in >1 patient, integrated data from pivotal studies [Volume 1.23, pages 8.115-8.119]

	Extended-release Codeine/CPM N = 81		Immediate-release Codeine/CPM N = 44	
	n	(%)	n	(%)
Subjects with any AE	52	(64.2)	29	(65.9)
Somnolence	18	(22.2)	7	(15.9)
Headache	16	(19.8)	8	(18.2)
Constipation	12	(14.8)	5	(11.4)
Fatigue	8	(9.9)	4	(9.1)
Nausea	7	(8.6)	3	(6.8)
Dizziness	5	(6.2)	5	(11.4)
Pruritus-generalized	3	(3.7)	1	(2.3)
Pharyngitis	3	(3.7)	0	(0)
Increased sweating	3	(3.7)	0	(0)
Abdominal distention	2	(2.5)	3	(6.8)
Dyspepsia	2	(2.5)	2	(4.5)
Dry throat	1	(1.2)	2	(4.5)

7.3.6. SAEs and deaths

There were no SAEs or deaths in the pivotal studies [Volume 1.23, page 8.104].

7.3.7. Withdrawals due to AEs

There was one patient who withdrew from the pivotal studies because of an AE. This patient, Subject number 16, who was treated with the extended-release suspension, withdrew from Study CD00800 because of a toothache [Volume 1.23, pages 8.104, 8.178].

7.3.8. Vital signs

All mean vital sign measurements remained within normal limits. No consistent changes in systolic or diastolic blood pressures or respiratory rate were noted in the three studies. Small increases of 3 to 5 bpm were noted towards the later time points in each of the three studies. One patient in Study CD00800 experienced a hypotensive episode (81/46 mm Hg) associated with dizziness and diaphoresis associated with a venipuncture. The episode resolved after the subject was placed in a supine position for two minutes. One patient in Study CD00900 experienced tachycardia (124 bpm) 12 hours after receiving the extended-release suspension. The patient experienced several elevated pulse rates intermittently throughout the study. No other vital sign abnormalities were reported as AEs [Volume 1.24, pages 8.238, 8.387-8.394; Volume 1.29, pages 8.1582, 8.1718-8-1751; Volume 1.33, pages 8.3262, 8.3389-8.3396].

Reviewer comment:
Vital signs data do not reveal any safety signal.

7.3.9. Physical examination

There were eight patients with changes in physical examination from normal at the screening visit to abnormal at the post-study visit. These abnormalities noted for these eight patients included left lower quadrant abdominal tenderness, dry rash and pruritus, otitis externa, rhinorrhea, pharyngitis, cough, nasal congestion, headache, and "jumpy arms" [Volume 1.23, pages 8.105, 8.191; Volume 1.24, pages 8.239-8.240; Volume 1.29, pages 8.1582-8.1583 ; Volume 1.33, page 8.3263].

Reviewer comment:
Physical examinations data do not reveal any safety signal.

7.3.10. Laboratory studies

Shifts from normal to abnormal for bacteria in the urine was noted in 17 patients and shifts from normal to abnormal for blood in the urine were noted in 11 patients. Shifts from normal to abnormal for ALT were noted in 3 patients and for AST in 5 patients. One of these subjects, Subject 12 in COD00900, had an ALT of 138 U/L and an AST of 94 U/L at the post study visit. Follow-up ALT and AST were normal. The remaining subjects with shifts in ALT and AST from normal to abnormal had AST and ALT values less than 100 U/L. [Volume 1.16, page 6.2210-6.2213; Volume 1.23, pages 8.182; Volume 1.26, pages 8.912-8.914].

Reviewer comment:
The significance of the fairly high number of patients who developed bacteriuria and hematuria is unclear. Attribution to a particular study treatment is not possible because the post-dose laboratory studies were performed after the second of the crossover study periods. Neither bacteriuria nor hematuria is an expected adverse event with either codeine or chlorpheniramine. It is not likely that the bacteriuria or hematuria are a result of urinary tract stasis due to anticholinergic effects of chlorpheniramine, as other associated cholinergic side effects, such as dry mouth or urinary retention, were not frequently reported. Both codeine and chlorpheniramine have an extensive OTC marketing history. It is not likely that these data represent a safety signal.

7.3.11. ECGs

There were no meaningful changes in mean values for ECG measurements. All changes in individual ECGs were considered to be clinically insignificant [Volume 1.23, pages 8.105, 8.192; Volume 1.24, pages 8.239, 8.396-8.397; Volume 1.29, pages 8.1582, 8.1754-8.1755 ; Volume 1.33, pages 8.3263, 8.3398-8.3394].

Reviewer comment:
This reviewer's examination of ECG data did not reveal any clinically significant changes.

7.4. Review of published literature on safety of codeine and chlorpheniramine

In the original NDA submission, the applicant submitted a review of the published literature on the safety of codeine and chlorpheniramine. The applicant's review in the original NDA submission suggested that the elderly and pediatric populations may be at higher risk for AEs, particularly from overdose or respiratory depression [Medical Officer Review, Charles E. Lee, M.D., NDA 21-369, N000, 4/13/01].

The applicant conducted an updated review of the published literature focusing on the safety of codeine and chlorpheniramine in the following subpopulations:

- Geriatric
- Pediatric
- Ethnic and Racial Groups
- Gender

The applicant's updated review is reviewed below.

7.4.1. Safety of codeine and chlorpheniramine geriatric patients

The applicant conducted a literature search in August 2003 using the MEDLINE database for the period of January 2001 through July 2003 and the EMBASE database for the period of January 1966 to July 2003. Search limits included codeine and adverse events, pharmacokinetics, cough cold medications, antitussive medications, heart, arrhythmia, smoking, renal insufficiency, elderly, and geriatrics. The applicant identified 30 citations, of which 16 were considered to be relevant to the NDA. This reviewer found two references to be of note. One study evaluated the risk of hip fractures in patients ≥65 years of age who were taking codeine or propoxyphene. There were 4500 patients and 24,041 controls, and the authors reported a 60% increased risk of hip fractures in patients taking either drug. [1] [Volume 1.23, pages 8.43-8.44].

The applicant conducted a similar search of the published literature for chlorpheniramine. Search limits were the same as for the codeine search, except chlorpheniramine was searched instead of codeine. The applicant identified 11 articles, of which six were considered to be relevant to the NDA. Of note was one study, which reported an 8% incidence of drowsiness among geriatric patients receiving chlorpheniramine 4 mg three times daily for seven days [2] [Volume 1.23, pages 8.45-8.46].

The applicant concluded that AEs noted in their review of the literature were similar to those previously noted to be associated with codeine and chlorpheniramine [Volume 1.23, pages 8.47].

Reviewer comment:
This reviewer concurs with the applicant that the literature review identifies no new safety information relevant to use in the geriatric population.

7.4.2. Safety of codeine and chlorpheniramine pediatric patients

The applicant conducted a literature search in August 2003 using the MEDLINE database for the period of January 2001 through July 2003 and the EMBASE database for the period of January 1966 to July 2003. Search limits included codeine and adverse events, pharmacokinetics, cough cold medications, antitussive medications, pediatric, and children. The applicant identified 45 citations, of which seven were considered to be relevant to the NDA. Of note were citations describing case reports of seizure, acute dystonic reaction, and cyanotic episodes in infants and children receiving codeine at higher than recommended doses and seizures in children receiving opiates at doses for palliative relief of pain. [3, 4, 5, 6] The applicant points out that these cases demonstrate the need for proper parental education regarding the appropriate use and side effects of cough-cold medications [Volume 1.23, pages 8.56-8.57].

The applicant conducted a similar search of the published literature for chlorpheniramine. Search limits were the same as for the codeine search, except chlorpheniramine was searched instead of codeine. The applicant identified 31 articles, of which seven were considered to be relevant to the NDA. None of these articles present new safety signals.

The applicant concluded that the AEs in the pediatric population noted in their review of the literature were similar to those previously noted to be associated with codeine and chlorpheniramine [Volume 1.23, pages 8.47, 8.59].

Reviewer comment:
This reviewer concurs with the applicant that the literature review identifies no new safety information relevant to use in the pediatric population.

7.4.3. Safety of codeine and chlorpheniramine in ethnic and racial groups

The applicant conducted a literature search in August 2003 using the MEDLINE database for the period of January 2001 through July 2003 and the EMBASE database for the period of January 1966 to July 2003. Search limits included codeine and race difference, ethnic and racial groups, Caucasian, Negro, Hispanic American, Latino, American Indian, Eskimo, Hawaiian, Asian American, and Asian. The applicant identified 23 citations, of which none were considered to be relevant to codeine's antitussive effects. A number of citations addressed racial and ethnic differences of codeine metabolism. The applicant noted that Asians and up to 10% of Caucasians are poor metabolizers of codeine due to genetic differences in the activity of CYP2D6, which is responsible for metabolism of codeine to morphine and is responsible for the metabolism of 10% of a total codeine dose. Treatment with a CYP2D6 inhibitor blocks the analgesic effect of codeine in normal metabolizers. [7, 8] The significance of CYP2D6 polymorphisms on the antitussive effects of codeine are unknown [Volume 1.23, pages 8.67-8.68].

The applicant conducted a similar search of the published literature for chlorpheniramine. The applicant identified one citation, which did not provide any new safety information [Volume 1.23, page 8.67].

7. Wilcox RA, Owen H. Anaesth Intensive Care 2000; 28:611-619.

8. Poulsen I, et. al. Eur J Clin Pharmacol 1996; 51:289-295.

9. Palmer RN, et. al. Lancet 1966 Sep; 2(7464):620-621.

10. Van Leeuwen G, Guthrie R, Stange F. Pediatrics 1965; 63:635-636.

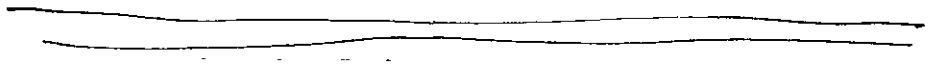
11. Khan K, Chang J. Arch Dis Child 1997; 76:59-60.

12. Mangurten HH. Pediatrics 1980 ; 62 :159-160.

8. BRIEF REVIEW OF PROPOSED LABEL

Proposed labeling was included in this submission [Volume 1.1, pages 2.2-2.19, 3.62-3.83]. This brief review focuses on major issues and concerns, which are noted below. Detailed and final comments on proposed labeling will be incorporated in the final labeling.

1. The following sentence should be deleted from the Geriatric Use subsection [Volume 1.1, page 2.13]:



This sentence detracts from the statement in the proposed label that cautions about use of sedating drugs in the elderly because of an increased risk of over-sedation and confusion. It also detracts from the statements in PRECAUTIONS, Special Risk Patients, which refers to use in elderly patients, and in the second paragraph of the Geriatric Use subsection, which recommends care in dose selection because the elderly are more likely to have decreased renal function.

2. The ADVERSE REACTIONS section of the proposed label states [Volume 1.1, page 2.13]:

This sentence should be deleted from the label. Somnolence, headache, constipation, and fatigue have been associated with codeine. These adverse events were reported by approximately 10% or more of patients receiving the extended-release suspension in the PK studies included in this submission.

3. In the approvable letter of February 13, 2002, the Division stated that the DRUG ABUSE AND DEPENDENCE section of the label should state:

> "Dependence and tolerance may develop upon repeated administration. An opioid withdrawal syndrome, indicating the development of dependence, may appear if the drug product is administered continuously for an extended time period."

The applicant has added additional language to the recommended text [Volume 1.1, page 2.14]:

"Dependence and tolerance may develop upon repeated administration. An opioid withdrawal syndrome, indicating the development of dependence, may appear if the drug product is administered continuously for an extended time period.

The text for this section of the label should include the language specified in the approvable letter. The phrases should be deleted.

4. In the approvable letter of February 13, 2002, the Division advised the applicant that the DRUG ABUSE AND DEPENDENCE section of the label should also adequately describe symptoms of neonatal opiate withdrawal. The applicant has proposed the following text [Volume 1.1, page 2.14]:

"Neonatal codeine withdrawal has occurred in infants born to addicted and non-addicted mothers who had been taking codeine-containing medications in the days prior to delivery. Typical symptoms of narcotic withdrawal include irritability, excessive crying, tremors, hyperreflexia, fever, vomiting, diarrhea, and poor feeding. These signs occur shortly after birth and

Seizures may also be associated with neonatal opiate withdrawal. This statement may also be misconstrued to mean that neonatal opiate withdrawal may not need treatment. The applicant should revise this sentence to read:

"Neonatal codeine withdrawal has occurred in infants born to addicted and non-addicted mothers who had been taking codeine-containing medications in the days prior to delivery. Typical symptoms of narcotic withdrawal may include irritability, excessive crying, tremors, hyperreflexia, seizures, fever, vomiting, diarrhea, and poor feeding. These signs occur shortly after birth and may require specific treatment."

