CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

81-051/S-009; S-011; S-012, S-013

Trade Name:	Lortab Elixir
Generic Name:	Hydrocodone Bitartrate and Acetaminophen Elixir; 7.5mg/500mg per 15 mL
Sponsor:	Mikart, Inc.
Approval Date:	October 1, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

81-051/S-009; S-011; S-012; S-013

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

81-051/S-009; S-011; S-012; S-013

APPROVAL LETTER

ANDA 81-051/S-009, S-011, S-012, S-013

Mikart, Inc.
Attention: Cerie B. McDonald
1750 Chattahoochee Avenue, N.W.
Atlanta, GA 30318-2112

OCT 1 1997

Dear Madam:

This is in reference to your supplemental new drug applications dated September 6, 1995, submitted pursuant to 21 CFR 314.70, regarding your abbreviated new drug application for Hydrocodone Bitartrate and Acetaminophen Elixir, 7.5 mg/500 mg per 15 mL.

Reference is also made to your amendments dated April 24, 1996, April 15 and June 13, 1997.

The supplemental applications provide for:

S-009: Formulation Revision - reformulation of the product.

S-011: Control Revision - [redacted]

S-012: Expiration Date - 18 months for S-009.

S-013: Labeling Revision - to reflect formulation revision (S-009).

We have completed the review of these supplemental applications, and they are approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/S/ for 10/1/97

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

81-051/ S-009; S-011; S-012; S-013

FINAL PRINTED LABELING

50474909

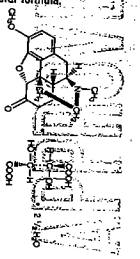
LORTAB® Elixir

HYDROCODONE* BITARTRATE AND ACETAMINOPHEN ELIXIR
7.5 mg/500 mg per 15 mL
***Warning: May be habit forming.**

OCT 1 1997

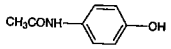
DESCRIPTION:
Hydrocodone bitartrate and acetaminophen is supplied in liquid form for oral administration.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one- tartrate- (1:1) hydrate (2:5). It has the following structural formula:



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2^1/_2H_2O$
M.W. 494.50

Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



$C_8H_9NO_2$ M.W. 151.17

Lortab Elixir contains:

	Per 5 mL	Per 15 mL
Hydrocodone Bitartrate (Warning: May be habit forming)	2.5 mg	7.5 mg
Acetaminophen	167 mg	500 mg
Alcohol	7%	7%

In addition, the liquid contains the following inactive ingredients: citric acid anhydrous, ethyl maltol, glycerin, liquid glucose, methylparaben, propylene glycol, propylparaben, purified water, saccharin sodium, sorbitol solution, sucrose, with D&C Yellow #10 and FD&C Yellow #6 as coloring and natural and artificial flavoring.

CLINICAL PHARMACOLOGY:
Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics: The behavior of the individual components is described below.

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects,

involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

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Pharmacokinetics: The behavior of the individual components is described below.

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6-α- and 6-β-hydroxy-metabolites.

See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See OVERDOSAGE for toxicity information.

INDICATIONS AND USAGE:

Lortab Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir) is indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS:

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.

WARNINGS:

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS:

General: Special Risk Patients: As with any narcotic analgesic agent, Lortab Elixir should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when Lortab Elixir is used postoperatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all narcotics, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease,

may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS:

General: Special Risk Patients: As with any narcotic analgesic agent, Lortab Elixir should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

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Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: Patients receiving narcotics, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with Hydrocodone Bitartrate and Acetaminophen Elixir may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO Inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy:

Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Lortab Elixir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all narcotics, administration of this product to the mother shortly before delivery may result in some degree

of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in the pediatric population have not been established.

ADVERSE REACTIONS:

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

Gastrointestinal System: Prolonged administration of Lortab Elixir may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on the brain stem respiratory centers (see OVERDOSAGE).

Dermatological: Skin rash, pruritis

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the OVERDOSAGE section.

