CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22279Orig1s000

PHARMACOLOGY REVIEW(S)

Secondary Pharmacology and Toxicology Review for NDA 22-279 Resubmission

TO: NDA 22-279 (Mikart, Inc.)

FROM: Marcie Wood, Ph.D.
Supervisory Pharmacologist
Division of Pulmonary, Allergy, and Rheumatology Drug Products

DATE: May 1, 2014

The proposed product in this NDA is for a hydrocodone bitartrate, pseudoephedrine hydrochloride, and guaifenesin oral solution. NDA 22-279 was originally submitted on August 22, 2008. A nonclinical pharmacology and toxicology review was completed on April 24, 2009, by Dr. Jean Wu and includes evaluation of the proposed doses for each of the components from the nonclinical perspective. Dr. Wu recommended approval of the application and there were no outstanding nonclinical issues except for labeling. However, the applicant received a complete response because the clinical data was considered inadequate to support approval and due to CMC deficiencies identified during the review. A resubmission was received on July 22, 2010, but a second complete response letter was issued on January 25, 2011, due to deficiencies identified in an audit of the bioanalytical site that made the clinical data unreliable. A second resubmission was received by the Division on July 18, 2011. However, a third complete response letter was issued due to lack of bioequivalence for the guaifenesin component with the reference product.

The current resubmission of December 4, 2014, includes additional bioequivalence data for guaifenesin to support approval of this product. No new nonclinical pharmacology and toxicology studies were included in this resubmission. Dr. Carol Galvis evaluated labeling only for this resubmission, as labeling was the only outstanding issue from a nonclinical perspective. See the review by Dr. Galvis dated April 23, 2014, for complete details. Dr. Galvis recommended revisions to the hydrocodone dose ratios in Section 8.1 (Pregnancy) and Section 13.1 (Carcinogenesis, Mutagenesis, and Impairment of Fertility) based on the maximum hydrocodone daily dose for the drug product. I concur with Dr. Galvis's recommendations.

There are no outstanding Pharmacology and Toxicology issues for this product.

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

/s/

MARCIE L WOOD
05/01/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 22-279
Supporting document/s:	SDN 43
Applicant's letter date:	12/2/2014
CDER stamp date:	12/4/2014
Product:	Hycofenix (hydrocodone bitartrate, pseudoephedrine hydrochloride, and guaifenesin) oral solution
Indication:	For symptomatic relief of cough, (b) (4) nasal congestion, and to loosen mucus associated with the common cold
Applicant:	Mikart, Inc.
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Reviewer:	Carol M. Galvis, PhD
Supervisor:	Marcie Wood, PhD
Division Director:	Badrul A. Chowdhury, MD, PhD
Project Manager:	Laura Musse

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 22-279 are owned by Mikart, Inc. or are data for which Mikart, Inc. has obtained a written right of reference.

Any information or data necessary for approval of NDA 22-279 that Mikart, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or

referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 22-279.

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1 Executive Summary

1.1 Introduction

This review evaluates the nonclinical sections of the label for Hycofenix (hydrocodone bitartrate, pseudoephedrine hydrochloride and guaifenesin) oral solution. Mikart, Inc. submitted a 505(b)(2) New Drug Application (NDA) on December 4, 2014 (third resubmission due to a complete response) for Hycofenix [hydrocodone bitartrate, pseudoephedrine hydrochloride, and guaifenesin (2.5 mg, 30 mg, and 200 mg; respectively, in 5 mL)] oral solution. The proposed indication is for the symptomatic relief of cough, (b) (4) nasal congestion, and to loosen mucus associated with the common cold in patients 18 years of age and older.

NDA 22-279 was originally submitted on August 22, 2008. A nonclinical pharmacology and toxicology review was completed on April 24, 2009, by Dr. Jean Wu and includes evaluation of the proposed doses for each of the components from the nonclinical perspective. Dr. Wu recommended approval of the application and there were no outstanding nonclinical issues except for labeling. However, the applicant received a complete response because the clinical data was considered inadequate to support approval and due to CMC deficiencies identified during the review. A resubmission was received on July 22, 2010, but a second complete response letter was issued on January 25, 2011, due to deficiencies identified in an audit of the bioanalytical site that made the clinical data unreliable.

A second resubmission was received by the Division on July 18, 2011. However, a third complete response letter was issued due to lack of bioequivalence for the guaifenesin component with the reference product. This third resubmission includes additional bioequivalence data for guaifenesin to support approval of this product. A review of the product labeling (nonclinical sections only) is included herein.

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical studies were submitted with this NDA. A nonclinical pharmacology and toxicology review completed on April 24, 2009, by Dr. Jean Wu recommended approval from the nonclinical perspective. There are no outstanding issues from the nonclinical perspective except for labeling, which is addressed herein.

1.3 Recommendations

1.3.1 Approvability

A nonclinical pharmacology and toxicology review was completed by Dr. Jean Wu on April 24, 2009. The NDA is recommended for approval from the pharmacology/toxicology perspective.

1.3.3 Labeling

The content of the nonclinical sections of the drug labeling (sections 8.1, 10, 12.1, and 13) was reviewed. Below is the proposed labeling.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Teratogenic Effects
Pregnancy Category C

There are no adequate and well controlled studies of HYCOFENIX (b) (4) in pregnant women. Reproductive toxicity studies have not been conducted with HYCOFENIX (b) (4); however, studies are available with an individual active ingredient or related active ingredient. Hydrocodone was teratogenic in hamsters. Codeine, an opiate related to hydrocodone, increased resorptions and decreased fetal weight in rats. Because animal reproduction studies are not always predictive of human response, HYCOFENIX (b) (4) should be used during pregnancy only if the benefit justifies the potential risk to the fetus.

Hydrocodone:
Hydrocodone has been shown to be teratogenic in hamsters when given in a dose approximately 35 times the maximum recommended human daily dose (MRHDD) (on a mg/m^2 basis at a single subcutaneous dose of 102 mg/kg on gestation day 8). Reproductive toxicology studies were also conducted with codeine, an opiate related to hydrocodone. In a study in which pregnant rats were dosed throughout organogenesis, a dose of codeine approximately 50 times the MRHDD of hydrocodone (on a mg/m^2 basis at an oral dose of 120 mg/kg/day of codeine) increased resorptions and decreased fetal weight; however, these effects occurred in the presence of maternal toxicity. In studies in which rabbits and mice were dosed throughout organogenesis, doses of codeine up to approximately 25 and 120 times, respectively, the MRHDD of hydrocodone (on a mg/m^2 basis at oral doses of 30 and 600 mg/kg/day, respectively), produced no adverse developmental effects.

Non-teratogenic Effects
Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose.

10 OVERDOSAGE

No human overdosage data are available for HYCOFENIX (b) (4)

Hydrocodone:
Overdosage with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, dizziness, ringing in the ears, confusion, blurred vision, eye problems, cold and clammy skin, and

sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest and death may occur.

Pseudoephedrine:
Overdosage with sympathomimetics such as pseudoephedrine may give rise to giddiness, headache, nausea, vomiting, sweating, thirst, tachycardia, precordial pain, palpitations, difficulty in micturition, muscle weakness and tenseness, anxiety, restlessness, and insomnia. Many patients can present a toxic psychosis with delusion and hallucinations. Some may develop cardiac arrhythmias, circulatory collapse, convulsion, coma, and respiratory failure.

Guaifenesin:
Overdosage with guaifenesin can cause depression of the central nervous system. While present in polypharmacy overdoses, one case of overdose with only significant levels of guaifenesin has been reported. Symptoms included slurred speech, shallow respirations, reduced heart rate with rhythm sinus bradycardia, followed by asystole.

