

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022424Orig1s000

PHARMACOLOGY REVIEW(S)

Secondary Pharmacology and Toxicology Review for NDA 22-424 Resubmission

TO: NDA 22-424 (Mikart, Inc.)

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

DATE: May 1, 2015

The proposed product in this NDA is for a hydrocodone bitartrate and guaifenesin oral solution. NDA 22-424 was originally submitted on November 29, 2010. A nonclinical pharmacology and toxicology review was completed on July 21, 2011, by Dr. Grace Lee and includes evaluation of the proposed doses for each of the components from the nonclinical perspective. Dr. Lee recommended approval of the application and there were no outstanding nonclinical issues except for labeling. However, the applicant received a complete response on September 28, 2011, due to an audit of the bioanalytical site that found serious deficiencies and the studies were found unreliable. In addition, guaifenesin did not meet the bioequivalence criteria and additional bioequivalence data were requested.

The current resubmission of November 18, 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 only a minor correction in Section 13.1 (Carcinogenesis, Mutagenesis, and Impairment of Fertility). I concur with Dr. Galvis's recommendation.

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

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/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 22-424
Supporting document/s: SDN 22
Applicant's letter date: 11/18/2014
CDER stamp date: 11/18/2014
Product: FLOWTUSS (hydrocodone bitartrate and
guaifenesin) oral solution
Indication: For symptomatic relief of cough 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 22-424 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 22-424 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 22-424.

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1 Executive Summary

1.1 Introduction

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

This NDA was originally submitted by Tiber Laboratories, LLC on November 29, 2010. A nonclinical pharmacology/toxicology review was completed by Dr. Grace Lee on July 21, 2011. This review includes an evaluation of the proposed doses for hydrocodone and guaifenesin, and it recommended approval of the NDA from the nonclinical perspective. However, the applicant received a complete response on September 28, 2011, due to an audit of the bioanalytical site that found serious deficiencies and the studies were found unreliable. In addition, guaifenesin did not meet the bioequivalence criteria and additional bioequivalence data were requested.

This complete response submission includes additional bioequivalence data for guaifenesin to support approval of this application. Nonclinical studies were not submitted with this complete response. A review of the proposed 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/toxicology review was completed by Dr. Grace Lee on July 21, 2011. Dr. Lee recommended approval of the application from the nonclinical perspective. There were no outstanding issues from the nonclinical perspective except for labeling, which is addressed in this review.

1.3 Recommendations

1.3.1 Approvability

A nonclinical pharmacology/toxicology review was completed by Dr. Grace Lee on July 21, 2011. 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. The proposed labeling follows.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category C

There are no adequate and well controlled studies of FLOWTUSS (b) (4) in pregnant women. Reproductive toxicity studies have not been conducted with FLOWTUSS (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, FLOWTUSS (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 27 times the maximum recommended human daily dose (MRHDD) (on a mg/m² 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 40 times the MRHDD of hydrocodone (on a mg/m² 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 20 and 100 times, respectively, the MRHDD of hydrocodone (on a mg/m² 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.

10 OVERDOSAGE

No human overdose data are available for FLOWTUSS (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.

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 FLOWTUSS (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.

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 FLOWTUSS (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 23 and 65 times, respectively, the MRHDD of hydrocodone on a mg/m² basis).

Guaifenesin:

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

2 Drug Information

2.1 Drug

Refer to Dr. Lee's pharmacology/toxicology review dated July 21, 2011.

2.3 Drug Formulation

Refer to Dr. Lee's pharmacology/toxicology review dated July 21, 2011.

2.6 Proposed Clinical Population and Dosing Regimen

FLOWTUSS was developed by Mikart, Inc. for the symptomatic relief of cough and to loosen mucus associated with the common cold. The proposed dosing regimen is 10 mL every 4-6 hours, not to exceed 6 doses (60 mL) in 24 hours. Each 5 mL of the oral solution contains 2.5 mg hydrocodone bitartrate and 200 mg guaifenesin. The maximum daily dose with 60 mL is 30 mg hydrocodone bitartrate and 2400 mg guaifenesin.