DRUG ABUSE AND DEPENDENCE:

Controlled Substance: Lortab Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir) is classified as a Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when Hydrocodone Bitartrate and Acetaminophen Elixir is used for a short time for the treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of

time for the treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE:

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms:

Hydrocodone: Serious overdose 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, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams, or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION:

Dosage should be adjusted according to severity of pain and response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one tablespoonful every four to six hours as

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The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION:

Dosage should be adjusted according to severity of pain and response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one tablespoonful every four to six hours as needed for pain. The total daily dose should not exceed 6 tablespoonfuls.

HOW SUPPLIED:

Lortab® Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir) is a yellow-colored tropical fruit punch flavored liquid containing hydrocodone bitartrate 7.5 mg (Warning: May be habit forming) and acetaminophen 500 mg per 15 mL, with 7% alcohol. It is supplied in containers of 1 pint (473 mL) NDC 50474-909-16.

Storage: Store at controlled room temperature, 15°-30°C (59°-86°F). Dispense in a tight, light-resistant container with a child-resistant closure.

CAUTION: Federal law prohibits dispensing without prescription.
A Schedule CIII Narcotic.

ucb Pharma

Manufactured For:
UCB PHARMA, INC.
Atlanta, GA 30080

Manufactured By:
MIKART, INC.
Atlanta, GA 30318

Revised 12/96
Code 707A00
P/N 6H12120

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

81-051/ S-009; S-011; S-012; S-013

CSO LABELING REVIEW(S)

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **81-051/S-013**

Date of Submission: **June 13, 1997**

Applicant's Name: **Mikart, Inc.**

Established Name: **Hydrocodone Bitartrate and Acetaminophen Elixir 7.5 mg/500 mg per 15 mL**

From a labeling standpoint, this supplement is satisfactory for approval.

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Professional Package Insert Labeling:
Satisfactory for approval with June 13, 1997 submission.

FOR THE RECORD: (brought forward from previous reviews)

1. This is a combined chemistry and labeling supplement for a reformulation involving changes in inactive ingredients.

2. The insert was the only labeling affected by this revision. The model for the labeling is the Labeling Guidance for Hydrocodone Bitartrate and Acetaminophen Tablets USP; Revised 4/94.

3. The alcohol content of the drug product is correct according to the chemist. See first labeling review, NOTE TO CHEMIST.

4. The firm has satisfactorily revised the DESCRIPTION section of the package insert to reflect the addition of [redacted] as an inactive ingredient.

5. Telephoned firm on June 9, 1997 to request nine additional copies of FPL. Had submitted only 3 in April 15, 1997 submission.

Date of Review: September 3, 1997

Date of Submission: June 13, 1997

Primary Reviewer: Adolph Vezza **Date:** 9/4/97

/S/

Team Leader: Charlie Hoppes **Date:** 9/5/97

/S/

cc: ANDA 81-051/S-013
Division File
HFD-613/AVezza/CHoppes (no cc:)
njg/9/4/97/X:\NEW\FIRMSAM\MIKART\LTRS&REV\81051S13.APL
Review of Supplement

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **81-051/S-013**

Date of Submission: **April 15, 1997**

Applicant's Name: **Mikart, Inc.**

Established Name: **Hydrocodone Bitartrate and Acetaminophen Elixir 7.5 mg/500 mg per 15 mL**

Labeling Deficiencies:

1. INSERT

   Satisfactory in final print. However, we note you have submitted three copies of final printed labeling. We require 12 final printed copies for approval. Prepare and submit 9 additional copies.

Please submit 9 additional copies of final printed labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? No

Professional Package Insert Labeling: Only 3 inserts submitted. Telephoned firm June 9, 1997 to inform firm.

FOR THE RECORD:

1. This is a combined chemistry and labeling supplement for a reformulation involving changes in inactive ingredients.

2. The insert was the only labeling affected by this revision. The model for the labeling is the Labeling Guidance for Hydrocodone Bitartrate and Acetaminophen Tablets USP; Revised 4/94.