9. COMMENTS FOR THE APPLICANT

The following comments regarding product labeling should be communicated to the applicant:

1. Delete the following sentence from the Geriatric Use subsection of the label:

2. Delete the following sentence from the first paragraph of the ADVERSE REACTIONS section of the label:

[redacted]

3. Revise the first paragraph of the "Dependence" subsection of DRUG ABUSE AND DEPENDENCE to read:

"Dependence and tolerance may develop upon repeated administration. An opioid withdrawal syndrome, indicating the development of dependence, may appear if the drug product is administered continuously for an extended time period."

4. Seizures may also be associated with neonatal opiate withdrawal. Treatment of neonatal opiate withdrawal may require specific medical treatment. Revise the second paragraph of the "Dependence" subsection of DRUG ABUSE AND DEPENDENCE to read:

"Neonatal codeine withdrawal has occurred in infants born to addicted and non-addicted mothers who had been taking codeine-containing medications in the days prior to delivery. Typical symptoms of narcotic withdrawal may include irritability, excessive crying, tremors, hyperreflexia, seizures, fever, vomiting, diarrhea, and poor feeding. These signs occur shortly after birth and may require specific treatment."

Reviewed by:

Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

Lydia Gilbert-McClain, M.D.
Team Leader, Division of Pulmonary and Allergy Drug Products

cc: Original NDA
HFD-570/Division File
HFD-570/McClain/Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-870/S. Kim/Clinical Pharmacology and Biopharmaceutics Reviewer
HFD-870/Fadiran/Clinical Pharmacology and Biopharmaceutics Team Leader
HFD-570/Yu/CSO

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/s/

Charles Lee
6/4/04 08:14:59 AM
MEDICAL OFFICER

Lydia McClain
6/7/04 01:31:36 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	IND 54,892	**TRADE NAME:**	Codeprex™
APPLICANT/SPONSOR:	Celltech Pharmaceuticals, Inc.	**USAN NAME:**	Codeine/chlorpheniramine maleate
MEDICAL OFFICER:	Charles E. Lee, M.D.		
TEAM LEADER:	Lydia Gilbert-McClain, M.D.	**CATEGORY:**	Antitussive/antihistamine
DATE:	1/17/03	**ROUTE:**	Oral, extended release suspension

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
1/8/03	1/9/03	IND 54,892 N020 PN, PI	Two pivotal clinical pharmacology protocols

RELATED APPLICATIONS

Document Date	Application Type	Comments
4/13/01	NDA 21-369 N000	NDA submission

REVIEW SUMMARY:

Celltech Pharmaceuticals, Inc. is developing an extended release suspension of chlorpheniramine maleate and codeine. The proposed tradename is Codeprex™ Extended Release Suspension. Each 5 mL of the proposed product contains 20 mg of codeine and 4 mg of chlorpheniramine maleate as active ingredients bound to a polistirex resin. The proposed indication is for the temporary relief of ———— cough, runny nose, sneezing, itching of the nose or throat, and itchy watery eyes, as may occur with the common cold, inhaled irritants, hay fever, or other respiratory allergies. The proposed dose for adults and adolescents ages 12 years and older is two teaspoonfuls (10 mL, 40 mg codeine/8 mg chlorpheniramine) every 12 hours, not to exceed four teaspoonfuls in 24 hours. The proposed dose for children ages 6 years to less than 12 years is one teaspoonful (5 mL, 20 mg codeine/4 mg chlorpheniramine) every 12 hours, not to exceed two teaspoonfuls in 24 hours. The product is not indicated for children under the age of 6 years. The sponsor's submitted an NDA under Section 505(b)(2) of the FD&C Act [NDA 21-369, 4/13/01}. Bioequivalence data supported the sponsor's conclusion that the extended release product was likely to have a similar degree of effectiveness as codeine and chlorpheniramine antitussive and antihistamine products specified in the OTC monograph. Although the application was approvable from the purely clinical perspective, an approvable action was taken because of CMC issues, including stability and dissolution specifications.

The sponsor has chosen to reformulate their product, and to conduct two new clinical pharmacology studies. The first study, CD-00900, is designed to compare the steady state bioavailability of the reformulated product against a reference immediate release product conforming to OTC monograph standards. It is essentially the same design as the previous pivotal study COD-02002. The second study, COD-00800, is designed to confirm that extended release performance of the product is maintained in a fed and fasted state. This study is essentially the same design as the previous pivotal study COD-02001. Protocols for the proposed studies are acceptable clinically. The Clinical Pharmacology and Biopharmaceutics teams will comment on the proposed analysis of pharmacokinetic data. Safety endpoints for the proposed studies are acceptable. The sponsor should provide descriptive analyses of adverse events, vital signs, physical examinations, and ECGs. It is safe for these studies to proceed.

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES:	X—SAFE TO PROCEED	CLINICAL HOLD
OTHER ACTION:	X—COMMENTS FOR THE SPONSOR	

1. BACKGROUND

Celltech Pharmaceuticals, Inc. is developing an extended release suspension of chlorpheniramine maleate and codeine. The proposed tradename is Codeprex™ Extended Release Suspension. Each 5 mL of the proposed product contains 20 mg of codeine and 4 mg of chlorpheniramine maleate as active ingredients bound to a polistirex resin. The proposed indication is for the temporary relief of ———— cough, runny nose, sneezing, itching of the nose or throat, and itchy watery eyes, as may occur with the common cold, inhaled irritants, hay fever, or other respiratory allergies. The proposed dose for adults and adolescents ages 12 years and older is two teaspoonfuls (10 mL, 40 mg codeine/8 mg chlorpheniramine) every 12 hours, not to exceed four teaspoonfuls in 24 hours. The proposed dose for children ages 6 years to less than 12 years is one teaspoonful (5 mL, 20 mg codeine/4 mg chlorpheniramine) every 12 hours, not to exceed two teaspoonfuls in 24 hours. The product is not indicated for children under the age of 6 years.

The sponsor previously submitted an NDA under Section 505(b)(2) of the FD&C Act [NDA 21-369, 4/13/01]. The application relied on the Agency's previous findings of safety of the active drugs as described in the appropriate OTC monographs. The application included three pivotal bioequivalence studies. These studies were:

- Study 1109/99, a product confirmation study employing three lots to select the final product performance characteristics for the pivotal trials, and an evaluation of vivo/in vitro release rates to confirm final dissolution release specifications
- Study COD-02002, a multiple dose PK study comparing a lot representative of the proposed commercial product against a reference immediate release product conforming to OTC monograph standards
- Study COD-02001, a single dose food effects study to confirm that extended release performance is maintained in a fed and fasted state

Bioequivalence data supported the sponsor's conclusion that the extended release product was likely to have a similar degree of effectiveness as codeine and chlorpheniramine antitussive and antihistamine products specified in the OTC monograph. AEs occurring commonly in patients taking the extended release product in the three pivotal biopharmaceutics studies included dizziness, constipation, erythema, dysmenorrhea, among others, and were similar to those expected from codeine and chlorpheniramine. There were no deaths or serious adverse events in these studies. Vital signs, physical examination, laboratory studies, and ECGs did not reveal any safety signal. Overall, these data supported the safety of the proposed product and dose in the proposed population. This application was approvable from the purely clinical perspective, but an approvable action was taken because of CMC issues, including stability and dissolution specifications.

The sponsor has chosen to reformulate their product, and to conduct two new clinical pharmacology studies. The first study, CD-00900, is designed to compare the steady state bioavailability of the reformulated product against a reference immediate release product conforming to OTC monograph standards. It is essentially the same design as the

previous pivotal study COD-02002. The second study, CD-00800, is designed to confirm that extended release performance of the product is maintained in a fed and fasted state. This study is essentially the same design as the previous pivotal study COD-02001.

Protocols for the new clinical pharmacology studies are briefly reviewed below.

2. PROPOSED CLINICAL PHARMACOLOGY STUDIES

2.1. Study CD-00900

Study CD-00900 is a multiple-dose PK study to compare the reformulated product to a reference immediate release product that conforms to OTC monograph standards and to link efficacy and safety for the intended indication and population. The study is to be a multiple dose, randomized, open-label, two way crossover study. Each period is seven days. There will be a washout period of at least seven days between treatment periods. Twenty-six healthy male and female subjects, 21-40 years of age, are to be enrolled. Each subject is to be randomly assigned to treatment for 6.5 days of either 10 mL of extended release suspension containing 40 mg codeine and 8 mg chlorpheniramine maleate dosed every 12 hours or 5 mL of immediate release solution containing 20 mg codeine and 4 mg chlorpheniramine maleate dosed every 6 hours. Blood samples are collected immediately before dosing (0 hours) and at 96, 120, 144, 144.5, 146, 147, 148, 149, 150, 150.5, 151, 152, 153, 154, 155, and 156 hours after the dose at time 0 hours. A total of 540 mL of blood is to be drawn. Patients who have donated blood within 30 days or plasma within 7 days of the start of the study are to be excluded. Plasma concentrations of codeine and chlorpheniramine are to be assayed. Safety endpoints are to include adverse events, vital signs, physical examination, hematology, blood chemistry, urinalyses, and ECGs [Pages 6-45 to 6-49, 6-51, 6-53].

2.2. Study CD-00800

Study CD-00800 is a bioavailability study designed to confirm the extended release product performance in both fed and fasted states. This study is a single center, randomized, open-label, single dose, two-way crossover study. Thirty six healthy male and female subjects, ages 21-40 years, are to be studied. Each subject was randomly assigned to receive 10 mL of the extended release suspension containing 40 mg codeine and 8 mg chlorpheniramine maleate after either a high fat breakfast or an overnight fast. The high fat breakfast consists of One Egg ——— one serving of hash brown potatoes, 8 ounces of whole milk, and 6 ounces of orange juice. Blood samples are to be taken at 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, and 24 hours for codeine and chlorpheniramine concentrations. Samples are also to be drawn at 36, 48, and 72 hours for chlorpheniramine concentrations. A total of 500 mL of blood is to be withdrawn. Patients who have donated blood within 30 days or plasma within 7 days of the start of the study are to be excluded. Safety endpoints are to include adverse events, vital signs, physical examination, laboratory tests on blood and urine, and ECGs [Pages 6-8 to 6-11, 6-17, 6-17].

Reviewer comment:
The sponsor has increased the number of patients in the food effects study to 36. Twenty subjects were to be enrolled in the food effects study submitted in the NDA, COD-02001. The Clinical Pharmacology and Biopharmaceutics teams will comment on the proposed analysis of pharmacokinetic data.

Safety endpoints are acceptable. The protocol does not state how the safety endpoints will be reported. The sponsor should provide descriptive analyses of adverse events, vital signs, physical examinations, and ECGs.

3. SUMMARY

Celltech Pharmaceuticals, Inc. is developing an extended release suspension of chlorpheniramine maleate and codeine. The proposed tradename is Codeprex™ Extended Release Suspension. Each 5 mL of the proposed product contains 20 mg of codeine and 4 mg of chlorpheniramine maleate as active ingredients bound to a polistirex resin. The proposed indication is for the temporary relief of ——————— cough, runny nose, sneezing, itching of the nose or throat, and itchy watery eyes, as may occur with the common cold, inhaled irritants, hay fever, or other respiratory allergies. The proposed dose for adults and adolescents ages 12 years and older is two teaspoonfuls (10 mL, 40 mg codeine/8 mg chlorpheniramine) every 12 hours, not to exceed four teaspoonfuls in 24 hours. The proposed dose for children ages 6 years to less than 12 years is one teaspoonful (5 mL, 20 mg codeine/4 mg chlorpheniramine) every 12 hours, not to exceed two teaspoonfuls in 24 hours. The product is not indicated for children under the age of 6 years. The sponsor's submitted an NDA application under Section 505(b)(2) of the FD&C Act [NDA 21-369, 4/13/01]. Bioequivalence data supported the sponsor's conclusion that the extended release product is likely to have a similar degree of effectiveness as codeine and chlorpheniramine antitussive and antihistamine products specified in the OTC monograph. Although the application was approvable from the purely clinical perspective, an approvable action was taken because of CMC issues, including stability and dissolution specifications.

The sponsor has chosen to reformulate their product, and to conduct two new clinical pharmacology studies. The first study, CD-00900, is designed to compare the steady state bioavailability of the reformulated product against a reference immediate release product conforming to OTC monograph standards. It is essentially the same design as the previous pivotal study COD-02002. The second study, CD-00800, is designed to confirm that extended release performance of the product is maintained in a fed and fasted state. This study is essentially the same design as the previous pivotal study COD-02001. Protocols for the proposed studies are acceptable clinically. The Clinical Pharmacology and Biopharmaceutics teams will comment on the proposed analysis of pharmacokinetic data. Safety endpoints for the proposed studies are acceptable. The sponsor should provide descriptive analyses of adverse events, vital signs, physical examinations, and ECGs. It is safe for these studies to proceed.

4. COMMENTS FOR THE SPONSOR

The protocol does not state how the safety endpoints will be reported. In the NDA submission, provide descriptive analyses of adverse events, vital signs, physical examinations, and ECGs.