Treatment of overdosage consists of discontinuation of HYCOFENIX (b) (4) together with institution of appropriate therapy. Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The opioid antagonist naloxone hydrochloride is a specific antidote for respiratory depression which may result from overdosage or unusual sensitivity to opioids including hydrocodone. Therefore, an appropriate dose of naloxone hydrochloride should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. For further information, see full prescribing information for naloxone hydrochloride. An antagonist should not be administered in the absence of clinically significant respiratory depression. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Gastric emptying may be useful in removing unabsorbed drug.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Hydrocodone is a semisynthetic narcotic antitussive and analgesic with multiple actions qualitatively similar to those of codeine. The precise mechanism of action of hydrocodone and other opiates is not known; however, hydrocodone is believed to act directly on the cough center. In excessive doses, hydrocodone will depress respiration. Hydrocodone can produce miosis, euphoria, and physical and physiological dependence.

Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine hydrochloride is recognized as an effective agent for the relief of nasal congestion due to upper respiratory allergies or common cold. Pseudoephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. It has the potential for excitatory side effects.

Guaifenesin is an expectorant the action of which promotes or facilitates the removal of secretions from the respiratory tract. The precise mechanism of action of guaifenesin is not known; however, it is thought to act as an expectorant by increasing the volume and reducing the viscosity of secretions in the trachea and bronchi. In turn, this may increase the efficiency of the cough reflex and facilitate removal of the secretions.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and reproductive studies have not been conducted with HYCOFENIX (b) (4) however, published information is available for the individual active ingredients or related active ingredients.

Hydrocodone:
Carcinogenicity studies were conducted with codeine, an opiate related to hydrocodone. In 2 year studies in F344/N rats and B6C3F1 mice, codeine showed no evidence of tumorigenicity at dietary doses up to 70 and 400 mg/kg/day, respectively (approximately 30 and 80 times, respectively, the MRHDD of hydrocodone on a mg/m^2 basis).

Pseudoephedrine:
Two-year feeding studies in rats and mice demonstrated no evidence of carcinogenic potential with ephedrine sulfate, a structurally related drug with pharmacological properties similar to pseudoephedrine, at dietary doses up to 10 and 27 mg/kg, respectively (approximately 0.3 and 0.5 times, respectively, the MRHDD of pseudoephedrine hydrochloride on a mg/m^2 basis).

Guaifenesin:
Carcinogenicity, genotoxicity, or reproductive toxicology studies have not been conducted with guaifenesin.

2 Drug Information

2.1 Drug

Details of the drug substance are included in Dr. Wu's review dated April 24, 2009.

2.3 Drug Formulation

Details of the drug product formulation are included in Dr. Wu's review dated April 24, 2009.

2.6 Proposed Clinical Population and Dosing Regimen

Hycofenix was developed for the symptomatic relief of cough, (b) (4) nasal congestion, and to loosen mucus associated with the common cold. The proposed dosing regimen is 10 mL every 4-6 hours, not to exceed 4 doses in 24 hours. Each 5 mL contains 2.5 mg hydrocodone bitartrate, 30 mg pseudoephedrine hydrochloride, and

200 mg guaifenesin. The maximum daily dose is 20 mg hydrocodone bitartrate, 240 mg pseudoephedrine hydrochloride, and 1600 mg guaifenesin.

2.7 Regulatory Background

- This 505(b)(2) NDA was originally submitted on August 22, 2008, by (b) (4) A complete response letter was issued on June 22, 2009, because the clinical data was not considered adequate to support approval (the study did not fulfill the bioavailability criteria for combination products) and due to CMC deficiencies.
- A resubmission was received on July 22, 2010, but a second complete response was issued on January 25, 2011, due to deficiencies identified in an audit of the bioanalytical site that made the data unreliable.
- A second resubmission was received on July 18, 2011. However, a third complete response letter was issued due to lack of bioequivalence of the guaifenesin component with the reference product.
- A third resubmission was received on December 4, 2014, and includes additional bioequivalence data for guaifenesin to support approval of this product.

4 Pharmacology

Refer to Dr. Wu's review for details on the pharmacology of the active ingredients.

6 General Toxicology

Nonclinical studies were not conducted with Hycofenix or any of the components individually. Each active ingredient has a long history of clinical use in the US. Refer to Dr. Wu's review dated April 24, 2009, for additional information.

11 Integrated Summary and Safety Evaluation

Mikart, Inc. submitted a 505(b)(2) New Drug Application (NDA) on December 4, 2014, (third resubmission after a complete response) for Hycofenix [hydrocodone bitartrate, pseudoephedrine hydrochloride, and guaifenesin (2.5 mg, 30 mg, and 200 mg; respectively, in 5 mL)] oral solution. The proposed indication is for the symptomatic relief of cough, (b) (4) nasal congestion, and to loosen mucus associated with the common cold in adult patients (18 years of age and older).

NDA 22-279 was originally submitted on August 22, 2008. A pharmacology/toxicology review was completed on April 24, 2009, by Dr. Jean Wu and includes evaluation of the proposed doses for each of the components from the nonclinical perspective. Dr. Wu recommended approval of the application and there were no outstanding nonclinical issues except for labeling. However, the applicant received a complete response because the clinical data was not considered adequate to support approval and because of CMC deficiencies identified during the review. A resubmission was received on July 22, 2010, but a second complete response was issued on January 25, 2011, due to deficiencies identified in an audit of the bioanalytical site that made the data unreliable.

A second resubmission was received by the Division on July 18, 2011, and a third complete response letter was issued due to lack of bioequivalence of the guaifenesin component with the reference product. This third resubmission includes additional bioequivalence data for guaifenesin to support approval of Hycofenix.

A review of the product labeling was conducted during this review cycle. The nonclinical sections of the drug label (section 8.1 "Pregnancy", section 10 "Overdosage", section 12.1 "Mechanism of Action", and section 13 "Nonclinical Toxicology") were reviewed and are discussed in this review. The labeling review was based upon comparison of the proposed labeling to the labeling from an approved product containing hydrocodone bitartrate and pseudoephedrine hydrochloride (i.e., Zutripro oral solution, approved on June 8, 2011, under NDA 22-439). The only recommended edit is to adjust the hydrocodone dose ratios in sections 8.1 and 13.1 based on the maximum hydrocodone daily dose for Hycofenix (20 mg/day). Refer to the table below.

Sponsor's proposed language	Recommended edits
8 USE IN SPECIFIC POPULATIONS **8.1 Pregnancy** ***Teratogenic Effects*** *Pregnancy Category C* There are no adequate and well controlled studies of HYCOFENIX (b) (4) in pregnant women. Reproductive toxicity studies have not been conducted with HYCOFENIX (b) (4); however, studies are available with an individual active ingredient or related active ingredient. Hydrocodone was teratogenic in hamsters. Codeine, an opiate related to hydrocodone, increased resorptions and decreased fetal weight in rats. Because animal reproduction studies are not always predictive of human response, HYCOFENIX (b) (4) should be used during pregnancy only if the benefit justifies the potential risk to the fetus. Hydrocodone: Hydrocodone has been shown to be teratogenic in hamsters when given in a dose approximately (b) (4) times the maximum recommended human daily	**8 USE IN SPECIFIC POPULATIONS** **8.1 Pregnancy** ***Teratogenic Effects*** *Pregnancy Category C* There are no adequate and well controlled studies of HYCOFENIX (b) (4) in pregnant women. Reproductive toxicity studies have not been conducted with HYCOFENIX (b) (4); however, studies are available with an individual active ingredient or related active ingredient. Hydrocodone was teratogenic in hamsters. Codeine, an opiate related to hydrocodone, increased resorptions and decreased fetal weight in rats. Because animal reproduction studies are not always predictive of human response, HYCOFENIX (b) (4) should be used during pregnancy only if the benefit justifies the potential risk to the fetus. Hydrocodone: Hydrocodone has been shown to be teratogenic in hamsters when given in a dose approximately 35 (b) (4) times the maximum recommended human daily