3. The alcohol content of the drug product is correct according to the chemist. See first labeling review, NOTE TO CHEMIST.

4. This comment brought forward from previous FTR:

   The firm has satisfactorily revised the DESCRIPTION section of the package insert to reflect the addition of [redacted] as an inactive ingredient.

5. Telephoned firm on June 9, 1997 to request nine additional copies of FPL.

Date of Review: June 9, 1997 for Jackie White

Date of Submission: April 15, 1997

Primary Reviewer: /S/ **Date:** 6/17/97

Secondary Reviewer: /S/ **Date:** 6/18/97

Team Leader: /S/ **Date:** 6/18/97

REVIEW OF PROFESSIONAL LABELING # 1

SUPPLEMENT

DRAFT - Insert Labeling

DATE OF REVIEW: April 23, 1996

ANDA #: 81-051/S-013

NAME OF FIRM: Mikart, Inc.

NAME OF DRUG: Hydrocodone Bitartrate and Acetaminophen Elixir 7.5 mg/500 mg per 15 mL

DATE OF SUBMISSION: September 6, 1995

COMMENTS:

INSERT:

1. GENERAL COMMENT

   The established name for this drug product is "Hydrocodone Bitartrate and Acetaminophen Elixir (capital "B"). Please revise throughout the text of the insert.

2. DESCRIPTION

   a. Revise the molecular weight of acetaminophen to be 151.17 as per USP 23.

   b. Align the quantities of active ingredients and percent alcohol to be under the proper per ___mL heading.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their insert labeling , then prepare and submit final print.

NOTE TO CHEMIST:

Has the firm accurately expressed the alcohol content of this drug product (7%)? Yes ARL 4/26/96

FOR THE RECORD:

The firm has satisfactorily revised the DESCRIPTION section of the package insert to reflect the addition of ——— as an inactive ingredient.

Adolph Vezza

NOTE: Adolph - I calculate the absolute alcohol - 20.10(d)(2) alcoholic content ... o/o volume ... It looks OK. ...

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

81-051/ S-009; S-011; S-012; S-013

CHEMISTRY REVIEW(S)

ANDA 81-051/S-009, S-011, S-012, S-013 (1st review)

NAME AND ADDRESS OF APPLICANT:
Mikart, Inc.
1750 Chattahoochee Avenue, N.W.
Atlanta, GA 30318-2112

PURPOSE OF AMENDMENT/SUPPLEMENT
S-009:
Formulation Revision - reformulation of the product.
S-011:
Control Revision -
S-012:
Expiration Date - 18 months for S-009.
S-013:
Labeling Revision - to reflect formulation revision (S-009).

DATE(S) OF SUBMISSION(S)
Firm: 9/6/95 - Original supplement

FDA: 12/7/95 - Bio. def. letter.

PHARMACOLOGICAL CATEGORY	TRADE NAME	NONPROPRIETARY NAME
Relief of moderate to moderately severe pain	None	Hydrocodone Bitartrate and Acetaminophen

DOSAGE FORM	POTENCY	RX OR OTC
Elixir	7.5 mg/500 mg per 15 mL	Rx

SAMPLES	RELATED IND/NDA/DMF	STERILIZATION
N/A	81-226 (500 mg/5 mg per 15 mL) 89-557 (500 mg/5 mg per 15 mL)	N/A

LABELING - Not Satisfactory
For S-013:
*** Insert: Not Satisfactory per Avezza 4-24-96

BIOEQUIVALENCY STATUS - Not Satisfactory
For S-009:
Letter from Bio. requesting evidence demonstrating *in vivo* bioavailability or information to permit waiver.

*** Pending response to Bio. letter.

ESTABLISHMENT INSPECTION - N/A

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS -

Redacted 3

pages of trade secret and /or confidential commercial information

ANDA 81-051/S-009, S-011, S-012, S-013 (2nd review)

NAME AND ADDRESS OF APPLICANT:
Mikart, Inc.
1750 Chattahoochee Avenue, N.W.
Atlanta, GA 30318-2112

PURPOSE OF AMENDMENT/SUPPLEMENT
S-009:
Formulation Revision - reformulation of the product.
S-011:
Control Revision - [redacted]
S-012:
Expiration Date - 18 months for S-009.
S-013:
Labeling Revision - to reflect formulation revision (S-009).