Reviewed by:

Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

Lydia Gilbert-McClain, M.D.
Team Leader, Division of Pulmonary and Allergy Drug Products

cc: Original IND
HFD-570/Division File
HFD-570/Gilbert-McClain/Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-870/Fadiran/Clinical Pharmacology and Biopharmaceutics Team Leader
HFD-570/V. Shah/CMC Reviewer
HFD-570/Yu/CSO

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/s/

Charles Lee
1/23/03 03:44:38 PM
MEDICAL OFFICER

Lydia McClain
1/27/03 06:44:25 AM
MEDICAL OFFICER

[illegible] CDER REVIEW [illegible] Drug Products (ELED 5420)

Application Number:	N21-369	**Application Type:**	NDA
Sponsor:	Celltech Pharmaceuticals, Inc.	**Proprietary Name:**	Codeprex™
Category of Drug:	Antitussive/antihistamine Codeine/chlorpheniramine	**USAN/Established Name:**	
		Route of Administration:	Oral, extended release suspension
Medical Reviewer:	Charles E. Lee, M.D.	**Review Date:**	1/23/02

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Application	Document Date:	CDER Stamp Date:	Submission Type	Comments:
N21-369 N000	4/13/01	4/13/01	NDA	51 volumes
N21-369 C7	7/13/01	7/18/01	NDA	New trade name
N21-369 N000BZ	8/24/01	8/27/01	NDA	PK, safety data

RELATED APPLICATIONS (if applicable):

Application	Document Date:	Application Type:	Comments:
I54,892	12/22/97	IND	Original IND

REVIEW SUMMARY:

This application is an NDA for Codeprex™ Extended Release Suspension. The sponsor is Celltech Pharmaceuticals, Inc. Each 5 mL of the proposed product contains 20 mg of codeine and 4 mg of chlorpheniramine maleate as active ingredients bound to a polistirex resin. The proposed indication is for the temporary relief of _____ cough, runny nose, sneezing, itching of the nose or throat, and itchy watery eyes, as may occur with the common cold, inhaled irritants, hay fever, or other respiratory allergies. The proposed dose for adults and adolescents ages 12 years and older is two teaspoonfuls (10 mL, 40 mg codeine/8 mg chlorpheniramine) every 12 hours, not to exceed four teaspoonfuls in 24 hours. The proposed dose for children ages 6 years to less than 12 years is one teaspoonful (5 mL, 20 mg codeine/4 mg chlorpheniramine) every 12 hours, not to exceed two teaspoonfuls in 24 hours. The product is not indicated for children under the age of 6 years. The sponsor's application is submitted under Section 505(b)(2) of the FD&C Act. This application relies on the Agency's previous findings of safety of the active drugs as described in the appropriate OTC monographs. The application includes three pivotal bioequivalence studies. Bioequivalence data support the sponsor's conclusion that the extended release product is likely to have a similar degree of effectiveness as codeine and chlorpheniramine antitussive and antihistamine products specified in the OTC monograph. AEs occurring commonly in patients taking the extended release product in the three pivotal biopharmaceutics studies included dizziness, constipation, erythema, dysmenorrhea, among others, and were similar to those expected from codeine and chlorpheniramine. There were no deaths or SAEs in these studies. Vital signs, physical examination, laboratory studies, and ECGs did not reveal any safety signal. Overall, these data support the safety of the proposed product and dose in the proposed population. This application is approvable from the purely clinical perspective. CMC issues, including stability and dissolution specifications, will prevent approval of the product at this time, however.

OUTSTANDING ISSUES:

The sponsor must address problems with stability and dissolution specifications.

RECOMMENDED REGULATORY ACTION:

NDA is: **Approvable: X**

SIGNED:

Medical Reviewer: **Date:**

Medical Team Leader: **Date:**

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EXECUTIVE SUMMARY

1. RECOMMENDATIONS

1.1. Recommendations on approvability

This application is approvable from the purely clinical perspective. The sponsor has successfully shown bioequivalence of the proposed product with an appropriate reference product. The proposed product is likely to have a similar degree of effectiveness as OTC monograph codeine and chlorpheniramine antitussive and antihistamine products. CMC issues, including stability and dissolution specifications, will prevent approval of the product at this time, however.

1.2. Recommendations on Phase 4 studies and risk management steps

Labeling warnings regarding use of the product in children and the elderly should be strengthened. If approved at some time in the future, AE reports should be followed closely for evidence of a safety signal in these populations.

2. SUMMARY OF CLINICAL FINDINGS

2.1. Brief overview of clinical program

This application is an NDA for Codeprex™ Extended Release Suspension. The sponsor is Celltech Pharmaceuticals, Inc. Each 5 mL of the proposed product contains 20 mg of codeine and 4 mg of chlorpheniramine maleate as active ingredients bound to a polistirex resin. The proposed indication is for the temporary relief of ——— cough, runny nose, sneezing, itching of the nose or throat, and itchy watery eyes, as may occur with the common cold, inhaled irritants, hay fever, or other respiratory allergies. The proposed dose for adults and adolescents ages 12 years and older is two teaspoonfuls (10 mL, 40 mg codeine/8 mg chlorpheniramine) every 12 hours, not to exceed four teaspoonfuls in 24 hours. The proposed dose for children ages 6 years to less than 12 years is one teaspoonful (5 mL, 20 mg codeine/4 mg chlorpheniramine) every 12 hours, not to exceed two teaspoonfuls in 24 hours. The product is not indicated for children under the age of 6 years.

The sponsor's application is submitted under Section 505(b)(2) of the FD&C Act, which permits approvals to be based upon bioavailability/bioequivalence of the proposed new drug to an approved reference product. This application relies on the Agency's previous findings of safety of the active drugs as described in the appropriate monographs.

Codeine is an opiate that is marketed in various forms as an antitussive and analgesic. Chlorpheniramine maleate is marketed in various forms as antihistamine. The proposed product contains the above active drugs in an extended release suspension containing polystirex resin. There are no currently marketed products containing codeine or chlorpheniramine maleate alone or in combination in such a form. The sponsor seeks to develop this product to meet a clinical need for patients ages 6 years and older for a

combination of codeine and chlorpheniramine in a single product for relief of symptoms that occur with allergies, the common cold, or from exposure to airborne irritants with a twice daily dosing frequency.

2.2. Efficacy

The sponsor's application is being submitted under Section 505(b)(2) of the FD&C Act, and this application relies on the Agency's previous findings of safety of the active drugs as described in the appropriate OTC monographs. Steady state bioequivalence criteria for codeine were met for AUC, but not for C_{max}, which was low, or for Cmin, which was high. The minimum plasma levels for codeine were above the trough levels for the reference product. Although the C_{max} of the proposed product is low as compared with the reference product, a margin of efficacy is provided, as one-half of the proposed dose would be within specifications of the monograph for the lowest nominal dose. No food effect was observed for codeine. Steady state bioequivalence criteria for chlorpheniramine were met for AUC and C_{max}. Furthermore, chlorpheniramine is probably effective for the proposed indication at lower doses than specified by the OTC monograph. No food effect was observed for chlorpheniramine. This reviewer concurs with the sponsor's conclusion that the extended release product is likely to have a similar degree of effectiveness as codeine antitussive and chlorpheniramine products specified in the OTC monograph.

2.3. Safety

AEs occurring commonly in patients taking the extended release product in the three pivotal biopharmaceutics studies included dizziness, constipation, erythema, and dysmenorrhea, among others. AEs appeared to be similar to those that are associated with use of codeine and chlorpheniramine. It is difficult to draw strong conclusions based on AE data in the three pivotal biopharmaceutics studies because of the small number of subjects and small number of AEs, but proposed doses of codeine and chlorpheniramine are within the specifications for the respective OTC monographs. There were no deaths or SAEs in these studies. Vital signs, physical examination, laboratory studies, and ECGs did not reveal any safety signal. Overall, these data support the safety of the proposed product and dose in the proposed population.

2.4. Dosing

A single dose of the extended release codeine and chlorpheniramine product given every 12 hours is equivalent to that administered with the highest monograph-specified dose every 6 hours given twice in an immediate-release form [21 CFR 341.72, 21 CFR 341.90]. Therefore the amount of the proposed product given over the 12-hour dosing period and over a 24-hour period is in concordance with the amount of the immediate release products specified by the monograph over these same periods. The concentration of codeine in the formulation is greater than the limit for exemption of codeine for prescription products, therefore the product will be classified as a Schedule C-III prescription product, in accordance with 21 CFR 1308.13(e)(2).

2.5. Special populations

The sponsor's summary of the literature reveals and this reviewer's examination of data from AERS DataMart suggest that the elderly and pediatric populations may be at higher risk for AEs, particularly from overdose or respiratory depression. Accordingly, labeling warnings regarding use of the product in children and the elderly should be strengthened. If approved at some point in the future, AE reports should be followed closely for evidence of a safety signal in these populations.

CLINICAL REVIEW

1. INTRODUCTION AND BACKGROUND

1.1. Introduction

This application is an NDA for Codeprex™ Extended Release Suspension. The sponsor is Celltech Pharmaceuticals, Inc. Each 5 mL of the proposed product contains 20 mg of codeine and 4 mg of chlorpheniramine maleate as active ingredients bound to a polistirex resin. The proposed indication is for the temporary relief of ——— cough, runny nose, sneezing, itching of the nose or throat, and itchy watery eyes, as may occur with the common cold, inhaled irritants, hay fever, or other respiratory allergies [Volume 1.1, pages 3.0003, 3.0005]. The proposed dose for adults and adolescents ages 12 years and older is two teaspoonfuls (10 mL, 40 mg codeine/8 mg chlorpheniramine) every 12 hours, not to exceed four teaspoonfuls in 24 hours. The proposed dose for children ages 6 years to less than 12 years is one teaspoonful (5 mL, 20 mg codeine/4 mg chlorpheniramine) every 12 hours, not to exceed two teaspoonfuls in 24 hours. The product is not indicated for children under the age of 6 years [Volume 1.1, page 3.0014]. The sponsor had previously submitted the trade name ——— but the Office of Postmarketing Drug Risk Assessment determined that this trade name was not acceptable because of its promotional character and possible confusion regarding the letter ——

Codeine is an opiate that is marketed in various forms as an antitussive and analgesic. Chlorpheniramine maleate is marketed in various forms as antihistamine. The proposed product contains the above active drugs in an extended release suspension containing polystirex resin. There are no currently marketed products containing codeine or chlorpheniramine maleate alone or in combination in such a form. Fisons previously marketed a discontinued product, Penntuss (NDA 18-928), containing 10 mg/5 mL of codeine and 4 mg/5mL of chlorpheniramine maleate. The sponsor, Celltech Pharmaceuticals, Inc. markets Tussionex (NDA 19-111), 10 mg/5mL of hydrocodone bitartrate and 8 mg/5mL of chlorpheniramine in an extended release suspension containing polystirex resin.

The sponsor seeks to develop this product to meet a clinical need for patients ages 6 years and older for a combination of codeine and chlorpheniramine in a single product for relief of symptoms that occur with allergies, the common cold, or from exposure to airborne irritants with a twice daily dosing frequency.

A single dose of the extended release codeine and chlorpheniramine product given every 12 hours is equivalent to that administered with the highest monograph-specified dose every 6 hours given twice in an immediate-release form [21 CFR 341.72, 21 CFR 341.74, 21 CFR 341.90]. Therefore the amount of the proposed product given over the 12-hour dosing period and over a 24 hour period is in concordance with the amount of the immediate release products specified by the monograph over these same periods. The concentration of codeine in the formulation is greater than the limit for exemption of

codeine for prescription products, therefore the product will be classified as a Schedule C-III prescription product, in accordance with 21 CFR 1308.13(e)(2).

The sponsor's application is being submitted under Section 505(b)(2) of the FD&C Act, which permits approvals to be based upon bioavailability/bioequivalence of the proposed new drug to an approved reference product. This application relies on the Agency's previous findings of safety of the active drugs as described in the appropriate monographs. The relevant monographs for the constituent drugs are:

- Final Monograph for Antitussive Drug Products, August 12, 1987, for codeine as a narcotic antitussive [21 CFR 341.74]
- Final Monograph for OTC Antihistamine Drug Products, December 9, 1992, for chlorpheniramine maleate as an antihistamine [21 CFR 341.72]
- Tentative Final Monograph for Combination Cough, Cold and Bronchodilator Drug Products, August 12, 1988, for the combination of codeine and chlorpheniramine maleate [53 FR 30561]

1.2. Foreign marketing and regulatory history

Products containing a combination of codeine and chlorpheniramine are currently or previously marketed in Canada, Africa, Europe, and Asia [Volume 1.1, page 3.0026]. The proposed product contains codeine and chlorpheniramine maleate in an extended release suspension containing polystirex resin. The sponsor's formulation of codeine polistirex and chlorpheniramine maleate has not been approved and is not marketed in any country.