dose (MRHDD) (on a mg/m^2 basis at a single subcutaneous dose of 102 mg/kg on gestation day 8). Reproductive toxicology studies were also conducted with codeine, an opiate related to hydrocodone. In a study in which pregnant rats were dosed throughout organogenesis, a dose of codeine approximately (b) (4) times the MRHDD of hydrocodone (on a mg/m^2 basis at an oral dose of 120 mg/kg/day of codeine) increased resorptions and decreased fetal weight; however, these effects occurred in the presence of maternal toxicity. In studies in which rabbits and mice were dosed throughout organogenesis, doses of codeine up to approximately (b) (4) times, respectively, the MRHDD of hydrocodone (on a mg/m^2 basis at oral doses of 30 and 600 mg/kg/day, respectively), produced no adverse developmental effects. ***Nonteratogenic Effects*** Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose.	dose (MRHDD) (on a mg/m^2 basis at a single subcutaneous dose of 102 mg/kg on gestation day 8). Reproductive toxicology studies were also conducted with codeine, an opiate related to hydrocodone. In a study in which pregnant rats were dosed throughout organogenesis, a dose of codeine approximately (b) (4) 50 times the MRHDD of hydrocodone (on a mg/m^2 basis at an oral dose of 120 mg/kg/day of codeine) increased resorptions and decreased fetal weight; however, these effects occurred in the presence of maternal toxicity. In studies in which rabbits and mice were dosed throughout organogenesis, doses of codeine up to approximately (b) (4) 25 and (b) (4) 120 times, respectively, the MRHDD of hydrocodone (on a mg/m^2 basis at oral doses of 30 and 600 mg/kg/day, respectively), produced no adverse developmental effects. ***Non-teratogenic Effects*** Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose.
10 OVERDOSAGE No human overdosage data are available for HYCOFENIX (b) (4) Hydrocodone: Overdosage with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence	No edits are recommended for this section. It was verified that the sponsor did not include animal data under this section, according with 21 CFR 201.57(c)(11).

progressing to stupor or coma, skeletal muscle flaccidity, dizziness, ringing in the ears, confusion, blurred vision, eye problems, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest and death may occur. Pseudoephedrine: Overdosage with sympathomimetics such as pseudoephedrine may give rise to giddiness, headache, nausea, vomiting, sweating, thirst, tachycardia, precordial pain, palpitations, difficulty in micturition, muscle weakness and tenseness, anxiety, restlessness, and insomnia. Many patients can present a toxic psychosis with delusion and hallucinations. Some may develop cardiac arrhythmias, circulatory collapse, convulsion, coma, and respiratory failure. Guaifenesin: Overdosage with guaifenesin can cause depression of the central nervous system. While present in polypharmacy overdoses, one case of overdose with only significant levels of guaifenesin has been reported. Symptoms included slurred speech, shallow respirations, reduced heart rate with rhythm sinus bradycardia, followed by asystole. Treatment of overdosage consists of discontinuation of HYCOFENIX (b) (4) [redacted] together with institution of appropriate therapy. Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The opioid antagonist naloxone hydrochloride is a specific antidote for respiratory depression which may result from overdosage or unusual	

sensitivity to opioids including hydrocodone. Therefore, an appropriate dose of naloxone hydrochloride should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. For further information, see full prescribing information for naloxone hydrochloride. An antagonist should not be administered in the absence of clinically significant respiratory depression. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Gastric emptying may be useful in removing unabsorbed drug.	
12 CLINICAL PHARMACOLOGY **12.1 Mechanism of Action** Hydrocodone is a semisynthetic narcotic antitussive and analgesic with multiple actions qualitatively similar to those of codeine. The precise mechanism of action of hydrocodone and other opiates is not known; however, hydrocodone is believed to act directly on the cough center. In excessive doses, hydrocodone will depress respiration. Hydrocodone can produce miosis, euphoria, and physical and physiological dependence. Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine hydrochloride is recognized as an effective agent for the relief of nasal congestion due to upper respiratory allergies or common cold. Pseudoephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. It has the potential for excitatory side effects. Guaifenesin is an expectorant the action of which promotes or facilitates the removal of secretions from the respiratory	No edits are recommended for this section.

tract. The precise mechanism of action of guaifenesin is not known; however, it is thought to act as an expectorant by increasing the volume and reducing the viscosity of secretions in the trachea and bronchi. In turn, this may increase the efficiency of the cough reflex and facilitate removal of the secretions.	
13 NONCLINICAL TOXICOLOGY **13.1 Carciniogenesis, Mutagenesis, Impairment of Fertility** Carcinogenicity, mutagenicity, and reproductive studies have not been conducted with HYCOFENIX (b) (4) ; however, published information is available for the individual active ingredients or related active ingredients. Hydrocodone: Carcinogenicity studies were conducted with codeine, an opiate related to hydrocodone. In 2 year studies in F344/N rats and B6C3F1 mice, codeine showed no evidence of tumorigenicity at dietary doses up to 70 and 400 mg/kg/day, respectively (approximately (b) (4) times, respectively, the MRHDD of hydrocodone on a mg/m^2 basis). Pseudoephedrine: Two-year feeding studies in rats and mice demonstrated no evidence of carcinogenic potential with ephedrine sulfate, a structurally related drug with pharmacological properties similar to pseudoephedrine, at dietary doses up to 10 and 27 mg/kg, respectively (approximately 0.3 and 0.5 times, respectively, the MRHDD of pseudoephedrine hydrochloride on a mg/m^2 basis). Guaifenesin: Carcinogenicity, genotoxicity, or reproductive toxicology studies have not	**13 NONCLINICAL TOXICOLOGY** **13.1 Carcin~~i~~ogenesis, Mutagenesis, Impairment of Fertility** Carcinogenicity, mutagenicity, and reproductive studies have not been conducted with HYCOFENIX (b) (4) ; however, published information is available for the individual active ingredients or related active ingredients. Hydrocodone: Carcinogenicity studies were conducted with codeine, an opiate related to hydrocodone. In 2 year studies in F344/N rats and B6C3F1 mice, codeine showed no evidence of tumorigenicity at dietary doses up to 70 and 400 mg/kg/day, respectively (approximately (b) (4) 30 and (b) (4) 80 times, respectively, the MRHDD of hydrocodone on a mg/m^2 basis). Pseudoephedrine: Two-year feeding studies in rats and mice demonstrated no evidence of carcinogenic potential with ephedrine sulfate, a structurally related drug with pharmacological properties similar to pseudoephedrine, at dietary doses up to 10 and 27 mg/kg, respectively (approximately 0.3 and 0.5 times, respectively, the MRHDD of pseudoephedrine hydrochloride on a mg/m^2 basis). Guaifenesin: Carcinogenicity, genotoxicity, or reproductive toxicology studies have not

been conducted with guaifenesin.	been conducted with guaifenesin.