2.7 Regulatory Background

- NDA 22-424 was originally submitted on November 29, 2010, by Tiber Laboratories, LLC. A complete response was sent to the sponsor on September 28, 2011, due to lack of bioequivalence for guaifenesin and because an FDA audit of the bioanalytical site found deficiencies, therefore; clinical data were considered unreliable.

4 Pharmacology

Refer to Dr. Lee's pharmacology/toxicology review dated July 21, 2011.

6 General Toxicology

Nonclinical studies were not conducted with FLOWTUSS oral solution or any of the components individually. Each active ingredient has a long history of clinical use in the US. Refer to Dr. Lee's pharmacology/toxicology review dated July 21, 2011.

11 Integrated Summary and Safety Evaluation

Mikart, Inc., submitted a 505(b)(2) NDA on November 18, 2014 (resubmission after a complete response), for FLOWTUSS [hydrocodone bitartrate and guaifenesin (2.5 mg and 200 mg; respectively, in 5 mL)] oral solution. The proposed indication is for the

symptomatic relief of cough and to loosen mucus associated with the common cold in adult patients 18 years of age and older.

NDA 22-424 was originally submitted on November 29, 2010, by Tiber Laboratories, LLC. A nonclinical pharmacology/toxicology review was completed on July 21, 2011, by Dr. Grace Lee during the first review cycle. Dr. Lee’s review includes an evaluation of the proposed doses for hydrocodone and guaifenesin and recommended approval of NDA 22-424 from the nonclinical pharmacology/toxicology perspective. However, the applicant received a complete response on September 28, 2011, due to an audit of the bioanalytical site that found serious deficiencies. The clinical data analyzed in this site was considered unreliable to support approval. In addition, guaifenesin did not meet the bioequivalence criteria and additional bioequivalence data were requested.

This complete response submission includes additional bioequivalence data for guaifenesin to support approval of this application. Nonclinical studies were not submitted with this complete response. Only a review of the proposed product labeling was conducted during the current 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 below (refer to the table). This labeling review was based upon comparison of the proposed labeling to the labeling from an approved product containing hydrocodone bitartrate and guaifenesin at the same levels (i.e., Obredon oral solution, approved on November 14, 2014, under NDA 205-474). The only recommended edit is one spelling correction under section 13.1 of the label.

Sponsor’s proposed language	Recommended edits
<p>8 USE IN SPECIFIC POPULATIONS</p> <p>8.1 Pregnancy</p> <p><i>Teratogenic Effects</i></p> <p><i>Pregnancy Category C</i></p> <p>There are no adequate and well controlled studies of FLOWTUSS (b) (4) in pregnant women. Reproductive toxicity studies have not been conducted with FLOWTUSS (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</p>	<p>There are no edits recommended for this section of the label.</p>

rats. Because animal reproduction studies are not always predictive of human response, FLOWTUSS (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 27 times the maximum recommended human daily dose (MRHDD) (on a mg/m² 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 40 times the MRHDD of hydrocodone (on a mg/m² 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 20 and 100 times, respectively, the MRHDD of hydrocodone (on a mg/m² 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

<p>dose.</p>	
<p>10 OVERDOSAGE</p> <p>No human overdose data are available for FLOWTUSS (b) (4)</p> <p><u>Hydrocodone:</u> 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.</p> <p><u>Guaifenesin:</u> 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 overdose consists of discontinuation of FLOWTUSS (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 overdose or unusual sensitivity to opioids including hydrocodone. Therefore, an appropriate dose of naloxone hydrochloride should be</p>	<p>There are no edits recommended for this section of the label.</p>

<p>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.</p>	
<p>12 CLINICAL PHARMACOLOGY</p> <p>12.1 Mechanism of Action</p> <p>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.</p> <p>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.</p>	<p>There are no edits recommended for this section of the label.</p>
<p>13 NONCLINICAL TOXICOLOGY</p> <p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p>Carcinogenicity, mutagenicity, and</p>	<p>13 NONCLINICAL TOXICOLOGY</p> <p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p>Carcinogenicity, mutagenicity, and</p>