2. CLINICALLY RELEVANT FINDINGS FROM CHEMISTRY, TOXICOLOGY, MICROBIOLOGY, BIOPHARMACEUTICS, STATISTICS AND/OR OTHER CONSULTANT REVIEWS

2.1. Chemistry, Manufacturing, and Controls

Each teaspoon (5 mL) of Codeprex Extended-Release Suspension contains 20 mg of codeine and 4 mg of chlorpheniramine maleate as active ingredients bound to a polystirex resin. Codeine is an opiate antitussive. Its empirical formula is $C_{18}H_{21}NO_3$. Its molecular weight is 299.37. Chlorpheniramine maleate is an antihistamine. Its empirical formula is $C_{20}H_{23}ClN_2O_4$. Its molecular weight is 390.87. The drug product contains the following excipients: citric acid (anhydrous), D&C Red No. 33, edetate sodium, ethylcellulose, flavor, glycerin, methylparaben, microcrystalline cellulose/carboxymethylcellulose sodium, polyethylene glycol 3350, polysorbate 80, propylparaben, propylene glycol, purified water, sodium hydroxide, sodium polystyrene sulfonate, sucrose, vegetable oil, and xanthan gum [Volume 1.1, page 3.0003].

An appropriate immediate release liquid combination product was not available to serve as a reference product. The sponsor developed an immediate release formulation, which was to comply with the antitussive, antihistamine, and combination monographs. The reference product used in the clinical studies in this NDA contained 20 mg/5 mL of

codeine and 4 mg/5 mL of chlorpheniramine as an immediate release solution [Volume 1.1, page 3.0053].

Dissolution studies revealed decreased release with aging and with higher temperatures, with failure of stability testing even as early as 3 months. These data could result in an approvable or not approvable action. More details may be found in Dr. Vibhakar Shah's CMC review.

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

The Division held an End-of-Phase 2 (EOP 2) meeting with the sponsor on 9/21/98. The Division remarked that comparisons of extended release and immediate release products should focus on the AUC, fluctuation index, and trough concentrations. This point was re-emphasized by the Division in a teleconference with the sponsor on 9/19/00.

Steady state bioequivalence criteria for codeine were met for AUC, but not for C_{max}, which was low, or for C_{min}, which was high. The sponsor points out that although there are few published studies on the antitussive efficacy of codeine, the available evidence indicates that the pharmacodynamic action of codeine is proportional to dose. The sponsor points out the minimum plasma levels for codeine are above the trough levels for the reference product. No food effect was observed for codeine. The sponsor concludes that the extended release suspension would be at least as effective as those currently available OTC monograph antitussive codeine products [Volume 1.37, page 8.0813].

The sponsor states that bioequivalence criteria were met for C_{max}, C_{min}, and AUC in the steady state for chlorpheniramine. No food effect was observed for chlorpheniramine. The sponsor concludes that the effectiveness of chlorpheniramine from the extended release formulation should be as good as that for the immediate release solution, which meets OTC monograph specifications [Volume 1.37, page 8.0814].

Reviewer comment:
At first glance, these data suggest a potential for decreased antitussive efficacy of the extended release product because of the low C_{max} as compared with the reference product. However, it is critical to note that the dose of codeine delivered by the proposed dose in both children and adults is twice the minimum dose specified in the monograph. Even though the C_{max} for the proposed dose of the extended release product is low compared with the reference product, a margin of efficacy is provided, as one-half of the proposed dose of the proposed product would be within specifications of the monograph for the lowest nominal dose. This would also provide for an increased safety margin because of the lower C_{max} for codeine as compared with the immediate release products. The experimental and OTC monograph products are compared below in Table 3.1.

Bioequivalence criteria were met for chlorpheniramine. Furthermore, chlorpheniramine is probably effective for the proposed indication at lower doses than specified by the OTC monograph, which provides an additional margin of efficacy. These data suggest that there is a margin of efficacy and safety for both codeine and chlorpheniramine for the proposed product. This reviewer concurs with the sponsor that the extended release

suspension is likely to be at least as effective as those currently available OTC monograph antitussive codeine and chlorpheniramine products.

Table 3.1. Comparison of Experimental and OTC monograph products [Volume 1.1, page 3.055, 21 CFR 341.72, 21 CFR 341.74].

Product	Formulation	Dosage Regimen	Total Daily Dose
[redacted]			
Proposed Product: Extended release	40 mg COD/8 mg CPM/10 mL	40 mg COD/8 mg CPM Q12H	80 mg COD/16 mg CPM
Reference Product Immediate Release	40 mg COD/8 mg CPM/10 mL	20 mg COD/4 mg CPM Q6H	80 mg COD/16 mg CPM
Codeine OTC Monograph 21 CFR 341.74	Per monograph	10 to 20 mg Q4-6H	40 to 120 mg
Chlorpheniramine OTC Monograph 21 CFR 341.72	Per monograph	4 mg Q4-6H	16 to 24 mg
[redacted]			
Proposed Product: Extended release	40 mg COD/8 mg CPM/10 mL	20 mg COD/4 mg CPM Q12H	40 mg COD/8 mg CPM
Reference Product Immediate Release	40 mg COD/8 mg CPM/10 mL	10 mg COD/2 mg CPM Q6H	40 mg COD/8 mg CPM
Codeine OTC Monograph 21 CFR 341.74	Per monograph	5 to 10 mg Q4-6H	20 to 60 mg
Chlorpheniramine OTC Monograph 21 CFR 341.72	Per monograph	2 mg Q4-6H	8 to 12 mg

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

The sponsor's development plan relied on the following studies:

- Study 1109/99, a product confirmation study employing three lots to select the final product performance characteristics for the pivotal trials, and an evaluation of vivo/in vitro release rates to confirm final dissolution release specifications
- Study COD-02002, a multiple dose PK study comparing a lot representative of the proposed commercial product against a reference immediate release product conforming to OTC monograph standards
- Study COD-02001, a single dose food effects study to confirm that extended release performance is maintained in a fed and fasted state

Study 405-01, an exploratory proof of concept study to confirm the feasibility of an extended release suspension and to identify target product performance characteristics, was not included in this application.

Table 1. Summary of studies, NDA 21-369.

Study Number	Study Type	Treatment Groups	Duration of treatment	Design	Number of subjects	Diagnosis, age of subjects,	Materials submitted in this efficacy supplement
1109/99	Single dose PK	polymer 40 mg COD[1]/8 mg CPM[2] polymer 40 mg COD/8 mg CPM polymer 40 mg COD/8 mg CPM Immediate release 20 mg COD/4 mg CPM	Single dose[3]	Single center, randomized, active-controlled, fasting, four-way crossover	19	Healthy males, 21-40 years	Protocol Study report Appropriate CRFs
COD-0202	Multiple dose PK	polymer 40 mg COD/8 mg CPM Q12h Immediate release 20 mg COD/4 mg CPM Q 6h	6.5 days	Single center, randomized, open-label, two-way crossover	27	Healthy females and males, 21-40 years	Protocol Study report Line listings Appropriate CRFs
COD-0201	Fed and fasted bioavailability	polymer 40 mg COD/8 mg CPM fed polymer 40 mg COD/8 mg CPM fasted	Single dose	Single center, randomized, open-labeled, fed and fasting, two-way crossover	18	Healthy females and males, 21-40 years	Protocol Study report Line listings Appropriate CRFs

[1]COD: codeine
[2]CPM: chlorpheniramine maleate
[3]Immediate release product dosed as two separate doses 6 hours apart

5. CLINICAL REVIEW METHODS

A summary of review methods follows, and includes a description of the conduct of the review and an assessment of data quality.

5.1. Conduct of the review

There were three pivotal biopharmaceutics studies included in this application. The sponsor's application was submitted under Section 505(b)(2) of the FD&C Act, which permits approvals to be based upon bioavailability/bioequivalence of the proposed new drug to an approved reference product. As this application relies on the Agency's previous findings of safety of the active drugs as described in the appropriate monographs, there were no clinical studies submitted.

The three pivotal biopharmaceutics studies were 1109/99, COD-02001, and COD-02002. These studies were individually reviewed, with a strong focus on safety findings. The sponsor submitted a brief Integrated Summary of Efficacy, which focused on the bioequivalence of the proposed product to the reference standard, as there were no clinical studies. The Integrated Summary of Efficacy was briefly reviewed.

Safety data supporting this application was reviewed in depth. These data included the sponsor's integrated safety data from the pivotal studies. These data also included supplemental safety data composed of a summary of the published literature on the safety of codeine and chlorpheniramine and a summary of commercial marketing experience and foreign regulatory actions. This reviewer also examined data from AERS DataMart data for codeine, chlorpheniramine, and Tussionex (NDA 19-111), 10 mg/5mL of hydrocodone bitartrate and 8 mg/5mL of chlorpheniramine in a similar extended-release suspension containing polystirex resin.

5.2. Data quality

The Division of Scientific Investigation (DSI) conducted a review of Study COD-02002. The clinical portion of the study was conducted at:

[redacted]

The analytical portion of the study was conducted at:

[redacted]

Both sites were inspected and there were no objectionable findings. No Form FDA-483 was issued. DSI concluded that the data from this study should be accepted for review [Memorandum from Michael F. Skelly, Ph.D., DSI, HFD-48, 11/28/01].

5.2.1. Ethical standards and financial disclosure

The following items were included in this submission:

- Debarment certification [Volume 1.1, page 16.0002]
- Financial disclosure statement [Volume 1.1, pages 19.0001-19.0003]
- Statements of Good Clinical Practice
  - The sponsor provided a statement of ethical and regulatory considerations and sound clinical research practice for conduct of the studies [Volume 1.39, pages 8.1503-8.1513, Volume 1.42, 8.2433-2444, Volume 1.46, pages 8.3910-8.3923, Volume 1.37, page 8.0816] [Volume 1.42, page 8.2433]

The sponsor certified that they did not would not use in any capacity the services of any person debarred under Section 306(a) and (b) of the Federal Food, Drug, and Cosmetic Act in connection with this application.

The sponsor certified that there was no financial arrangement with the clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study. The sponsor certified that the clinical investigators did not have a proprietary interest in the proposed product or a significant equity in the sponsor. The sponsor certified that no investigator was the recipient of significant payments.

Overall, the data in this application appear to be acceptable for review in this reviewer's opinion.

6. INTEGRATED REVIEW OF EFFICACY

The sponsor's application is being submitted under Section 505(b)(2) of the FD&C Act, which permits approvals to be based upon bioavailability/bioequivalence of the proposed new drug to an approved reference product. This application relies on the Agency's previous findings of safety of the active drugs as described in the appropriate OTC monographs. The proposed product will provide a total dose that is equivalent to that approved for an immediate-release product given every 6 hours. An immediate release solution formulation, which complied with the OTC monographs, served at the reference material to support this 505(b)(2) application.

As such, there were only PK studies included in this application. There were no clinical studies of the efficacy of the product required.

As previously noted, steady state bioequivalence criteria for codeine were met for AUC, but not for C_{max}, which was low, or for C_{min}, which was high. The sponsor points out that although there are few published studies on the antitussive efficacy of codeine, the available evidence indicates that the pharmacodynamic action of codeine is proportional to dose. The sponsor points out the minimum plasma levels for codeine are above the trough levels for the reference product. No food effect was observed for codeine. The sponsor concludes that the extended release suspension would be at least as effective as those currently available OTC monograph antitussive codeine products [Volume 1.37, page 8.0813].

Reviewer comment:
The nominal amount of codeine delivered by the proposed dose in both children and adults is twice the minimum dose specified in the monograph. Even though the C_{max} for the proposed dose of the extended release product is low compared with the reference product, a margin of efficacy is provided, as one-half of the proposed dose of the proposed product would be within specifications of the monograph for the lowest nominal dose. This would also provide for an increased safety margin because of the lower C_{max} for codeine as compared with the immediate release products.

The sponsor states that bioequivalence criteria were met for C_{max}, C_{min}, and AUC in the steady state for chlorpheniramine. No food effect was observed for chlorpheniramine. The sponsor concludes that the effectiveness of chlorpheniramine from the extended release formulation should be as good as that for the immediate release solution, which meets OTC monograph specifications [Volume 1.37, page 8.0814].

Reviewer comment:
Bioequivalence criteria were met for chlorpheniramine. Furthermore, chlorpheniramine is probably effective for the proposed indication at lower doses than specified by the OTC monograph, which provides an additional margin of efficacy. These data suggest that there is a margin of efficacy and safety for both codeine and chlorpheniramine for the proposed product. This reviewer concurs with the sponsor that the extended release suspension is likely to have a similar degree of effectiveness as codeine and chlorpheniramine antitussive and antihistamine products specified in the OTC monograph.

7. INTEGRATED REVIEW OF SAFETY

Integrated review of safety data supporting this application follows below.