12 Appendix/Attachments

Appendix 1: Pharm/Tox review dated April 24, 2009.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-279**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**August 22, 2008**
PRODUCT:	**Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution**
INTENDED CLINICAL POPULATION:	**Adults** (b) (4) **, who need the symptomatic relief of cough,** (b) (4) (b) (4) **nasal congestion, and** (b) (4) **to loosen** (b) (4)
SPONSOR:	(b) (4)
DOCUMENTS REVIEWED:	**Module 1, Vol. 1, Module 2, Vol. 1.1, Module 4, Vol. 1.1**
REVIEW DIVISION:	**Division of Pulmonary and Allergy Products**
PHARM/TOX REVIEWER:	**Jean Q. Wu, M.D., Ph.D.**
PHARM/TOX SUPERVISOR (Acting)	**Molly Shea, Ph.D.**
DIVISION DIRECTOR:	**Badrul Chowdhury, M.D., Ph.D.**
PROJECT MANAGER:	**Carol Hill**

Date of review submission to Division File System (DFS): April 24, 2009

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Approval

B. Recommendation for nonclinical studies: None

C. Recommendations on labeling: Labeling review will be completed at a later time when a labeling negotiation is needed.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

No preclinical pharmacology or toxicology studies were conducted with Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution. The active ingredient, hydrocodone bitartrate, was approved as an antitussive in a sustained release resin suspension in 1987 (NDA 19-111, Tussionex) and in Hycodan Tablet and Syrup in 1943 (NDA 05-213). It was not included in the OTC monograph process and is available on a prescription only basis. It is generally recognized as safe and effective. Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the recommended human dose. The other two active ingredients, guaifenesin and pseudoephedrine, are recognized OTC monograph drugs (21 CFR 341.18 and 21 CFR 341.20). They are generally recognized as safe and effective. The acute and chronic toxicity studies in animals demonstrated no adverse pathological findings for glyceryl guaiacolate (guaifenesin) based on OTC monograph review. Animal studies to assess carcinogenicity, genotoxicity, fertility, developmental or teratogenic effects of guaifenesin have not been conducted. In animal studies, pseudoephedrine reduced average weight, length, and rate of skeletal ossification in animal fetus (USP Convention. USPDI – Drug Information for the Health Care Professional. 16th edition Volume I, Rockville, MD: U.S. Pharmaceutical Convention, Inc. 1996 (Plus updates), pg. 2508.).

B. Pharmacologic activity

Hydrocodone bitartrate is a recognized antitussive, with efficacy established in DESI Notice #5213, dated June 1, 1982. It is also a controlled prescription opioid. The precise mechanism of action of hydrocodone and other opiates is not known. However, it is believed to act directly on the cough center.

Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa (21 CFR 314.20). Pseudoephedrine is recognized as an effective agent for the relief of nasal congestion due to allergic rhinitis, the common cold, hay fever, or other upper

respiratory allergies, and nasal congestion associated with sinusitis. Pseudoephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. It has the potential for excitatory side effects (21 CFR 314.80).

Guaifenesin is a recognized expectorant (21 CFR 341.18) that promotes or facilitates the evacuation of secretions from the bronchial airways to provide for the temporary relief of cough due to minor throat and bronchial irritation as may occur with upper respiratory infection. This may be accomplished by reducing the thickness of these secretions or by augmenting the formation of a more fluid secretion.

C. Nonclinical safety issues relevant to clinical use: None.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: NDA 22-279
Review number: 001
Sequence number/date/type of submission: 000/August 22, 2008/Original
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: (b) (4)

Manufacturer for drug substance:

Hydrocodone (DMF (b) (4)):

Pseudoephedrine (DMF (b) (4)):

Guaifenesin (DMF (b) (4)):

(b) (4)

Reviewer name: Jean Q. Wu
Division name: Division of Pulmonary and Allergy Drug Products
HFD #: 570
Review completion date: April 24, 2009

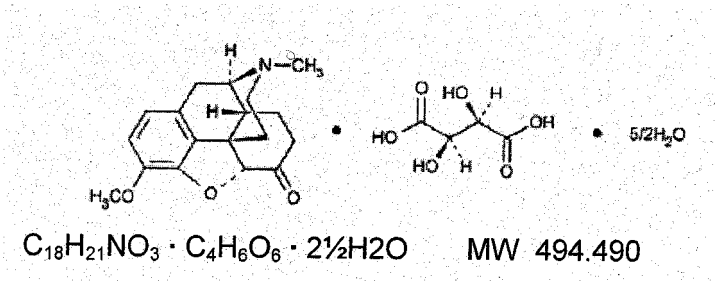
Drug:

Trade name: N/A
Generic name: Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution

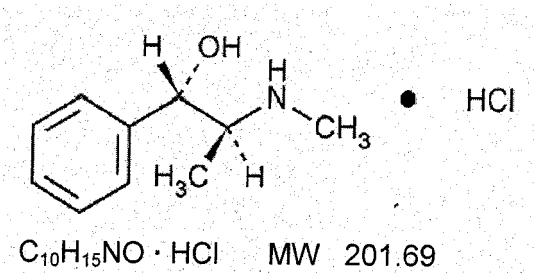
Three active pharmaceutical ingredients (API) in the following list:

Generic Name: Hydrocodone bitartrate (HC)
Chemical name:
4,5(alpha)-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)

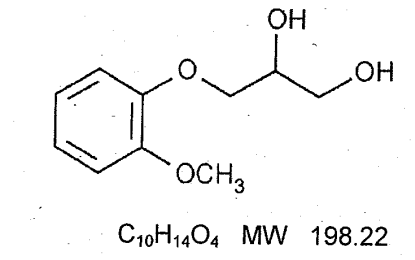
Molecular formula/MW: $C_{18}H_{21}NO_3 .C_4H_6O_6 .2\ ½\ H_2O$/494.5
Drug Class: Narcotic analgesic and antitussive
Related: NDA 19-111 (Tussionex Suspension), NDA 5-213 (Hycodan Tablets and Syrup), NDA 19-410 (Hycomine Syrup), DMF (b) (4)
Structure:



Generic Name: Pseudoephedrine HCl
Chemical name: Benzenmethanol,-[1-(methylamino)ethyl]-,[*S*-(*R**, *R**)]-, hydrochloride
Molecular formula/MW: $C_{10}H_{15}NO{\cdot}HCl$/201.7
Drug Class: Nasal decongestant
Related: NDA 21-585 (Mucinex® D, guaifenesin with pseudoephedrine HCl), DMF (b) (4)
Structure:



Generic Name: Guaifenesin
Chemical name: 1,2-Propanediol, 3-(2-methoxyphenoxy)-, (±)-
Molecular formula/MW: $C_{10}H_{14}O_4$/198.2
Drug Class: Expectorant
Related: NDA 21-620 (Mucinex®DM---guaifenesin with dextromethorphan), NDA 21-282 (Mucinex™---Guaifenesin extended release tablets), NDA 21-585 (Mucinex® D, guaifenesin with pseudoephedrine HCl), DMF (b) (4)
Structure:



Relevant INDs/NDAs/DMFs:
IND 76365 (Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution)

Other relevant INDs/NDAs/DMFs are listed above with each relevant active ingredient.

Drug class:

Hydrocodone bitartrate --- narcotic analgesic and antitussive
Pseudoephedrine hydrochloride --- nasal decongestant (an alkaloid obtained from Ephedra spp.)
Guaifenesin--- expectorant (a glyceryl guaiacolate)

Intended clinical population: adults (b) (4) who need the symptomatic relief of cough, (b) (4) nasal congestion, and (b) (4) to loosen (b) (4)

Clinical formulation: The product is an oral solution (5 mL) 2.5 mg hydrocodone bitartrate, 200 mg guaifenesin and 30 mg pseudoephedrine HCl per 5 mL. The composition and function of each component is shown below (excerpted from Module 2, Vol. 1. Section 2.3. P.2. page 20).

% w/v	mg/5mL	Ingredient	Function	g per Liter
0.050	2.5	Hydrocodone Bitartrate USP	Active Ingredient	0.500
4.000	200.0	Guaifenesin USP	Active Ingredient	40.00
0.600	30.0	Pseudoephedrine Hydrochloride USP	Active Ingredient	6.00
(b) (4)		Sorbitol (b) (4) USP		(b) (4)
		Glycerin USP		
		Polyethylene Glycol (b) (4) NF		
		Methylparaben NF		
		Propylparaben NF		
		Citric Acid (b) (4) USP		
		Sodium Citrate (b) (4) USP		
		Saccharin Sodium		
		D & C Red #33		
		FD & C Blue #1		
		(b) (4) Black Raspberry Flavor (b) (4)		
		Purified Water USP		

Route of administration: Oral

Propose to use:
Recommended dose for adults (b) (4):
Two teaspoons (10 mL) every 4 hours, NTE 4 doses in 24 hours

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: The sponsor intended to obtain approval through a 505(b)(2) application.