<p>reproductive studies have not been conducted with FLOWTUSS (b) (4); however, published information is available for the individual active ingredients or related active ingredients.</p> <p><u>Hydrocodone:</u> 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 23 and 65 times, respectively, the MRHDD of hydrocodone on a mg/m² basis).</p> <p><u>Guaifenesin:</u> Carcinogenicity, genotoxicity, or reproductive toxicology studies have not been conducted with guaifenesin.</p>	<p>reproductive studies have not been conducted with FLOWTUSS (b) (4); however, published information is available for the individual active ingredients or related active ingredients.</p> <p><u>Hydrocodone:</u> 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 23 and 65 times, respectively, the MRHDD of hydrocodone on a mg/m² basis).</p> <p><u>Guaifenesin:</u> Carcinogenicity, genotoxicity, or reproductive toxicology studies have not been conducted with guaifenesin.</p>
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12 Appendix/Attachments

Appendix 1: Pharmacology/toxicology review dated July 21, 2011.

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/s/

CAROL M GALVIS
04/23/2015

MARCIE L WOOD
04/23/2015
I concur

INTEROFFICE MEMO

TO: NDA 22-424 (Tiber Laboratories, LLC; Hydrocodone Bitartrate and Guaifenesin Oral Solution)

FROM: Timothy W. Robison, Ph.D., D.A.B.T.
Pharmacology and Toxicology Team Leader

DATE: August 31, 2011

The proposed product in this NDA is for an aqueous oral solution containing hydrocodone bitartrate and guaifenesin. The combination drug product is proposed as a prescription product, which was submitted under the 505(b)(2) process. No nonclinical pharmacology and toxicology studies were conducted with Hydrocodone Bitartrate and Guaifenesin Oral Solution. The applicant (Tiber Laboratories, LLC) relied on the previously approved product NDAs and OTC monograph reviews and labeling for the individual products. Each active ingredient is widely used in the US and is generally recognized as safe and effective.

I concur with Dr. Grace Lee's review dated July 21, 2011 that recommended approval from a nonclinical pharmacology and toxicology perspective. There was no review of product labeling in the present cycle.

There are no outstanding pharmacology/toxicology issues at this time.

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/s/

TIMOTHY W ROBISON
08/31/2011

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PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 22-424
Supporting document/s: 1; 4
Applicant's letter date: November 29, 2010; April 14, 2011
CDER stamp date: November 29, 2010; April 14, 2011
Product: Hydrocodone Bitartrate and Guaifenesin Oral
Solution
Indication: [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
Applicant: Tiber Laboratories, LLC
5400 Laurel Springs Parkway, Suite 803
Suwanee, GA 30024
Review Division: Division of Pulmonary, Allergy, and
Rheumatology Products
Reviewer: Grace S. Lee, Ph.D.
Supervisor/Team Leader: Timothy W. Robison, Ph.D., D.A.B.T.
Division Director: Badrul Chowdhury, MD, Ph.D.
Project Manager: Sadaf Nabavian, Pharm.D.

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 22-424 are owned by Tiber Laboratories, LLC or are data for which Tiber Laboratories, LLC has obtained a written right of reference.

Any information or data necessary for approval of NDA 22-424 that Tiber Laboratories, LLC 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 22-424.

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1 Executive Summary

1.1 Introduction

The proposed product in this NDA is for an aqueous oral solution containing hydrocodone bitartrate and guaifenesin, and this combination drug product is proposed as a prescription product. Hydrocodone bitartrate is a generally recognized antitussive, with efficacy established in DESI Notice #5213, dated June 1, 1982, whereas guaifenesin is an accepted expectorant in the OTC Drug Monograph (21 CFR 341.18). Each active ingredient is widely used in the US and is generally recognized as safe and effective.

1.2 Brief Discussion of Nonclinical Findings

No nonclinical pharmacology or toxicology studies were conducted with the Hydrocodone Bitartrate and Guaifenesin Oral Solution. The applicant (Tiber Laboratories, LLC) relied on the previously approved product NDAs and OTC monograph review and labeling for the individual products. Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the recommended human dose. 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.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical pharmacology and toxicology standpoint, the application is recommended for approval.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

A labeling review will be completed at a later time when labeling negotiations are needed.