7.1. Summary and conclusions

AEs occurring commonly in patients taking the extended release product in the three pivotal biopharmaceutics studies included dizziness, constipation, erythema, and dysmenorrhea, among others. AEs appeared to be similar to those that are associated with use of codeine and chlorpheniramine. It is difficult to draw strong conclusions based on AE data in the three pivotal biopharmaceutics studies because of the small number of subjects and small number of AEs, but proposed doses of codeine and chlorpheniramine are within the specifications for the respective OTC monographs. There were no deaths or SAEs in these studies. Vital signs, physical examination, laboratory studies, and ECGs did not reveal any safety signal. The sponsor's summary of the literature reveals and this reviewer's examination of data from AERS DataMart suggest that the elderly and pediatric populations may be at higher risk for AEs, particularly from overdose or respiratory depression.

7.2. Content

The following data were reviewed in preparation of this overview of safety:

- Sponsor's integrated safety data from the following pivotal studies
  - 1109/99

- COD-0201
- COD-0202

- Sponsor's supplemental safety data
  - Summaries of the published literature on the safety of codeine and chlorpheniramine
  - Commercial marketing experience and foreign regulatory actions
- AERS DataMart data for codeine, chlorpheniramine, and Tussionex (NDA 19-111), 10 mg/5mL of hydrocodone bitartrate and 8 mg/5mL of chlorpheniramine in a similar extended-release suspension containing polystirex resin.

7.3. Integrated safety data, pivotal studies

7.3.1. Description of pivotal studies

Integrated safety data for this application included three pivotal studies:

- Study 1109/99, a product confirmation study employing three lots to select the final product performance characteristics for the pivotal trials, and an evaluation of vivo/in vitro release rates to confirm final dissolution release specifications
- Study COD-02002, a multiple dose PK study comparing a lot representative of the proposed commercial product against a reference immediate release product conforming to OTC monograph standards
- Study COD-02001, a single dose food effects study to confirm that extended release performance is maintained in a fed and fasted state

These studies are summarized below in Table 7.1.

Table 7.1. Summary of studies, NDA 21-369.

Study Number	Study Type	Design	Treatment Groups	Duration	Number of subjects	Diagnosis, age of subjects
1109/99	Single dose PK	Single center, randomized, active-controlled, fasting, four-way crossover	— polymer 40 mg COD[1]/8 mg CPM[2] — polymer 40 mg COD/8 mg CPM — polymer 40 mg COD/8 mg CPM Immediate release 20 mg COD/4 mg CPM	Single dose[3]	19	Healthy males, 21-40 years
COD-0202	Multiple dose PK	Single center, randomized, open-label, two-way crossover	— polymer 40 mg COD/8 mg CPM Q12h Immediate release 20 mg COD/4 mg CPM Q 6h	6.5 days	27	Healthy females and males, 21-40 years

Study Number	Study Type	Design	Treatment Groups	Duration	Number of subjects	Diagnosis, age of subjects
COD-0201	Fed and fasted bioavailability	Single center, randomized, open-labeled, fed and fasting, two-way crossover	[redacted] polymer 40 mg COD/8 mg CPM fed [redacted] polymer 40 mg COD/8 mg CPM fasted	Single dose	18	Healthy females and males, 21-40 years

[1]COD: codeine
[2]CPM: chlorpheniramine maleate
[3]Immediate release product dosed as two separate doses 6 hours apart

7.3.2. Demographics

The majority of subjects in the pivotal studies were of male gender. Males represented from 71.2% to 87.2% of each of the treatment groups. Mean age was approximately 28 years, and ranged from 21 to 39 years in the treatment groups. Patients of Caucasian race were represented most frequently, followed by patients of "Other", Hispanic, and Black races.

Table 7.2. Demographics, pivotal studies, NDA 21-369 [Volume 1.37, page 8.0831]

Characteristic	Extended release COD/CPM N = 66		Immediate release COD/CPM N = 47		Total N = 66	
Gender	n	(%)	n	(%)	n	(%)
Female	19	(28.8)	6	(12.8)	19	(28.8)
Male	47	(71.2)	41	(87.2)	47	(71.2)
Age, years						
Mean age	28.1		28.0		28.1	
Range	21 – 39		21 – 39		21 – 39	
Race	n	(%)	n	(%)	n	(%)
Black	6	(9.1)	5	(10.6)	6	(9.1)
Hispanic	16	(24.2)	10	(21.3)	16	(24.2)
Other	16	(24.2)	16	(34.0)	16	(24.2)
Caucasian	28	(42.4)	16	(34.0)	28	(42.4)

7.3.3. Disposition

Subject disposition is summarized in Table 7.3. A total of 66 subjects were randomized to the extended release suspension, and 47 of these subjects were also exposed to the immediate release solution. The frequency of withdrawals was similar, with a slightly higher frequency for withdrawal due to AE in the extended release group (6.1%) than in the immediate release group (4.2%).

Table 7.3. Disposition, pivotal studies, NDA 21-369 [Volume 1.37, page 8.0833]

	Extended release COD/CPM N = 66		Immediate release COD/CPM N = 47	
	n	(%)	n	(%)
Subjects randomized	66	(100)	47	(100)
Subjects completed	61	(92.4)	43	(91.4)

	Extended release COD/CPM N = 66		Immediate release COD/CPM N = 47	
	n	(%)	n	(%)
Withdrawals	5	(7.6)	4	(8.5)
AE	4	(6.1)	2	(4.2)
Consent withdrawn	0	(0)	1	(2.1)
Personal reasons	1	(1.5)	1	(2.1)

7.3.4. Exposure

Exposure to study medication is summarized in Table 7.4. Subjects were exposed a single dose of extended release 40 mg codeine/8 mg chlorpheniramine up to 6.5 days of extended release 40 mg codeine/8 mg chlorpheniramine given BID. There were a total of 66 subjects exposed to the extended release suspension and 47 exposed to the immediate release solution.

Table 7.4. Exposure, pivotal studies, NDA 21-369 [Volume 1.37, page 8.0834]

Characteristic	Drug tested	Subjects randomized	Daily dose, duration
Study 4109/99			
	ER 40 mg COD/8 mg CPM — coat	19	Single dose, one day
	ER 40 mg COD/8 mg CPM, — coat	20	Single dose, one day
	ER 40 mg COD/8 mg CPM, — coat	19	Single dose, one day
	IR 20 mg COD/4 mg CPM	19	Two doses, one day
Study COD-02001			
	ER 40 mg COD/8 mg CPM, high fat	19	Single dose, one day
	ER 40 mg COD/8 mg CPM, fasted	18	Single dose, one day
Study COD-02002			
	ER 40 mg COD/8 mg CPM, high fat	25	BID for 6.5 days
	IR 20 mg COD/4 mg CPM, fasted	24	QID for 6.5 days

7.3.5. Adverse events

AEs occurring in more than one patient and more frequently in the extended release suspension are summarized in Table 7.5. The frequency of AEs was similar in the extended (33.3%) and immediate release (38.3%) suspensions. Dizziness, constipation, erythema, abdominal pain, dysmenorrhea, nausea, pain, and toothache occurred more frequently in the extended release group. It is difficult to draw strong conclusions based on these data because of the small number of AEs.

Table 7.5. AEs occurring in >1 patient and more frequently in extended release suspension, integrated data from pivotal studies, NDA 21-369 [Volume 1.37, page 8.0837-8.0839]

	Extended release COD/CPM N = 66		Immediate release COD/CPM N = 47	
	n	(%)	n	(%)
Subjects with any AE	22	(33.3)	18	(38.3)
Dizziness	4	(6.1)	0	(0)
Constipation	3	(4.5)	1	(2.1)
Erythema	3	(4.5)	2	(4.3)
Abdominal pain	2	(3.0)	1	(2.1)
Dysmenorrhea	2	(3.0)	0	(0)
Nausea	2	(3.0)	0	(0)
Pain	2	(3.0)	0	(0)

	Extended release COD/CPM N = 66		Immediate release COD/CPM N = 47	
	n	(%)	n	(%)
Toothache	2	(3.0)	0	(0)

AEs known to be associated with codeine, antihistamines, or anticholinergic medications are summarized in Table 7.6. The frequency of AEs was similar in the extended (33.3%) and immediate release (38.3%) suspensions. Constipation, nausea, and tachycardia were more common in subjects treated with the extended release suspension. Headache, pruritus, asthenia, and somnolence were more common in subjects treated with the immediate release solution. It is difficult to draw strong conclusions on differences between treatments in the frequency of these AEs because of the low numbers.

Table 7.6. AEs known to be associated with codeine, antihistamines, or anticholinergic drugs, integrated data from pivotal studies, NDA 21-369 [Volume 1.37, page 8.0837-8.0839]

	Extended release COD/CPM N = 66		Immediate release COD/CPM N = 47	
	n	(%)	n	(%)
Subjects with any AE	22	(33.3)	18	(38.3)
Headache	5	(7.6)	6	(12.8)
Pruritus	4	(6.1)	9	(19.1)
Asthenia	3	(4.5)	6	(12.8)
Somnolence	3	(4.5)	3	(6.4)
Constipation	3	(4.5)	1	(2.1)
Nausea	2	(3.0)	0	(0)
Tachycardia	1	(1.5)	0	(0)
Dry mouth	1	(1.5)	1	(2.1)
Confusion	1	(1.5)	1	(2.1)
Urinary hesitancy	1	(1.5)	1	(2.1)
Mydriasis	0	(0)	1	(2.1)

7.3.6. SAEs and deaths

There were no SAEs or deaths in the pivotal studies (see appropriate subsections of each individual study review, Section 11 of this document).

7.3.7. Withdrawals due to AEs

There were 5 patients who withdrew from the pivotal studies because of AEs. Subject 012, who was treated with extended release suspension, withdrew from COD-02001 because of a headache. Subject 007, who was treated with the extended release suspension, withdrew from study COD-02002 because of mild laryngismus and mild pruritus. Subject 010, who was treated with immediate release solution, withdrew from COD-02002 because of mild pruritus and a mild rash. Subject 021, who was treated with the immediate release solution, withdrew from COD-02002 because of a mild rash. Finally, subject 026, who was treated with the extended release suspension, withdrew from COD-02002 because of a moderate headache [Volume 1.37, page 8.0827].

7.3.8. Vital signs

The sponsor provided no integrated summary of data from vital signs. There was a mean increase from baseline in systolic BP of 3.7mm Hg, a mean increase in diastolic BP of

4.3 mm Hg, and mean increase in pulse of 14.3 bpm in COD-02002 [Volume 1.46, page 8.3718]. There were no AEs reported for tachycardia or for hypertension. The increase in pulse may be a manifestation of the anticholinergic activity of chlorpheniramine. One would not expect a change in BP from anticholinergic activity, however. Although these changes in vital signs are not clinically significant, they may represent a drug effect.

7.3.9. Physical examination

The sponsor provided no integrated summary of data from physical examinations. This reviewer's examination of physical examination data for the individual studies did not reveal any clinically significant changes (see appropriate subsections of each individual study review, Section 11 of this document).

7.3.10. Laboratory studies

The sponsor reported no clinically significant abnormalities from laboratory data in these studies [Volume 1.37, page 8.0828]. There was one woman in study COD-02001 who developed a mild anemia (see Section 11.2.2 of this review). Other than this one subject, this reviewer concurs with the sponsor that there were no clinically significant laboratory abnormalities. No safety signal is revealed by these data.

7.3.11. ECGs

The sponsor provided no integrated summary of data from ECG data. This reviewer's examination of ECG data for the individual studies did not reveal any clinically significant changes (see appropriate subsections of each individual study review, Section 11 of this document).

7.4. Supplemental safety data

The sponsor provided the following data in support of safety:

- Sponsor's supplemental safety data
  - Summaries of the published literature on the safety of codeine and chlorpheniramine
  - Commercial marketing experience and foreign regulatory actions

These data are described below.

7.4.1. Summary of published literature

The sponsor provided a short review of the literature that focused primarily on the safety of codeine and chlorpheniramine in the elderly and in the pediatric population.

The sponsor's review revealed that there is insufficient data to draw firm conclusions from codeine and chlorpheniramine pharmacokinetics to guide dosing in the elderly [Volume 1.34, page 8.0093]. Impaired codeine clearance in the elderly is to be expected because of decreased glomerular filtration rate, and the sponsor notes that renal monitoring should be considered [Volume 1.34, page 8.0085]. Drowsiness and over-sedation are possible, and therefore a increased potential for falls and fractures in the elderly exists [Volume 1.34, page 8.0084]. Exaggerated central nervous system effects

7.5. AERS DataMart

This reviewer screened AERS DataMart data reports of deaths and life-threatening reactions with the use of codeine in children 0 months to 13 years of age. There were 7 deaths and one life-threatening reaction in children under the age of 3 years listed for codeine-containing products. Two of these were listed as accidental overdoses. There were 4 deaths listed for codeine-containing products in children from 3 years to 13 years of age. One of these deaths was listed as an accidental overdose. Most of these deaths appeared to be from respiratory depression.