Studies reviewed within this submission: None

Studies not reviewed within this submission: None

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary
Not applicable (N/A)

2.6.2.2 Primary pharmacodynamics
N/A

2.6.2.3 Secondary pharmacodynamics
N/A

2.6.2.4 Safety pharmacology
N/A

2.6.2.5 Pharmacodynamic drug interactions
N/A

2.6.3 PHARMACOLOGY TABULATED SUMMARY
N/A

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary
N/A

2.6.4.2 Methods of Analysis:
N/A

2.6.4.3 Absorption
N/A

2.6.4.4 Distribution
N/A

2.6.4.5 Metabolism
N/A

2.6.4.6 Excretion
N/A

2.6.4.7 Pharmacokinetic drug interactions
N/A

2.6.4.8 Other Pharmacokinetic Studies
N/A

2.6.4.9 Discussion and Conclusions

N/A

2.6.4.10 Tables and figures to include comparative TK summary

N/A

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

N/A

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

N/A

2.6.6.2 Single-dose toxicity

N/A

2.6.6.3 Repeat-dose toxicity

N/A

2.6.6.4 Genetic toxicology

N/A

2.6.6.5 Carcinogenicity

N/A

2.6.6.6 Reproductive and developmental toxicology

N/A

2.6.6.7 Local tolerance

N/A

2.6.6.8 Special toxicology studies

N/A

2.6.6.9 Discussion and Conclusions

N/A

2.6.6.10 Tables and Figures

N/A

2.6.7 TOXICOLOGY TABULATED SUMMARY

N/A

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusion:
Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (Rx Only) contains hydrocodone bitartrate, pseudoephedrine hydrochloride and guaifenesin in a 5-mL oral solution. This combination drug product is proposed as a prescription product. The application is submitted under the 505(b)(2) process. No preclinical pharmacology and toxicology studies were conducted with Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution. Each active ingredient is widely used in the US and is generally recognized as safe and effective.

Hydrocodone is a semisynthetic narcotic antitussive and analgesic with multiple actions qualitatively similar to those of codeine. The precise mechanism of action of hydrocodone and other opiates is not known; however, hydrocodone is believed to act directly on the cough center. Hydrocodone bitartrate is a recognized antitussive, with efficacy established in Drug Efficacy Study Implementation (DESI) Notice 5213, dated June 1, 1982. Hydrocodone bitartrate is not included in any OTC monograph and is available on a prescription (Rx only) basis. Currently, there are several approved formulations containing hydrocodone including Hycodan® (NDA 05-213, 1943) and Tussionex® (NDA 19-111, 1987). Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the recommended human dose (Label of Tussionex® Extended Release Suspension, Rev. 01/2008 1E). In excessive doses, hydrocodone, like other opium derivatives, will depress respiration. Hydrocodone can produce miosis, euphoria, and physical and psychological dependence. The approved dose in Hycodan® is shown in the table below.

Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa (21 CFR 314.20). Pseudoephedrine is recognized as an effective agent for the relief of nasal congestion due to allergic rhinitis, the common cold, hay fever, or other upper respiratory allergies, and nasal congestion associated with sinusitis. Pseudoephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. It has the potential for excitatory side effects (21 CFR 314.80). In animal studies, pseudoephedrine reduced average weight, length, and rate of skeletal ossification in the animal fetus (USP Convention. USPDI – Drug Information for the Health Care Professional. 16th edition Volume I, Rockville, MD: U.S. Pharmaceutical Convention, Inc. 1996 (Plus updates), pg. 2508.). The monograph recommended dose (21 CFR 314.80) is listed in the table below.

Guaifenesin has been used widely in the US as a recognized monograph drug (21 CFR 341.18). It is a recognized expectorant that promotes or facilitates the evacuation of secretions from the bronchial airways to provide for the temporary relief of cough due to minor throat and bronchial irritation as may occur with upper respiratory infection. This may be accomplished by reducing the thickness of these secretions or by augmenting the formation of a more fluid secretion. The OTC monograph review for guaifenesin in Advanced Notice of Proposed Rulemaking, FR, Vol 41, No 176, 9/9/76, pp 38362

referenced that acute and chronic toxicity studies in animals demonstrated no adverse pathological findings for glyceryl guaiacolate (guaifenesin). Animal studies to assess carcinogenicity, genotoxicity, fertility, developmental or teratogenic effects of guaifenesin have not been conducted. The monograph recommended dose (21 CFR 341.78) is listed in the table below.

Active ingredient administered/Age Group		Adults and children 12 years of age and over	Children 6 to12 years of age
Hydrocodone (in Hycodan®)	q 4-6 hr.	5 mg	2.5 mg
	NTE in 24 hr.	30 mg	15 mg
Pseudoephedrine	q 4-6 hr.	60 mg, q 4-6 hr	30 mg, q 4 hr
	NTE in 24 hr.	240 mg	120 mg
Guaifenesin	q 4 hr.	200-400 mg	100-200 mg
	NTE in 24 hr.	2400 mg	1200 mg

The recommended dosage of each active ingredient for this NDA is within the dose ranges recommended in OTC monographs and the approved products. The OTC monograph 21 CFR 341.40 recognizes the combination of any single monograph oral antitussive drug (such as codeine phosphate) with any single monograph nasal decongestant and any single expectorant to be a permitted combination in OTC cough/cold products. Although hydrocodone is not an OTC monograph antitussive, hydrocodone combination product containing monograph active ingredients has been accepted based on the precedent (Tussionex, NDA 19-111), for which approval can be based on establishment of bioequivalence (see details in the clinical review of this NDA by Dr. Xu Wang, finalized on April 23, 2009).

The Applicant, (b) (4) informed the Agency in a facsimile dated April 15, 2009, that the ownership of NDA 22-279 has been transferred to (b) (4) The new ownership of the NDA was effective on March 25, 2009. The proposed drug product will be manufactured by a new contractor that has not been announced by the new owner of this NDA.

Unresolved toxicology issues (if any): None

Recommendations: From a preclinical perspective, approval is recommended for the application pending a labeling review.

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/s/

Jean Wu
4/24/2009 11:16:41 AM
PHARMACOLOGIST

Molly Shea
4/24/2009 11:21:32 AM
PHARMACOLOGIST
I concur.

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/s/

CAROL M GALVIS
04/23/2015

MARCIE L WOOD
04/23/2015
I concur

INTEROFFICE MEMO

TO: NDA 22-279
Sequence number/date/type of submission:
#030/July 18, 2011/Resubmission

FROM: Timothy W. Robison, Ph.D., D.A.B.T.
Pharmacology/Toxicology Team Leader
Division of Pulmonary, Allergy and Rheumatology Products

DATE: December 20, 2011

NDA 22-279 is for the combination drug product, Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution.

I concur with Dr. Grace Lee's review dated November 1, 2011.

There are no outstanding PharmTox issues for this application at this time.