DATE(S) OF SUBMISSION(S)
Firm: 9/6/95 - Original supplement.
4/24/96 - Respons to Bio. letter.
4/15/97 - Response to 1st def. letter (chem. & labeling).
6/13/97 - Response to phone memo, labeling.

FDA: 12/7/95 - Bio. def. letter.
5/14/96 - 1st def. letter (chem. & labeling).
9/13/96 - Bio. review, waiver granted.

PHARMACOLOGICAL CATEGORY	TRADE NAME	NONPROPRIETARY NAME
Relief of moderate to moderately severe pain	None	Hydrocodone Bitartrate and Acetaminophen

DOSAGE FORM	POTENCY	RX OR OTC
Elixir	7.5 mg/500 mg per 15 mL	Rx

SAMPLES	RELATED IND/NDA/DMF	STERILIZATION
N/A	81-226 (500 mg/5 mg per 15 mL) 89-557 (500 mg/5 mg per 15 mL)	N/A

LABELING - Adolph Vezza on 9/3/97
For S-013:
Insert: Satisfactory in FPL.

BIOEQUIVALENCY STATUS - Satisfactory
For S-009:
Waiver of *in vivo* bioequivalence study requirements granted on 9/13/96 by Larry Ouderkirk.

ESTABLISHMENT INSPECTION - N/A

Redacted 3

pages of trade secret and /or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

81-051/ S-009; S-011; S-012; S-013

CORRESPONDENCE

9 PIs with this submiss
3 PIs with 4/15/97 subs

MIKART, INC.

PHARMACEUTICAL MANUFACTURERS

labeling review done
labeling OK for approval
9/3/97

FPL

SUPPL AMENDEMENT
SL-013 AM

June 13, 1997

Mr. Douglas Sporn, Director
Office of Generic Drugs
Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II (MPN II)
Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: ANDA 81-051 Hydrocodone Bitartrate and Acetaminophen Elixir 7.5 mg/500 mg per 15 mL
TELEPHONE AMENDMENT TO A SUPPLEMENTAL APPLICATION S-013

Dear Mr. Sporn:

Per the telephone request of Ms. Carol Holquist, Mikart is resubmitting nine copies of final printed insert labeling.

Thank you for your cooperation in the review of this material.

Sincerely,

Cerie B. McDonald
Executive Vice-President

CBM/ag

Enc.

RECEIVED
JUN 19 1997
GENERIC DRUGS

1750 CHATTAHOOCHEE AVENUE, N.W., ATLANTA, GEORGIA 30318-2112 PHONE: 404-351-4510 FAX: 404-350-043

MIKART, INC.
PHARMACEUTICAL MANUFACTURERS

April 15, 1997

AMENDMENT
SC009 AM, SC011 AM
SC012 AM, S/013 AM

Mr. Douglas Sporn, Director
Office of Generic Drugs
Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II (MPN II)
Room 150
7500 Standish Place
Rockville, MD 20855-2773

only 3 inserts need 12 - will inform firm
/S/ 6-9-97
called 6/9/97

Re: ANDA 81-051 Hydrocodone Bitartrate and Acetaminophen Elixir
7.5 mg/500 mg per 15 mL
MINOR AMENDMENT TO SUPPLEMENTAL APPLICATIONS S-009, S-011, S-012 AND S-013

Dear Mr. Sporn:

Mikart has received your letter of May 9, 1996 regarding the above supplemental applications. We would like to respond now to the issues raised. We have used the outline of your letter to organize our response. With the submission of this information, there are no longer any outstanding deficiencies, and we respectfully request that these supplemental applications be approved.

Thank you for your cooperation in the review of this material. Please feel free to contact us should you require any additional information.