AERS DataMart data reports of deaths and life-threatening reactions with the use of codeine in patients 65 years of age and greater were screened by this reviewer. There were 63 reports listed. Most cases involved multiple medications. There were 3 deaths listed as accidental overdoses in this age group.

Tussionex (NDA 19-111), 10 mg/5mL of hydrocodone bitartrate and 8 mg/5mL of chlorpheniramine, is a extended-release suspension containing polystirex resin, similar to the sponsor's proposed product. AERS DataMart data reports of deaths and life-threatening reactions with the use of Tussionex (NDA 19-111) in children 0 months to 13 years of age were screened by this reviewer. There were three deaths and one life-threatening reaction. Two deaths were in 5 year olds. One was listed as accidental overdose and the other was listed as death not otherwise specified. One death from apnea was in a 3 year old. The life threatening reaction was respiratory depression in an 11-month old.

There was a single AERS DataMart reports of a death from a GI tract hemorrhage with the use of Tussionex (NDA19-111) in a 96 year old woman who was taking multiple medications, including Coumadin.

Reviewer comment:
It is difficult to draw strong conclusions from the AERS data because of the sketchy nature of the reports. It is likely that the sponsor's product has the potential to produce similar AEs in the pediatric and elderly populations. AE reports should be followed for any early sign of a safety signal in the elderly and pediatric populations.

7.6. References

1. Taylor JA, et. al. Efficacy of cough suppressants in children. J Pediatr 1993; 122:799-802.
2. von Muhlendahl KE, et. al. Codeine intoxication in childhood. Lancet 1976 Aug 7; 2(7980):303-305.
3. Ivey HH, Kattwinkel J. Letter: Danger of Actifed-D. Pediatrics 1976; 57:164-165.

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

The proposed dose for adults and adolescents ages 12 years and older is two teaspoonfuls (10 mL, 40 mg codeine/8 mg chlorpheniramine) every 12 hours, not to exceed four teaspoonfuls in 24 hours. The proposed dose for children ages 6 years to less than 12

years is one teaspoonful (5 mL, 20 mg codeine/4 mg chlorpheniramine) every 12 hours, not to exceed two teaspoonfuls in 24 hours. The product is not recommended in children under 6 years of age [Volume 1.1, page 3.0014].

A single dose of the extended release codeine and chlorpheniramine product given every 12 hours is equivalent to that administered with the highest monograph-specified dose every 6 hours given twice in an immediate-release form [21 CFR 341.72, 21 CFR 341.74, 21 CFR 341.90]. Therefore the amount of the proposed product given over the 12-hour dosing period and over a 24 hour period is in concordance with the amount of the immediate release products specified by the monograph over these same periods. A comparison of the proposed and experimental products with the OTC monograph specifications is found earlier in this review in Table 3.1.

The concentration of codeine in the formulation is greater than the limit for exemption of codeine for prescription products, therefore the product will be classified as a Schedule C-III prescription product, in accordance with 21 CFR 1308.13(e)(2).

A consultation from the Controlled Substances Staff (CSS) notes that the product meets the requirements of a Schedule C-III narcotic. Additional labeling warning on neonatal opiate withdrawal, including description of the symptoms of this syndrome was recommended. Additional labeling stating that dependence and tolerance may develop with repeated administration of the product was also recommended [Memorandum, Michael Klein, Ph.D., CSS, HFD-009, 12/20/01].

Reviewer recommendations and comments on product labeling be incorporated into final product labeling at a later date, and are not included in this document.

9. USE IN SPECIAL POPULATIONS

There were only 66 patients that took part in the biopharmaceutics studies in this application, and therefore too few for a subgroup analysis of safety by gender or race for these studies. The age range of patients in these biopharmaceutics studies was also narrow, from 21 to 39 years, and no subgroup analysis of safety for children or the elderly is possible [Volume 1.37, page 8.0822].

Safety data from the sponsor's literature review raise concerns that these special populations, the elderly and children, may be at higher risk for adverse events. Labeling should include clear warnings that these populations are at higher risk for significant AEs, such as respiratory depression. AE reports should be followed for any early sign of a safety signal in the elderly and pediatric populations.

The sponsor has requested a waiver of pediatric studies. The sponsor states that both active drugs are well characterized in published literature and widely used in OTC and Rx markets. The sponsor points out that both codeine and chlorpheniramine have undergone DESI review and are classified in the OTC monograph as safe and effective. Children 6 years of age and older are covered in accordance with the Agency's previous findings for safety and effectiveness [IND 54,892 N017 RW, PW, 1/12/01].

Reviewer comment:
Because of concerns of a likely higher risk for AEs in the pediatric population, no waiver should be granted at this time. It would be appropriate, however, to defer pediatric studies until the extent of use in this population is known, and while AE reports are followed closely for evidence of a safety signal in this population.

10. CONCLUSIONS AND RECOMMENDATIONS

The sponsor's application is being submitted under Section 505(b)(2) of the FD&C Act, which permits approvals to be based upon bioavailability/bioequivalence of the proposed new drug to an approved reference product. This application relies on the Agency's previous findings of safety of the active drugs as described in the appropriate OTC monographs. Steady state bioequivalence criteria for codeine were met for AUC, but not for C_{max}, which was low, or for C_{min}, which was high. The minimum plasma levels for codeine were above the trough levels for the reference product. Although the C_{max} of the proposed product is low compared with the reference product, a margin of efficacy is provided, as one-half of the proposed dose of the proposed product would be within specifications of the monograph for the lowest nominal dose. No food effect was observed for codeine. Steady state bioequivalence criteria for chlorpheniramine were met for AUC and C_{max}. Furthermore, chlorpheniramine is probably effective for the proposed indication at lower doses than specified by the OTC monograph. No food effect was observed for chlorpheniramine. This reviewer concurs with the sponsor's conclusion that the extended release product is likely to have a similar degree of effectiveness as codeine antitussive and chlorpheniramine products specified in the OTC monograph.

AEs occurring commonly in patients taking the extended release product in the three pivotal biopharmaceutics studies included dizziness, constipation, erythema, and dysmenorrhea, among others. AEs appeared to be similar to those that are associated with use of codeine and chlorpheniramine. It is difficult to draw strong conclusions based on AE data in the three pivotal biopharmaceutics studies because of the small number of subjects and small number of AEs, but proposed doses of codeine and chlorpheniramine are within the specifications for the respective OTC monographs. There were no deaths or SAEs in these studies. Vital signs, physical examination, laboratory studies, and ECGs did not reveal any safety signal. The sponsor's summary of the literature reveals and this reviewer's examination of data from AERS DataMart suggest that the elderly and pediatric populations may be at higher risk for AEs, particularly from overdose or respiratory depression.

Dissolution studies revealed decreased release with aging and with higher temperatures, with failure of stability testing even as early as 3 months. These data could result in an approvable or not approvable action, and dissolution and stability will require additional study.

From the purely clinical perspective, this application is approvable. Labeling warnings regarding use of the product in children and the elderly should be strengthened. If

approved at some time in the future, AE reports should be followed closely for evidence of a safety signal in these populations.

11. APPENDIX, CLINICAL STUDIES

11.1. Study 405-01, PK proof-of-concept study

The sponsor did not include a final study report in the NDA for this study because it was considered exploratory. The study report was submitted previously to IND 54,892 on 1/22/99. Study 405-01 was a PK study used to establish the proof-of-concept for the codeine/chlorpheniramine extended-release suspension. Four batches of suspension were manufactured with coated codeine polystirex with coating levels from —— . Based on observations from this study, the sponsor prepared optimized formulations for Study 1109/99 [Volume 1.1, page 3.0059].

11.2. Study 1109/99

Title: Four-way crossover bioavailability study of new codeine/chlorpheniramine extended-release suspension

Date, start of study period 1: 11/27/99
Date, start of study period 4: 12/19/99
Date of study report: 9/22/00

Study 1109/99 was a PK study to establish the final product performance characteristics for the pivotal trials and to establish an in vitro/in vivo correlation for future scale-up.

The study was a randomized, single dose, four-way crossover bioavailability study. The study was designed to quantify the rate and extent of absorption of three different formulations of the proposed product. The formulations studied included a — polymer coat with an in vitro —release of codeine and chlorpheniramine maleate, a —— polymer coat with —— release of codeine and chlorpheniramine maleate, and a — polymer coat with — release of codeine and chlorpheniramine maleate. The formulations studied are displayed in Table 11.2.1. The —polymer — release formulation was stored at —— RH for —— to simulate aged product. Blood samples were taken immediately before dosing (0 hours) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, and 24 hours for measurement of codeine and chlorpheniramine concentrations. Blood samples were also drawn at 36, 48, and 72 hours for chlorpheniramine concentrations.

Table 11.2.1. Study treatments, Study 1109/99 [Volume 1.1, page 3.0044, Volume 1.39, page 8.1353].

Treatment A	Extended release suspension, — polymer coating, — coating level 40 mg codeine and 8 mg chlorpheniramine/10 mL Batch #CL99035A Single dose
Treatment B*	Extended release suspension, — polymer coating — coating level 40 mg codeine and 8 mg chlorpheniramine/10 mL Batch #CL99034A Single dose
Treatment C	Extended release suspension —polymer coating, — coating level 40 mg codeine and 8 mg chlorpheniramine/10 mL Batch #8027-121A Stored at — RH for —— to simulate aged product Single dose

Treatment D	Immediate release, reference solution 20 mg codeine and 4 mg chlorpheniramine/5 mL No batch number provided Two doses separated by 6 hours

*Formulation used in subsequent studies

The study was to enroll 20 healthy, non-smoking, male subjects, ages 21-40 years [Volume 1.39, page 8.1491]. Twenty healthy male subjects were enrolled and 19 subjects completed all four periods of the study. One subject, #13, withdrew from the study after period 1. This subject was not replaced. Each subject received a complete medical history vital signs and physical examination, 12-lead ECG and clinical laboratory tests on blood and urine. Physical examination and clinical laboratory tests were repeated at the end of the study. Subjects were observed and questioned throughout the study for the occurrence of any adverse events.

There were 20 subjects exposed to study treatments. Review of demographic data revealed that the majority of subjects were Hispanic/Caucasian (15/20, 75.0%). There were two subjects that were Black (2/20, 10.0%), and two subjects that were Caucasian (2/20, 10.0%). One subject was Hispanic/Black (1/20, 5.0%) [Volume 1.39, page 8.1520]. The mean age for subjects in this study was 30.7 years. Subjects ranged from 21 to 39 years of age [Volume 1.39, page 8.1520].

11.2.1. Clinical pharmacology outcomes

PK analyses were based on the data for the 19 subjects who completed all four periods of the study. PK results from this study are presented in Table 11.2.2. Please see Dr. Choi's biopharmaceutics review for additional information.

Table 11.2.2. Mean PK parameters for codeine and chlorpheniramine, Study 1101/99 [Volume 1.39, pages 8.1373, 8.1376]

	C_{max}, ng/mL N = 19	C_{12}, ng/mL N = 19	T_{max}, h N = 19	$AUC_{0\text{-}inf}$, ng.h/mL N = 19	$AUC_{0\text{-}12}$, ng.h/mL N = 19
Codeine					
Treatment A			3.632	426.575	267.87
Treatment B*			3.579	447.489	238.52
Treatment C			5.053	480.625	190.95
Treatment D**			3.132	437.272	359.39
Chlorpheniramin					
Treatment A			7.342	330.42	51.89
Treatment B*			8.132	318.685	52.86
Treatment C			12.000	306.780	35.24
Treatment D**			8.526	344.181	83.56

*Formulation used in subsequent studies
**Two doses given, one dose Q6H

The C_{max} for codeine was lower for Treatments A, B, and C than for Treatment D, the immediate release reference solution. The C_{max} for codeine for the extended release suspensions was highest for Treatment A (— polymer coating, — ng/mL), and lowest for Treatment C (— polymer coating, — ng/mL). The T_{max} for codeine was shortest for Treatment D, the immediate-release reference solution (— h). The T_{max} for Treatment C was longest (— polymer coating, — — . $AUC_{0\text{-}inf}$ for codeine were fairly similar among treatments, with the highest $AUC_{0\text{-}inf}$ for

Treatment C (polymer coating, , ng.h/mL) and lowest for Treatment A (polymer coating, ng.h/mL) [Volume 1.39, pages 8.1373].

The C_{max} for chlorpheniramine was lower for Treatments A, B, and C than Treatment D, the immediate release reference solution. The C_{max} for the extended release suspensions was highest for Treatment B (polymer coating, ng/mL), and lowest for Treatment C (polymer coating, , ng/mL). The T_{max} for chlorpheniramine was shortest for Treatment A, polymer coating, h). The T_{max} for Treatment C was longest (polymer coating, , 12.000 h). AUC0-inf for chlorpheniramine was fairly similar among treatments, with the highest AUC_{0-inf} for Treatment D (immediate release reference solution, ng.h/mL) and lowest for Treatment C (polymer coating, ng.h/mL) [Volume 1.39, pages 8.1376].