2 Drug Information

2.1 Drug

Generic Name: Hydrocodone and Guaifenesin Combination Oral Solution

Two active pharmaceutical ingredients (API) in the following:

Generic Name: Hydrocodone Bitartrate

CAS Registry Number: 34195-34-1

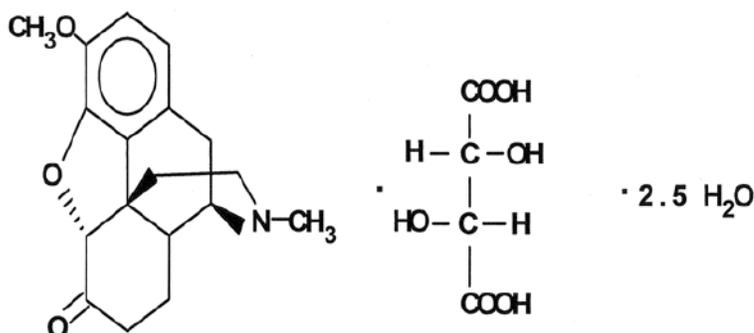
Chemical Name: Morphinan-6-one, 4,5- α -epoxy-3-methoxy-17-methyl-, (5 α)-, [R(R*,R*)]-2,3-dihydroxybutanedioate (1:1), hydrate, (2:5)

Or

4,5 α -Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)

Molecular Formula/Molecular Weight: C₁₈H₁₂NO₃·C₄H₆O₆·2.5 H₂O/ 494.490

Structure:



Pharmacologic Class: Analgesic and antitussive

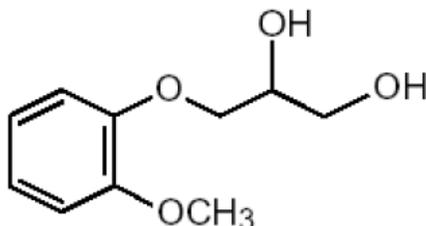
Generic Name: Guaifenesin

CAS Registry Number: 93-14-1

Chemical Name: 1,2-Propanediol,3-(2-methoxyphenoxy)-(+/-)-

Molecular Formula/Molecular Weight: C₁₀H₁₄O₄/ 198.22

Structure:



Pharmacologic Class: Expectorant

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 76365 (Hydrocodone and Guaifenesin Oral Solution; Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution; Tiber Laboratories, LLC)

NDA 22-279 (Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution; Tiber Laboratories, LLC)

DMF (b) (4) (Hydrocodone Bitartrate; (b) (4))

DMF (b) (4) (Guaifenesin; (b) (4))

2.3 Drug Formulation

The product is an oral solution with 5 mL containing 2.5 mg hydrocodone bitartrate and 200 mg guaifenesin. The composition of the drug product is shown in Table 1. As shown in the table, the formulation for the drug product in this NDA (on the right column) is identical to the formulation for the triple combination product of NDA 22-279 (on the left column), except for the absence of pseudoephedrine (b) (4).

Table 1: Formulations of double combination product for this NDA vs. triple combination product (NDA 22-279)

Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution			Hydrocodone and Guaifenesin Oral Solution	
% w/v	mg/5mL	Ingredient	% w/v	mg/5mL
0.050	2.5	Hydrocodone Bitartrate USP	0.050	2.5
4.000	200.0	Guaifenesin USP	4.000	200.0
0.600	30.0	Pseudoephedrine Hydrochloride USP	----	----
(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		

2.4 Comments on Novel Excipients

(b) (4) black raspberry flavor (b) (4) has not been used in US-approved drug products. Upon the request from the Agency, the applicant provided additional information on (b) (4) this flavoring agent (b) (4)

In general, (b) (4)

would be acceptable for the use as excipients in the drug product (Email communication with Drs. Abby Jacobs and Paul Brown on April 26, 2011). This favoring agent is also used in the triple combination oral solution of hydrocodone, pseudoephedrine and guaifenesin as shown in Table 1. The CMC reviewer Dr. Arthur Shaw for this NDA also found justification of the safety (b) (4) (see NDA 22-279 Chemistry Review #1 dated April 30, 2009).