Sincerely,

Cerie B. McDonald
Executive Vice-President

CBM/ag

Enc.

RECEIVED
APR 2 1 1997
GENERIC DRUGS

Nadine 4-28-97

1750 CHATTAHOOCHEE AVENUE, N.W., ATLANTA, GEORGIA 30318-2112 PHONE: 404-351-4510 FAX: 404-350-0432

ANDA 81-051/S-009, S-011, S-012, S-013

Mikart, Inc.
Attention: Cerie B. McDonald
1750 Chattahoochee Avenue, N.W.
Atlanta, GA 30318-2112

MAY 14 1996

Dear Madam:

This is in reference to your supplemental new drug applications dated September 26, 1995, submitted pursuant to 21 CFR 314.70, regarding your abbreviated new drug application for Hydrocodone Bitartrate and Acetaminophen Elixir, 7.5 mg/500 mg per 15 mL.

The supplemental applications provide for:

S-009: Formulation Revision - reformulation of the product.

S-011: Control Revision - [redacted]

S-012: Expiration Date - 18 months for S-009.

S-013: Labeling Revision - to reflect formulation revision (S-009).

The supplemental applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

For S-009:

Please respond to the incomplete submission letter dated December 7, 1995 from the Division of Bioequivalence. Until you have satisfactorily addressed this issue raised in that letter, this supplement will remain deficient. Please do not respond to this letter until the bioequivalence issues have been addressed.

For S-011:

[ ]

For S-012:

[ ]

B. Labeling Deficiencies For S-013:

INSERT:

1. GENERAL COMMENT

The established name for this drug product is "Hydrocodone Bitartrate and Acetaminophen Elixir (capital "B"). Please revise throughout the text of the insert.

2. DESCRIPTION

a. Revise the molecular weight of acetaminophen to be 151.17 as per USP 23.

b. Align the quantities of active ingredients and percent alcohol to be under the proper per ___mL heading.

Please revise your insert labeling , then prepare and submit final print.

The file on these supplemental applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw these supplemental applications. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed.

The responses to this letter will be considered as MINOR amendments and should be so designated in your cover letter. You have been notified in a separate letter of deficiencies identified in the bioequivalence portion of your supplemental

application. If you have substantial disagreement with our reasons for not approving these supplemental applications, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 5/13/96

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

MIKART, INC.
PHARMACEUTICAL MANUFACTURERS

NAI
"Bio Amendment" Assigned to Reviewer (Order) /S/ DH 5/2/96 JW

RECEIVED
APR 30 1996
GENERIC DRUGS

yes needs BIOAVAILABILITY NEW CORRESP to SC-009 [redacted] NC

April 24, 1996

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II (MPN II)
Room 150
7500 Standish Place
Rockville, MD 20857-2773

NAI 51697 NRL

Re: ANDA 81-051 Hydrocodone Bitartrate and Acetaminophen Elixir 7.5 mg/ 500 mg per 15 mL
AMMENDEMENT TO SUPPLEMENT 009

Dear Mr. Sporn:

In response to your letter dated December 7, 1995 Mikart would like to submit the following information to permit the FDA to waive *in vivo* bioavailability studies (21 CFR 320.22).

1. A side-by-side comparison of the:
   a. new proposed formula;
   b. old formulation;
   c. the reference listed drug; and
   d. all, if any previous changes to the formulation.
2. A physicochemical comparison, comparing the appropriate physicochemical properties (i.e., pH, viscosity, osmolarity) for the:
   a. New propsosed formulation
   b. Old formulation
   c. The reference listed drug
3. A request for a waiver of in vivo bioequivalence as specified under 21 CFR 320.22

Cerie B. McDonald
Executive Vice-President

April, 1996

Nadine 5.2.96

1750 CHATTAHOOCHEE AVENUE, N.W., ATLANTA, GEORGIA 30318-2112 PHONE: 404-351-4510 FAX: 404-350-0432

ANDA 81-051/S-009

DEC 7 1995

Mikart, INC
Attention: Cerie B. McDonald
1750 Chattahoochee Avenue N.W.
Atlanta, Georgia 30318-2112