Statistical comparisons were performed to determine if the extended release suspensions were bioequivalent to the immediate release reference product. These comparisons showed the extended release suspensions to be equivalent to the reference solution for codeine for the log-transformed C_{12} and AUC_{0-inf}. The extended release suspensions were not equivalent for codeine for the log transformed C_{24}, AUC_{0-12}, and C_{max}, and the non-log transformed T_{max}. These comparisons showed the extended release suspensions to be equivalent to the reference solution for chlorpheniramine for the log-transformed AUC_{0-inf}. The extended release suspensions were not equivalent for chlorpheniramine for the log transformed C_{12}, C_{24}, AUC_{0-12}, and C_{max}, and the non-log transformed T_{max}. Based on results of this study, the release rate profile of the medium release product was identified as the target for the lots to be used in the pivotal trials [Volume 1.1, page 3.0060].

11.2.2. Safety outcomes

Safety endpoints included adverse events, vital signs, physical examination, and laboratory tests on blood and urine [Volume 1.39, page 8.1492].

There were two adverse events (AEs). Both AEs were self-limited [Volume 1.39, pages 8.1518, 8.1519]. Subject #06 in Period 1 developed a toothache. He was taking Treatment B, the extended release, polymer suspension [Volume 1.39, page 8.1522]. Subject #05 developed nausea without vomiting. He was also taking Treatment B, the extended release, polymer suspension [Volume 1.39, page 8.1523]. There were no other AEs. There were no SAEs or deaths. There was one withdrawal, subject #13, who did not return for the second study period and was lost to follow-up. He was treated with Treatment B, the extended release, polymer suspension [Volume 1.39, page 8.1521]. There was no additional information on the withdrawal. It is interesting to note that both AEs and the withdrawal were taking Treatment B, the polymer suspension, however it is difficult to draw any conclusions based on the small numbers of subjects in this study. The sponsor reported that there were no significant changes in physical examinations, laboratory studies or ECGs in this study [Volume 1.39, page 8.1518]. Initially, the sponsor did not submit line listings and summaries for safety endpoints for this study and the sponsor was asked in an information request to provide line listings and summaries of physical examinations and laboratory study results. These

data were submitted by the sponsor and were reviewed [Volume 3.1, pages 001-042]. This reviewer concurs that there were no significant changes in physical examination or laboratory studies.

Although it is difficult for this reviewer to draw any conclusions based on the small amount of safety data contributed by this study, there are no concerning safety signals noted.

11.3. Study COD-02001

Title: Food effect bioavailability study of an extended-release suspension of codeine 40 mg/chlorpheniramine maleate 8 mg

Date first subject screened: July 11, 2000
Date last subject completed: August 14, 2000
Date of study report: January 19, 2001

Study COD-02001 was a bioavailability study designed to confirm the extended release product performance in both fed and fasted states.

This study was a single center, randomized, open-label, two-way crossover study. Twenty healthy male and female subjects, ages 21-40 years, were to be studied. Eighteen subjects completed the study. Each subject was randomly assigned to receive 10 mL of the extended release suspension containing 40 mg codeine and 8 mg chlorpheniramine maleate after either a high fat breakfast or an overnight fast. The high fat breakfast consisted of One Egg ' ——— , one serving of ——— hash brown potatoes, 8 ounces of whole milk, and 6 ounces of orange juice [Volume 1.42, page 8.2257]. Blood samples were taken at 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, and 24 hours for codeine and chlorpheniramine concentrations. Samples were also drawn at 36, 48, and 72 hours for chlorpheniramine concentrations [Volume 1.42, page 8.2257].

The study report did not include a batch number and description of the coating level of the drug product. The drug product used in this study was described in the CMC section of the application, and is displayed below in Table 11.3.1. The drug product used was the same lot as used in Study COD-02002.

Table 11.3.1. Study treatment formulation, Study COD-02001 [Volume 1.1, page 3.0044].

Finished product			Coated codeine polistirex
Dosage form	Coating level	Lot number	Lot number
COD/CPM* extended release suspension	———	CL00047A	CL00046-PC1

*COD/CPM: Codeine/chlorpheniramine

There were 19 subjects enrolled in the study. One subject withdrew because of an adverse event. Review of demographic data revealed that the majority of subjects were Caucasian (12/19, 63.2%). There were six Hispanic subjects (6/19, 31.6%) and one Black subject (1/19, 5.3%). The majority of subjects were women (13/19, 68.4%). There were six male subjects (6/16, 31.6%). The mean age for subjects in this study was 28.4 years, and subjects ranged from 21 years to 38 years of age [Volume 1.42, pages 8.2279, 8.2292].

11.3.1. Clinical pharmacology outcomes

PK analyses were based on the data for the 18 subjects who completed both periods of the study. Additional information may be found in Dr. Choi's biopharmaceutics review. PK results from this study are presented in Table 11.3.2.

Table 11.3.2. PK parameters for codeine and chlorpheniramine, Study COD-02001 [Volume 1.42, pages 8.2284, 8.2286]

	C_{max}, mean ng/mL N = 18	T_{max}, median h N = 18	$AUC_{0\text{-inf}}$, mean ng.h/mL N = 18
Codeine			
Fasted	[redacted]	5.0	468.67
Fed	[redacted]	4.5	495.70
Chlorpheniramine			
Fasted	[redacted]	8.0	376.04
Fed	[redacted]	15.0	368.60

C_{max} for codeine was fairly similar in fasted (28.91 ng/mL) and fed (32.48 ng/mL) states. T_{max} for and $AUC_{0\text{-inf}}$ for codeine were also similar in fasted and fed states. C_{max} and $AUC_{0\text{-inf}}$ for chlorpheniramine were similar in the fasted and fed states. T_{max} for chlorpheniramine was shorter for fasted subjects (8.0 h) than for fed subjects (15.0 h). Although this is a large difference in the T_{max} between subject groups, the PK profile reveals only small differences in chlorpheniramine concentrations between 8.0 and 15.0 h for both fed and fasted subjects [Volume 1.42, page 8.2270].

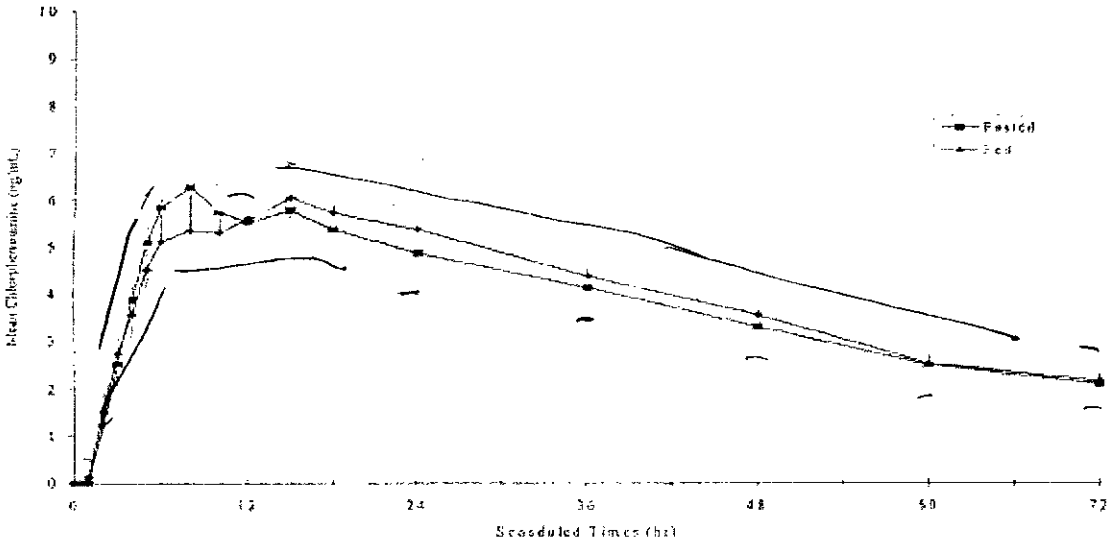

Figure 11.3.1. PK profile for chlorpheniramine, fed and fasted states [from sponsor's Figure 5.2, Volume 1.42, page 8.2270].

The sponsor concludes that there is no food effect for chlorpheniramine because the LS Mean ratio and 90% confidence intervals for C_{max}, $AUC_{0\text{-inf}}$, and $AUC_{0\text{-last}}$ were within the 80% to 125% confidence limits for bioequivalence. The sponsor also concludes that there is no food effect for codeine because the LS Mean ratio and 90% confidence intervals for C_{max}, $AUC_{0\text{-inf}}$, and $AUC_{0\text{-last}}$ were within the 80% to 125% confidence limits for bioequivalence [Volume 1.42, pages 8.2263, 8.2264]. These data are displayed below in Table 11.3.3.

Table 11.3.3. PK parameters for codeine and chlorpheniramine, Study COD-02001 [Volume 1.42, pages 8.2285, 8.2287]

	LS Mean			90% CI of Ratio	
Parameter	Fasted	Fed	Ratio, fed/fasted, %	Low, %	High, %
Codeine					
C_{max}, ng/mL	[redacted]	[redacted]	[redacted]	101.92	124.64
$AUC_{0\text{-}inf}$, ng.hr/mL	453.10	474.97	104.83	99.04	110.95
$AUC_{0\text{-}last}$, ng.hr/mL	346.83	390.99	112.73	104.17	122.00
Chlorpheniramine					
C_{max}, ng/mL	[redacted]	[redacted]	[redacted]	88.46	100.63
$AUC_{0\text{-}inf}$, ng.hr/mL	349.55	348.08	99.58	91.45	108.43
$AUC_{0\text{-}last}$, ng.hr/mL	254.72	262.80	103.17	97.53	109.14

11.3.2. Safety outcomes

Safety endpoints included adverse events, vital signs, physical examination, laboratory tests on blood and urine, and ECGs [Volume 1.42, page 8.2248]. There were 18 adverse events that occurred in seven of the 19 subjects exposed to treatment in this study. The most common AEs included headache, dizziness, pain, somnolence, and asthenia. Headache occurred in 3 subjects (3/19, 15.8%) and dizziness, pain, somnolence, and asthenia each occurred in two subjects (2/19, 10.5%) [Volume 1.42, page 8.2280]. All AEs were mild, except for one headache that was reported as severe. There were no deaths or SAEs in the study.

There was one subject who withdrew from the study because of an AE. This was Subject 012, a 31 year-old white woman who developed a severe headache on the Day 2 of the study. She also reported photophobia, nausea and drowsiness [Volume 1.42, page 8.2569]. Although not reported as an AE, the CRF indicates that the subject also had dysmenorrhea [Volume 1.42, page 8.2570]. She was in the fed treatment group, Treatment A [Volume 1.42, page 8.2565]. The subject withdrew from the study on Day 8. She received treatment with two doses of 1000 mg of acetaminophen. She also took a single dose of 600 mg of ibuprofen and took 400 mg of ibuprofen BID for two days [Volume 1.42, page 8.2570]. This subject's codeine and chlorpheniramine blood levels 24 hours post-dose were comparable with other subjects in the study [Volume 1.42, page 8.2555].

The sponsor reported that there were no clinically significant changes in any of the laboratory data during the study [Volume 1.42, page 8.2265]. This reviewer examined the laboratory summary data and the individual listings for lab values for this study [Volume 1.42, pages 8.2407 to 8.2414, 8.2369 to 8.2406]. This reviewer concurs that there were no clinically significant changes in mean values for laboratory data in this study. However, laboratory data line listings revealed that one subject had a change in hematocrit from [redacted] and RBC from [redacted] [Volume 1.42, page 8.2382]. Interestingly, this was subject 012, the 31-year old woman discussed previously who withdrew because of headache and required treatment with acetaminophen and ibuprofen. The changes in hematocrit and RBC are more likely to be due to the ibuprofen than study treatment, although it is possible that the headache may have been treatment-related.

The sponsor reported that there were no clinically significant findings or changes in vital signs, physical examinations, or ECGs in any of the study subjects [Volume 1.42, pages 8.2265, 8.2266]. This reviewer examined line listings and summaries for these safety endpoints [Volume 1.42, pages 8.2342 to 8.2367]. This reviewer noted no clinically significant findings or changes in these safety endpoints. Although this was a small study, no important safety signal is noted.

11.4. Study COD-02002

Title: Steady state bioavailability study of an extended-release suspension of codeine 40 mg/chlorpheniramine maleate 8 mg relative to an immediate-release solution of codeine 20 mg/chlorpheniramine maleate 4 mg

Date first subject screened: June 29, 2000
Date last subject completed: August 22, 2000
Date of study report: February 20, 2001

Study COD-02002 was a multiple-dose PK study that compared a lot representative of the to-be-marketed product with a reference immediate release product which conformed to OTC monograph standards to link efficacy and safety for the intended indication and population.