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/s/

TIMOTHY W ROBISON
12/20/2011

INTEROFFICE MEMO

TO: NDA 22-279
Sequence number/date/type of submission:
#030/July 18, 2011/Resubmission

FROM: Grace S. Lee, Ph.D.
Pharmacology/Toxicology Reviewer
Division of Pulmonary, Allergy and Rheumatology Products

DATE: November 1, 2011

NDA 22-279 for the combination drug product, Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution, was submitted as a 505(b)(2) application on August 22, 2008. Dr. Jean Wu was the nonclinical reviewer for the originally submitted NDA and recommended approval from a PharmTox perspective (see Review dated April 24, 2009). No nonclinical studies were submitted for review for either the individual monoproducts or the combination drug product. The applicant relied on the previously approved monoproduct NDAs and OTC monograph reviews and labeling for the individual products. Reference is made to NDAs 19-111 and 05-213 for hydrocodone bitartrate and to the OTC monographs 21 CFR 341.20 and 21 CFR 341.18 for pseudoephedrine hydrochloride and guaifenesin, respectively, for safety assessments supporting approval of each monoproduct. Additionally, the OTC monograph 21 CFR 341.40 recognizes the combination of any single monograph oral antitussive drug with any single monograph antihistamine and any single monograph nasal decongestant. Although hydrocodone is not an OTC monograph antitussive, hydrocodone combination products containing monograph active ingredients have been accepted based on the prior regulatory precedent of approving Tussionex® (the combination of hydrocodone and chlorpheniramine; NDA 19-111), for which approval can be based on establishment of bioequivalence only. Due to clinical pharmacology and CMC deficiencies, the originally submitted NDA was not approved.

On July 18, 2011, the applicant resubmitted their NDA for the third cycle resubmission. No new nonclinical information was included in this submission.

There are no outstanding pharmacology/toxicology issues for this NDA application. There will be no labeling review for this resubmission.

_____
Grace S. Lee, Ph.D.
Pharmacology/Toxicology Reviewer

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/s/

GRACE S LEE
11/01/2011

TIMOTHY W ROBISON
11/01/2011
I concur

INTEROFFICE MEMO

TO: NDA 22-279
Sequence number/date/type of submission:
#000/August 22, 2008/original NDA

FROM: Molly E. Shea, Ph.D.
Acting Pharmacology/Toxicology Supervisor
Division of Pulmonary and Allergy Products

DATE: June 17, 2009

[redacted] submitted NDA 22-279 for the combination drug product Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution. [redacted] provided a Letter of Authorization from [redacted] the hydrocodone drug substance manufacturer, allowing the Agency to review the drug master file for hydrocodone (DMF [redacted]) in relation to this NDA. The chemistry reviewer, Dr. Arthur Shaw, made reference to an on-going toxicology review of DMF [redacted] regarding a potentially genotoxic impurity, [redacted] in the NDA chemistry review dated April 30, 2009. On May 22, 2009, Dr. Marcus S. Delatte of Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) completed the toxicology review of DMF [redacted] for [redacted] and concluded that [redacted] is not a genotoxic impurity with the concurrence of the Genetic Toxicology Tertiary Review Committee. Therefore, the issue of genotoxic potential for [redacted] in DMF [redacted] has been resolved and is not an approvability issue for this NDA.

_____
Molly E. Shea, Ph.D.
Acting Pharmacology/Toxicology Supervisor

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/s/

Molly Shea
6/17/2009 11:48:59 AM
PHARMACOLOGIST

INTEROFFICE MEMO

TO: NDA 22-279
Sequence number/date/type of submission:
#000/August 22, 2008/original NDA

FROM: Molly E. Shea, Ph.D.
Acting Pharmacology/Toxicology Supervisor
Division of Pulmonary and Allergy Products

DATE: April 30, 2009

NDA 22-279 was submitted under the 505(b)(2) process for the combination drug product Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution on August 24, 2008. No nonclinical studies were submitted for review for either the individual monoproducts or the combination drug product. The sponsor has relied on the previously approved monoproduct NDA and OTC monograph reviews and labeling for the individual products. Reference is made to NDAs 19-111 and 05-213 for hydrocodone bitartrate and to the OTC monographs 21 CFR 341.18 and 21 CFR 341.20 for guaifenesin and pseudoephedrine hydrochloride, respectively, for safety assessments supporting approval of each monoproduct. (b) (4) informed the Agency in a facsimile dated April 15, 2009 that the ownership of NDA 22-279 has been transferred to (b) (4) effective March 25, 2009. For this submission, there were no labeling negotiations.

_____
Molly E. Shea, Ph.D.
Acting Pharmacology/Toxicology Supervisor

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/s/

Molly Shea
4/30/2009 08:28:39 PM
PHARMACOLOGIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-279**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**August 22, 2008**
PRODUCT:	**Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution**
INTENDED CLINICAL POPULATION:	**Adults** [redacted] (b) (4) **, who need the symptomatic relief of cough** (b) (4) [redacted] **nasal congestion, and** (b) (4) **to loosen** (b) (4) [redacted]
SPONSOR:	(b) (4) [redacted]
DOCUMENTS REVIEWED:	**Module 1, Vol. 1, Module 2, Vol. 1.1, Module 4, Vol. 1.1**
REVIEW DIVISION:	**Division of Pulmonary and Allergy Products**
PHARM/TOX REVIEWER:	**Jean Q. Wu, M.D., Ph.D.**
PHARM/TOX SUPERVISOR (Acting)	**Molly Shea, Ph.D.**
DIVISION DIRECTOR:	**Badrul Chowdhury, M.D., Ph.D.**
PROJECT MANAGER:	**Carol Hill**

Date of review submission to Division File System (DFS): April 24, 2009

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Approval

B. Recommendation for nonclinical studies: None

C. Recommendations on labeling: Labeling review will be completed at a later time when a labeling negotiation is needed.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

No preclinical pharmacology or toxicology studies were conducted with Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution. The active ingredient, hydrocodone bitartrate, was approved as an antitussive in a sustained release resin suspension in 1987 (NDA 19-111, Tussionex) and in Hycodan Tablet and Syrup in 1943 (NDA 05-213). It was not included in the OTC monograph process and is available on a prescription only basis. It is generally recognized as safe and effective. Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the recommended human dose. The other two active ingredients, guaifenesin and pseudoephedrine, are recognized OTC monograph drugs (21 CFR 341.18 and 21 CFR 341.20). They are generally recognized as safe and effective. The acute and chronic toxicity studies in animals demonstrated no adverse pathological findings for glyceryl guaiacolate (guaifenesin) based on OTC monograph review. Animal studies to assess carcinogenicity, genotoxicity, fertility, developmental or teratogenic effects of guaifenesin have not been conducted. In animal studies, pseudoephedrine reduced average weight, length, and rate of skeletal ossification in animal fetus (USP Convention. USPDI – Drug Information for the Health Care Professional. 16th edition Volume I, Rockville, MD: U.S. Pharmaceutical Convention, Inc. 1996 (Plus updates), pg. 2508.).

B. Pharmacologic activity

Hydrocodone bitartrate is a recognized antitussive, with efficacy established in DESI Notice #5213, dated June 1, 1982. It is also a controlled prescription opioid. The precise mechanism of action of hydrocodone and other opiates is not known. However, it is believed to act directly on the cough center.

Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa (21 CFR 314.20). Pseudoephedrine is recognized as an effective agent for the relief of nasal congestion due to allergic rhinitis, the common cold, hay fever, or other upper

respiratory allergies, and nasal congestion associated with sinusitis. Pseudoephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. It has the potential for excitatory side effects (21 CFR 314.80).

Guaifenesin is a recognized expectorant (21 CFR 341.18) that promotes or facilitates the evacuation of secretions from the bronchial airways to provide for the temporary relief of cough due to minor throat and bronchial irritation as may occur with upper respiratory infection. This may be accomplished by reducing the thickness of these secretions or by augmenting the formation of a more fluid secretion.