Dear Sir/Madam

Reference is made to the following supplemental applications submitted September 6, 1995, for Hydrocodone Bitartrate and Acetaminophen Elixir 7.5 mg/500 mg per 15 mL. This correspondence is specific for the formulation revision supplement (S-009):

S-009	Formulation Revision
S-010	Package Revision
S-011	Control Revision
S-012	Expiration Date
S-013	Labeling Revision

The Office of Generic Drugs has pre-reviewed the submitted data and determined that the data submitted to support the proposed formulation revision (S-009) is not complete for the following reason:

The data submitted to support the requested change failed to include the bioequivalence data, as specified under 21 CFR 320.21(c), which specifies that any person submitting a supplemental application to the Food and Drug Administration (FDA) shall include in the application either:

1. Evidence demonstrating the *in vivo* bioavailability of the drug product (21 CFR 320.24); or

2. Information to permit FDA to waive the submission of evidence demonstrating *in vivo* bioavailability (21 CFR 320.22).

Until such data is submitted the bioequivalence assessment of your proposed change cannot be made.

Please be advised that a request for a wavier of *in vivo* bioequivalence should contain at a minimum the following information:

1. A side-by-side formulation comparison of the:

    a. new proposed formulation;
    b. old formulation;
    c. the reference listed drug; and
    d. all, if any previous changes to the formulation.

2. A physicochemical comparison, comparing the appropriate physicochemical properties (i.e., pH, viscosity, osmolarity) for the:

    a. new proposed formulation;
    b. old formulation; and
    c. the reference listed drug

3. A request for a waiver of in vivo bioequivalence as specified under 21 CFR 320.22

As described under 21 CFR 314.97 an action which will amend this supplemental application is required, if you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

ORIGINAL

BIOAVAILABILITY

NDA NO. 50009

NDA SUPPL FOR Formulation RW

~~50010~~

Deleted per Greg 2/22/96.

NDA SUPPL FOR ~~Package Insert~~

50011

NDA SUPPL FOR Control RW

RECEIVED

SEP 11 1995

GENERIC DRUGS

MIKART, INC.

PHARMACEUTICAL MANUFACTURERS

September 6, 1995

Mr. Charles Ganley, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II (MPN II)
Room 150
7500 Standish Place
Rockville, MD 20857-2773

Labeling Review completed-model L.C. Rev 4/94 S.I. 04/23/96

Re: ANDA 81-051 Hydrocodone Bitartrate and Acetaminophen Elixir
7.5 mg/500 mg per 15 mL

NDA NO. _____ REF. NO. 50012

NDA SUPPL FOR Expiration Date

NDA NO. _____ REF. NO. 50013

NDA SUPPL FOR Label RW

SUPPLEMENT TO AN APPROVED APPLICATION

Dear Mr. Sporn:

Mikart would like to supplement the above application to provide for the reformulation of the product and _____ in accordance with 21 CFR 314.70 (b) (2).

Enclosed please find two copies of the supplemental application. Items affected by this supplemental application have been numbered to agree with the corresponding sections of the ANDA. Please note that information previously submitted in the original application is not being resubmitted. A Table of Contents has been included for the reviewer's convenience. The reformulated biobatches were manufactured following the same standard operating procedures, utilizing the same type equipment, and packaged in the same container/closure systems as the previously approved product.

Hydrocodone Bitartrate and Acetaminophen Elixir 7.5 mg/500 mg per 15 mL is manufactured by Mikart, Incorporated of Atlanta, Georgia, in accordance with current good manufacturing practices.

Should you have any questions, please do not hesitate to call or write. Thank you for your cooperation in the review of this material.

Sincerely,

Cerie B. McDonald
Executive Vice-President

CBM/sw

Enclosures

Marketed

1750 CHATTAHOOCHEE AVENUE, N.W. ATLANTA, GEORGIA 30318-2112 PHONE: 404-351-4510 FAX: 404-350-043