The study was a multiple dose, randomized, open-label, two way crossover study. Each period was seven days. There was a washout period of at least seven days between treatment periods. Twenty-six healthy male and female subjects were to be enrolled. Twenty-seven subjects were actually enrolled, and 22 subjects completed the study. Each subject was randomly assigned to treatment for 6.5 days of either 10 mL of extended release suspension containing 40 mg codeine and 8 mg chlorpheniramine maleate dosed every 12 hours or 5 mL of immediate release solution containing 20 mg codeine and 4 mg chlorpheniramine maleate dosed every 6 hours. Blood samples were collected immediately before dosing (0 hours) and at 96, 120, 144, 144.5, 146, 147, 148, 149, 150, 150.5, 151, 152, 153, 154, 155, and 156 hours after the dose at time 0 hours. Plasma concentrations of codeine and chlorpheniramine were assayed [Volume 1.45, page 8.3207].

The study report did not include a batch number and description of the coating level of the drug product. The drug product used in this study was described in the CMC section of the application, and is displayed below in Table 11.4.1. The drug product was the same lot as used in Study COD-02001.

Table 11.4.1. Study treatment formulation, Study COD-02002 [Volume 1.1, page 3.0044].

Finished product			Coated codeine polistirex
Dosage form	Coating level	Lot number	Lot number
COD/CPM* extended release suspension	[redacted]	CL00047A	CL00046-PC1

*COD/CPM: Codeine/chlorpheniramine

There were 27 subjects enrolled in the study. Four subjects withdrew because of an adverse event. One subject voluntarily withdrew. Review of demographic data revealed that the majority of subjects were Caucasian (14/27, 51.9%). There were 10 Hispanic subjects (10/27, 37.0%) and three Black subjects (3/27, 11.1%). The majority of subjects were men (21/27, 77.8%). There were six female subjects (6/27, 22.2%). The mean age for subjects in this study was 25.8 years, and subjects ranged from 21 years to 34 years of age [Volume 1.45, pages 8.3245, 8.3246].

11.4.1. Clinical pharmacology outcomes

PK analyses were based on the data for the 22 subjects who completed both periods of the study. Additional information may be found in Dr. Choi's biopharmaceutics review. PK results from this study are presented in Table 11.4.2.

Table 11.4.2. PK parameters for codeine and chlorpheniramine, steady state, Study COD-02002 [Volume 1.45, pages 8.3208, 8.3209]

	Extended-Release N = 22	Immediate-Release N = 22	Ratio ER/IR, % (90% CI)	
Codeine				
C_{max}, ng/mL			69.9	(64.9-75.3)
AUC_{ss}, ng.hr/mL	554.30	602.95	90.9	(86.2-95.8)
C_{min}, ng/mL			141.9	(132.6-151.9)
T_{max}, hr	3.0	1.0	NA	
Chlorpheniramine				
C_{max}, ng/mL			87.8	(83.4-92.3)
AUC_{ss}, ng.hr/mL	365.90	421.33	85.8	(82.5-89.2)
C_{min}, ng/mL			90.2	(84.9-95.8)
T_{max}, hr	6.2	3.0	NA	

The steady state C_{max} for codeine was significantly lower for the extended-release suspension ( ) than for the immediate release solution . The geometric least squares mean ratio for C_{max} was 69.9%, with 90% CI of 64.9% to 75.3%. The steady state C_{min} for codeine was higher for the extended-release suspension than for the immediate-release solution. The geometric least squares mean ratio for C_{min} was 141.9%, with 90% CI of 132.6%-151.9%. The AUC_{ss} for codeine from the extended-release suspension was similar to that of the immediate-release solution. The geometric least squares mean ratio for AUC_{ss} was 90.9%, with 90% CI of 86.2% to 95.8% [Volume 1.45, page 8.3209].

The steady state C_{max} for chlorpheniramine was slightly lower for the extended-release suspension and the immediate release solution ( ). The geometric least squares mean ratio for C_{max} was 87.8%, with 90% CI of 83.4% to 92.3%. The steady state C_{min} for chlorpheniramine was slightly lower for the extended-release suspension and the immediate-release solution). The geometric least squares mean ratio for C_{min} was 90.2 %, with 90% CI of 84.9%-95.8%. The AUC_{ss} for chlorpheniramine for the extended-release suspension (365.9 ng.hr/mL) was slightly lower than that of the immediate-release solution (421.3 ng.hr/mL). The geometric least squares mean ratio for AUC_{ss} was 90.9%, with 90% CI of 86.2% to 95.8%. The 90% CI for the means are within the 80% to 125% range for bioequivalence [Volume 1.45, page 8.3209].

11.4.2. Safety outcomes

Safety endpoints included adverse events, vital signs, physical examination, hematology, blood chemistry, urinalyses, and ECGs [Volume 1.45, page 8.3207, Volume 1.45 8.3229].

All 27 subjects who enrolled in this study received study treatment. Five subjects withdrew during the first treatment period in this two period crossover study. A total of

25 subjects received the extended-release suspension and 24 subjects received the immediate-release solution [Volume 1.45, page 8.3227].

AEs were frequent in this study. The frequency of AEs over both periods of the study was 285% (77/27). Of subjects exposed to study treatment, 21 of 27 reported AEs (77.8%). AEs were more frequent in the immediate-release treatment (52/24, 217%) than in the extended- release treatment (25/25, 100%). The most common AEs included pruritus, asthenia, headache, erythema, pharyngitis, and somnolence, among others. Pruritus, asthenia, headache, and somnolence were more frequent in the immediate-release solution than in the extended-release suspension. Erythema was more common in the extended-release suspension than in the immediate release solution. [Volume 1.45, pages 8.3254 to 8.3257]. AEs occurring at a frequency of >10% are displayed in Table 2.7. There were no deaths or SAEs in the study [Volume 1.45, page 8.3228].

Table 11.4.3. AEs occurring at a frequency >10%, Study COD-02002 {Volume 1.45, pages 8.3254 to 8.3257]

Adverse event	Extended-release N = 25		Immediate-release N = 24		All subjects N = 27	
Subjects with AEs	13	(52.0)	18	(75.0)	21	(77.8)
Pruritus	4	(16.0)	9	(37.5)	13	(48.1)
Asthenia	2	(8.0)	6	(25.0)	8	(29.6)
Headache	2	(8.0)	6	(25.0)	8	(29.6)
Erythema	3	(12.0)	2	(8.3)	5	(18.5)
Pharyngitis	2	(8.0)	2	(8.3)	4	(14.8)
Somnolence	1	(4.0)	3	(12.5)	4	(14.8)
Abdominal pain	2	(8.0)	1	(4.2)	3	(11.1)
Constipation	2	(8.0)	1	(4.2)	3	(11.1)

There were four subjects who withdrew from the study because of AEs. Subject 007, a 21 year-old white woman who was being treated with the extended-release suspension who developed throat tightness on the Day 2 of the study. She also developed pruritus on study day 4 and withdrew from the study on that day [Volume 1.45, pages 8.3228, 8.3279]. Subject 010 was a 24 year-old black man who was being treated with the immediate-release solution who developed pruritus and rash on study day 3. This patient required treatment with diphenhydramine [Volume 1.45, pages 8.3228 to 8.3229, 8.3279]. Subject 021, a 24 year-old white man who was treated with the immediate-release solution who developed a mild rash on study day 4 [Volume 1.45, pages 8.3228 to 8.3229, 8.3280]. Subject 026, a 29 year-old Hispanic woman who was treated with the extended-release suspension who developed a moderate headache on Day 1 of the study. This patient required treatment with acetaminophen [Volume 1.45, pages 8.3229, 8.3280].

The sponsor reported that there were no clinically significant changes in any of the laboratory data during the study [Volume 1.45, page 8.3230]. This reviewer examined the laboratory summary data and the individual listings for lab values for this study [Volume 1.46, pages 8.3887 to 8.3892, 8.3748 to 8.3886]. This reviewer concurs that there were no clinically significant changes in laboratory data in this study.

The sponsor reported that there were no clinically significant findings or changes in vital signs or ECGs in any of the study subjects [Volume 1.45, page 8.3230]. This reviewer

examined line listings and summaries for these safety endpoints [Volume 1.46, pages 8.3701 to 8.3707, 8.3718]. This reviewer noted no clinically significant findings or changes in ECGs. There was a mean increase from baseline in systolic BP of 3.7mm Hg, a mean increase in diastolic BP of 4.3 mm Hg, and mean increase in pulse of 14.3 bpm [Volume 1.46, page 8.3718]. There were no AEs reported for tachycardia or for hypertension. The increase in pulse may be a manifestation of the anticholinergic activity of chlorpheniramine. One would not expect a change in BP from anticholinergic activity, however. Although these changes in vital signs are not clinically significant, they may represent a drug effect.

12. APPENDIX, REVIEW OF PROPOSED LABEL

12.1. Brief review of proposed label

Annotated package labeling was included in this submission [Volume 1.1, pages 3.002-3.0015]. Only a brief clinical review of proposed labeling was performed because this application will not receive an approval action because of CMC issues. This brief review focuses on major issues and concerns, which are noted below. Comments to be communicated to the sponsor are presented in the following section. Additional comments have been provided by the Controlled Substance Staff and by the Division of Medication Errors and Technical Support, Office of Drug Safety [Memorandum, Michael Klein, Ph.D., CSS, HFD-009, 12/20/01; Memorandum, Carol Holquist, R.Ph., Jerry Phillips, R.Ph., HFD-400, 1/18/02]. Additional, more detailed clinical comments on labeling will be provided for the sponsor prior to approval of this product.

1. Indications and Usage section:

The sponsor's application is being submitted under Section 505(b)(2) of the FD&C Act, and this application relies on the Agency's previous findings of safety of the active drugs as described in the appropriate OTC monographs. Therefore, labeling should reflect OTC monograph labeling. The proposed indication and usage section combines OTC monograph language for antitussive and antihistamine drug products. However, the common cold indication is appropriate for the antitussive product, but not the antihistamine product. An example of acceptable language for this section follows:

"Codeprex [redacted] is indicated for the temporary relief of [redacted] cough, as may occur with the common cold or inhaled irritants, and for the temporary relief of runny nose, sneezing, itching or the nose or throat, and itchy watery eyes due to hay fever, other respiratory allergies, or allergic rhinitis." [21 CFR 341.72, 21CFR 341.74].

2. The professional labeling section for codeine from the OTC monograph suggests that recommendations be included in the label for instructions to be given to parents. These instructions for parents include obtaining and using a calibrated measuring device for administering the drug to a child, using extreme caution in measuring the dosage, and not exceeding the recommended daily dosage [21 CFR 341.90]. Similar language should be included in the labeling for the proposed product.

3. The WARNINGS, Respiratory Conditions section of the label states the following: "Benefit to risk ratio should be carefully considered especially in pediatric patients

with respiratory embarrassment (e.g., croup)." [redacted]

[redacted] [Volume 1.1, page 3.0007]

4. The Nursing Mothers section includes the following statement: "Caution should be exercised when [redacted] [Codeprex] [redacted] is administered to a nursing woman." [redacted] [Volume 1.1, page 3.0010].

5. The following sentence should be deleted from the Geriatric Use subsection: "[redacted] the [redacted] This sentence detracts from cautions in the label about increased sedation and confusion with the use of sedating drugs in the elderly and cautions about the greater frequency of decreased hepatic, renal, or cardiac function in the elderly [Volume 1.1, page 3.0010].

6. The following sentence should be deleted from the ADVERSE REACTIONS section: [redacted]

[Volume 1.1, page 3.0011]

7. [redacted] should be added to genitourinary adverse reactions [Volume 1.1, page 3.0011]

12.2. Comments on labeling to be communicated to the sponsor

Comments to be communicated to the sponsor are presented in the following section.

Indications and Usage section:

[redacted]

Your application is being submitted under Section 505(b)(2) of the FD&C Act, and this application relies on the Agency's previous findings of safety of the active drugs as described in the appropriate OTC monographs. Therefore, labeling should reflect OTC monograph labeling. The proposed indication and usage section combines OTC monograph language for antitussive and antihistamine drug products. However, the common cold indication is appropriate for the antitussive product, but not for the antihistamine product. An example of acceptable language for this section follows:

"Codeprex [redacted] is indicated for the temporary relief of [redacted] cough, as may occur with the common cold or inhaled irritants, and for the temporary relief of runny nose, sneezing, itching or the nose or throat, and itchy

watery eyes due to hay fever, other respiratory allergies, or allergic rhinitis." [21 CFR 341.72, 21CFR 341.74].

Additional, more detailed labeling comments will be provided prior to approval of the application.

Reviewed by:

_____

Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

_____

Mary Purucker, M.D., Ph.D.
Team Leader, Division of Pulmonary and Allergy Drug Products

cc: Original NDA
HFD-570/Division File
HFD-570/Purucker/Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-870/Choi/Clinical Pharmacology Reviewer
HFD-570/Yu/CSO

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/s/

Charles Lee
2/1/02 11:22:50 AM
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