C. Nonclinical safety issues relevant to clinical use: None.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: NDA 22-279
Review number: 001
Sequence number/date/type of submission: 000/August 22, 2008/Original
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: (b) (4)

Manufacturer for drug substance:

Hydrocodone (DMF (b) (4)):

Pseudoephedrine (DMF (b) (4)):

Guaifenesin (DMF (b) (4)):

(b) (4)

Reviewer name: Jean Q. Wu
Division name: Division of Pulmonary and Allergy Drug Products
HFD #: 570
Review completion date: April 24, 2009

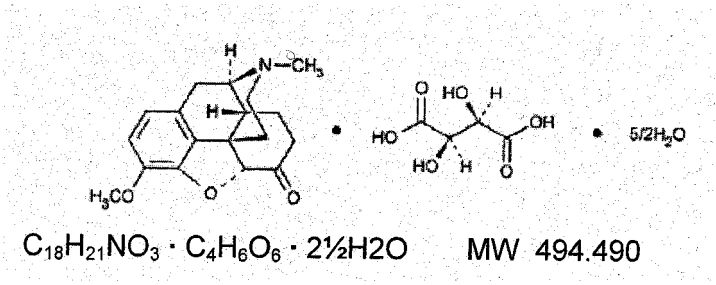
Drug:

Trade name: N/A
Generic name: Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution

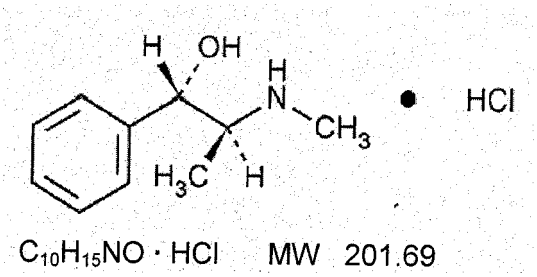
Three active pharmaceutical ingredients (API) in the following list:

Generic Name: Hydrocodone bitartrate (HC)
Chemical name:
4,5(alpha)-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)

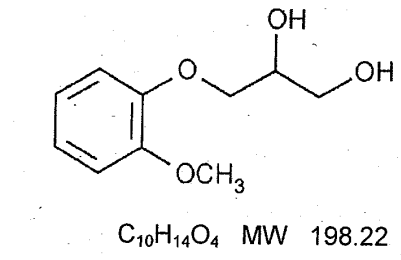
Molecular formula/MW: $C_{18}H_{21}NO_3 .C_4H_6O_6 .2\ ½\ H_2O$/494.5
Drug Class: Narcotic analgesic and antitussive
Related: NDA 19-111 (Tussionex Suspension), NDA 5-213 (Hycodan Tablets and Syrup), NDA 19-410 (Hycomine Syrup), DMF (b) (4)
Structure:



Generic Name: Pseudoephedrine HCl
Chemical name: Benzenmethanol,-[1-(methylamino)ethyl]-,[*S*-(*R**, *R**)]-, hydrochloride
Molecular formula/MW: $C_{10}H_{15}NO{\cdot}HCl$/201.7
Drug Class: Nasal decongestant
Related: NDA 21-585 (Mucinex® D, guaifenesin with pseudoephedrine HCl), DMF (b) (4)
Structure:



Generic Name: Guaifenesin
Chemical name: 1,2-Propanediol, 3-(2-methoxyphenoxy)-, (±)-
Molecular formula/MW: $C_{10}H_{14}O_4$/198.2
Drug Class: Expectorant
Related: NDA 21-620 (Mucinex®DM---guaifenesin with dextromethorphan), NDA 21-282 (Mucinex™---Guaifenesin extended release tablets), NDA 21-585 (Mucinex® D, guaifenesin with pseudoephedrine HCl), DMF (b) (4)
Structure:



Relevant INDs/NDAs/DMFs:
IND 76365 (Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution)

Other relevant INDs/NDAs/DMFs are listed above with each relevant active ingredient.

Drug class:

Hydrocodone bitartrate --- narcotic analgesic and antitussive
Pseudoephedrine hydrochloride --- nasal decongestant (an alkaloid obtained from Ephedra spp.)
Guaifenesin--- expectorant (a glyceryl guaiacolate)

Intended clinical population: adults (b) (4) who need the symptomatic relief of cough, (b) (4) nasal congestion, and (b) (4) to loosen (b) (4)

Clinical formulation: The product is an oral solution (5 mL) 2.5 mg hydrocodone bitartrate, 200 mg guaifenesin and 30 mg pseudoephedrine HCl per 5 mL. The composition and function of each component is shown below (excerpted from Module 2, Vol. 1. Section 2.3. P.2. page 20).

% w/v	mg/5mL	Ingredient	Function	g per Liter
0.050	2.5	Hydrocodone Bitartrate USP	Active Ingredient	0.500
4.000	200.0	Guaifenesin USP	Active Ingredient	40.00
0.600	30.0	Pseudoephedrine Hydrochloride USP	Active Ingredient	6.00
(b) (4)		Sorbitol (b) (4) USP		(b) (4)
		Glycerin USP		
		Polyethylene Glycol (b) (4) NF		
		Methylparaben NF		
		Propylparaben NF		
		Citric Acid (b) (4) USP		
		Sodium Citrate (b) (4) USP		
		Saccharin Sodium		
		D & C Red #33		
		FD & C Blue #1		
		(b) (4) Black Raspberry Flavor (b) (4)		
		Purified Water USP		

Route of administration: Oral

Propose to use:
Recommended dose for adults (b) (4):

Two teaspoons (10 mL) every 4 hours, NTE 4 doses in 24 hours

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: The sponsor intended to obtain approval through a 505(b)(2) application.

Studies reviewed within this submission: None

Studies not reviewed within this submission: None

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary
Not applicable (N/A)

2.6.2.2 Primary pharmacodynamics
N/A

2.6.2.3 Secondary pharmacodynamics
N/A

2.6.2.4 Safety pharmacology
N/A

2.6.2.5 Pharmacodynamic drug interactions
N/A

2.6.3 PHARMACOLOGY TABULATED SUMMARY
N/A

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary
N/A

2.6.4.2 Methods of Analysis:
N/A

2.6.4.3 Absorption
N/A

2.6.4.4 Distribution
N/A

2.6.4.5 Metabolism
N/A

2.6.4.6 Excretion
N/A

2.6.4.7 Pharmacokinetic drug interactions
N/A

2.6.4.8 Other Pharmacokinetic Studies
N/A

2.6.4.9 Discussion and Conclusions

N/A

2.6.4.10 Tables and figures to include comparative TK summary

N/A

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

N/A

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

N/A

2.6.6.2 Single-dose toxicity

N/A

2.6.6.3 Repeat-dose toxicity

N/A

2.6.6.4 Genetic toxicology

N/A

2.6.6.5 Carcinogenicity

N/A

2.6.6.6 Reproductive and developmental toxicology

N/A

2.6.6.7 Local tolerance

N/A

2.6.6.8 Special toxicology studies

N/A

2.6.6.9 Discussion and Conclusions

N/A

2.6.6.10 Tables and Figures

N/A

2.6.7 TOXICOLOGY TABULATED SUMMARY

N/A

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusion:
Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (Rx Only) contains hydrocodone bitartrate, pseudoephedrine hydrochloride and guaifenesin in a 5-mL oral solution. This combination drug product is proposed as a prescription product. The application is submitted under the 505(b)(2) process. No preclinical pharmacology and toxicology studies were conducted with Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution. Each active ingredient is widely used in the US and is generally recognized as safe and effective.