(b) (4)

2.5 Comments on Impurities/Degradants of Concern

There is no concern for impurities (see Dr. Xiaobin Shen's Chemistry Review of NDA 22-424 dated April 27, 2011).

2.6 Proposed Clinical Population and Dosing Regimen

Each 5 mL (1 teaspoonful) of the oral solution contains 2.5 mg of hydrocodone bitartrate and 200 mg of guaifenesin. (b) (4)

Table 3: Recommended Dosage for the Hydrocodone Bitartrate and Guaifenesin Oral Solution

Product	Formulation	Dosage Regimen	Total Daily Dose (b) (4)
Hydrocodone Bitartrate and Guaifenesin Oral Solution	2.5 mg/ 200 mg per 5 mL		

2.7 Regulatory Background

The Applicant Tiber Laboratories, LLC also holds NDA 22-279 (Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution Rx Only).

3 Studies Submitted

None

4 Pharmacology

No study submitted

5 Pharmacokinetics/ADME/Toxicokinetics

No study submitted

6 General Toxicology

No study submitted

7 Genetic Toxicology

No study submitted

8 Carcinogenicity

No study submitted

9 Reproductive and Developmental Toxicology

No study submitted

10 Special Toxicology Studies

No study submitted

11 Integrated Summary and Safety Evaluation

The proposed product in this NDA is for an aqueous oral solution containing hydrocodone bitartrate and guaifenesin. Hydrocodone is an opioid derived from codeine that has antitussive and analgesic effects, whereas guaifenesin is a recognized expectorant. The combination drug product is proposed as a prescription product, which was submitted under the 505(b)(2) process. No nonclinical pharmacology and toxicology studies were conducted with Hydrocodone Bitartrate and Guaifenesin Oral Solution. The applicant (Tiber Laboratories, LLC) relied on the previously approved product NDAs and OTC monograph reviews and labeling for the individual products. Each active ingredient is widely used in the US and is generally recognized as safe and effective.

Hydrocodone is a semi-synthetic narcotic antitussive and analgesic with multiple actions qualitatively similar to those of codeine. Although the precise mechanism of action of hydrocodone and other opiates is not known, 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. 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.

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.

(b) (4)



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 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.

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

/s/

GRACE S LEE
07/21/2011

TIMOTHY W ROBISON
07/21/2011
I concur

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 22424

**Applicant: Tiber Laboratories,
LLC**

**Stamp Date: November 29,
2010**

**Drug Name: Hydrocodone and NDA Type: New
Guaifenesin Oral Solution**

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		Note that this is a 505(b)(2) application that the Sponsor relies on information from the literature and monographs
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?		X	Need to request to the Sponsor: Provide published scientific literature and reports on carcinogenicity, mutagenicity, teratogenicity, effects on fertility, and acute and repeat dose adult animal studies for hydrocodone and guaifenesin
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			Not applicable Note that this is a 505(b)(2) application that the Sponsor relies on information from the literature and monographs.
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			Not applicable Note that this is a 505(b)(2) application that the Sponsor relies on information from the literature and monographs.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement

Reference ID: 2893813

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		Extensive revision on labeling is needed.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		Although there is no issue at this moment, issues on impurities may arise during the detailed review. Will consult with CMC reviewer during the review cycle.
11	Has the applicant addressed any abuse potential issues in the submission?			Defer to the Medical Reviewer
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? _____ Yes _____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The Sponsor should be asked to provide literature references as follows:
 “Provide published scientific literature and reports on carcinogenicity, mutagenicity, teratogenicity, effects on fertility, and acute and repeat dose adult animal studies for hydrocodone and guaifenesin”

Grace S. Lee, Ph.D. January 20, 2011

 Reviewing Pharmacologist Date

Timothy W. Robison, Ph.D., D.A.B.T. January 20, 2011

 Acting-Team Leader, Pharmacologist Date

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

/s/

GRACE S LEE
01/20/2011

TIMOTHY W ROBISON
01/20/2011