Hydrocodone is a semisynthetic narcotic antitussive and analgesic with multiple actions qualitatively similar to those of codeine. The precise mechanism of action of hydrocodone and other opiates is not known; however, hydrocodone is believed to act directly on the cough center. Hydrocodone bitartrate is a recognized antitussive, with efficacy established in Drug Efficacy Study Implementation (DESI) Notice 5213, dated June 1, 1982. Hydrocodone bitartrate is not included in any OTC monograph and is available on a prescription (Rx only) basis. Currently, there are several approved formulations containing hydrocodone including Hycodan® (NDA 05-213, 1943) and Tussionex® (NDA 19-111, 1987). Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the recommended human dose (Label of Tussionex® Extended Release Suspension, Rev. 01/2008 1E). In excessive doses, hydrocodone, like other opium derivatives, will depress respiration. Hydrocodone can produce miosis, euphoria, and physical and psychological dependence. The approved dose in Hycodan® is shown in the table below.

Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa (21 CFR 314.20). Pseudoephedrine is recognized as an effective agent for the relief of nasal congestion due to allergic rhinitis, the common cold, hay fever, or other upper respiratory allergies, and nasal congestion associated with sinusitis. Pseudoephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. It has the potential for excitatory side effects (21 CFR 314.80). In animal studies, pseudoephedrine reduced average weight, length, and rate of skeletal ossification in the animal fetus (USP Convention. USPDI – Drug Information for the Health Care Professional. 16th edition Volume I, Rockville, MD: U.S. Pharmaceutical Convention, Inc. 1996 (Plus updates), pg. 2508.). The monograph recommended dose (21 CFR 314.80) is listed in the table below.

Guaifenesin has been used widely in the US as a recognized monograph drug (21 CFR 341.18). It is a recognized expectorant that promotes or facilitates the evacuation of secretions from the bronchial airways to provide for the temporary relief of cough due to minor throat and bronchial irritation as may occur with upper respiratory infection. This may be accomplished by reducing the thickness of these secretions or by augmenting the formation of a more fluid secretion. The OTC monograph review for guaifenesin in Advanced Notice of Proposed Rulemaking, FR, Vol 41, No 176, 9/9/76, pp 38362

referenced that acute and chronic toxicity studies in animals demonstrated no adverse pathological findings for glyceryl guaiacolate (guaifenesin). Animal studies to assess carcinogenicity, genotoxicity, fertility, developmental or teratogenic effects of guaifenesin have not been conducted. The monograph recommended dose (21 CFR 341.78) is listed in the table below.

Active ingredient administered/Age Group		Adults and children 12 years of age and over	Children 6 to12 years of age
Hydrocodone (in Hycodan®)	q 4-6 hr.	5 mg	2.5 mg
	NTE in 24 hr.	30 mg	15 mg
Pseudoephedrine	q 4-6 hr.	60 mg, q 4-6 hr	30 mg, q 4 hr
	NTE in 24 hr.	240 mg	120 mg
Guaifenesin	q 4 hr.	200-400 mg	100-200 mg
	NTE in 24 hr.	2400 mg	1200 mg

The recommended dosage of each active ingredient for this NDA is within the dose ranges recommended in OTC monographs and the approved products. The OTC monograph 21 CFR 341.40 recognizes the combination of any single monograph oral antitussive drug (such as codeine phosphate) with any single monograph nasal decongestant and any single expectorant to be a permitted combination in OTC cough/cold products. Although hydrocodone is not an OTC monograph antitussive, hydrocodone combination product containing monograph active ingredients has been accepted based on the precedent (Tussionex, NDA 19-111), for which approval can be based on establishment of bioequivalence (see details in the clinical review of this NDA by Dr. Xu Wang, finalized on April 23, 2009).

The Applicant, (b) (4) informed the Agency in a facsimile dated April 15, 2009, that the ownership of NDA 22-279 has been transferred to (b) (4). The new ownership of the NDA was effective on March 25, 2009. The proposed drug product will be manufactured by a new contractor that has not been announced by the new owner of this NDA.

Unresolved toxicology issues (if any): None

Recommendations: From a preclinical perspective, approval is recommended for the application pending a labeling review.

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/s/

Jean Wu
4/24/2009 11:16:41 AM
PHARMACOLOGIST

Molly Shea
4/24/2009 11:21:32 AM
PHARMACOLOGIST
I concur.

NDA Pharmacology Fileability Check List

NDA No: 22-279

Date of submission: August 22, 2008

Date of Fileability meeting: October 6, 2008

Information to Sponsor Yes ( ) No (X)

Date of check list: October 6, 2008

(1) On its face, is the Pharm/Tox section of the NDA organized in a manner to allow substantive review? Yes (X) No ( ) NA ()

(2) On its face, is the Pharm/Tox section of the NDA legible for review?
Yes (X) No ( ) NA ()

(3) Are final reports of all required and requested preclinical studies submitted in this NDA? Yes () No ( ) NA (X)

	Yes	No	NA
Pharmacology	()	( )	(x)
ADME	()	( )	(x)
Toxicology (duration, route of administration and species specified)			
acute	()	( )	(x)
subchronic and chronic studies	()	( )	(x)
reproductive studies	()	( )	(x)
carcinogenicity studies	()	( )	(x)
mutagenicity studies	()	( )	(x)
special studies (Impurity)	()	( )	(x)
others	( )	( )	(x)

(4) If the formulation to be marketed is different from the formulation used in the toxicology studies, is repeating or bridging the studies necessary? Yes ( ) No ( ) NA (X)

If no, state why not?

If yes, has the applicant made an appropriate effort to repeat the studies using the to be marketed product, to bridge the studies or to explain why such repetition or bridging should not be required? Yes ( ) No ( ) NA ()

(5) Are the proposed preclinical labeling sections (carcinogenesis, mutagenesis and impairment of fertility, pregnancy category and overdosage) appropriate (including

human dose multiples expressed in either mg/m^2 or comparative systemic exposure levels) and in accordance with 201.57? Yes () No (X*).

**In the annotated labeling, Section 8, Teratogenic Effects, the sponsor need to clarify which unit (mg/m^2 or comparative systemic exposure levels) was used to express the multiples of human dose based on animal studies for hydrocodone.*

(6) Has the applicant submitted all special studies/data requested by the Division prior to the submission including but not limited to pre-NDA discussion? Yes () No ( ) NA (X)

(7) On its face, does the route of administration used in the pivotal toxicity studies appear to be the same as the intended clinical route? Yes () No ( ) NA (X)

If not, has the applicant submitted a rationale to justify the alternative route?
Yes ( ) No ( ) NA ()

(8) Has the applicant submitted a statement(s) that all of the toxicity studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? Yes () No ( ) NA (X)

(9) Has the applicant submitted any studies or data to address any impurity or extractable issues (if any)? Yes () No ( ) NA (X)

(10) Are there any outstanding preclinical issues? Yes () No (X)
If yes, identify those below.

(11) From a preclinical perspective, is this NDA fileable? Yes (X) No ( )

If no, state below why it is not.

(12) Should any additional information/data be requested? Yes ( ) No (X)

NDA Planning Timeline

NDA No.: 22-279

Date of planning timeline:

PDUFA Due Date: June 22, 2009

Projected review completion date: April 29, 2009

	Milestone Dates
Pharmacology and ADME	April 29, 2009
Toxicology	April 29, 2009
General toxicity studies	April 29, 2009
Carcinogenicity studies and mutagenicity studies	April 29, 2009
a. Statistical consult request for CA studies	N/A
b. Submission of CA studies for CAC concurrence	N/A
Reproductive studies	April 29, 2009
Special studies and Others	April 29, 2009
Labeling	March 23, 2009

Signatures (optional):

Reviewer Signature _____
Jean Q. Wu, MD., Ph.D.

Supervisor Signature _____
Luqi Pei, Ph.D.

Concurrence Yes ___ No ___

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/s/

Jean Wu
10/3/2008 03:14:10 PM
PHARMACOLOGIST

Luqi Pei
10/7/2008 07:31:04 AM
PHARMACOLOGIST
I concur.