CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

89-557/S-003

Generic Name: Hydrocodone bitartrate and Acetaminophen Elixir 7.5mg/500mg per mL

Sponsor: Mikart, Inc.

Approval Date: August 14, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89-557/S-003

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89-557/S-003

APPROVAL LETTER

ANDA 89-557/S-003

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

AUG 14 2000

Dear Madam:

This is in reference to your supplemental new drug application dated October 29, 1997, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug application for Hydrocodone Bitartrate and Acetaminophen Elixir, 5 mg/500 mg per 15 mL.

Reference is also made to your amendment dated June 19, 2000.

The supplemental application provides for revisions to the container labels and insert labeling to be in conformance with the April 1994 Labeling Guidance for Hydrocodone Bitartrate and Acetaminophen Tablets USP.

We have completed the review of this supplemental application and it is approved. However, at the time of next printing we ask that your revise your insert labeling as follows.

DESCRIPTION

Revise the molecular weights of Hydrocodone Bitartrate and Acetaminophen to read "494.490" and "151.16", respectively per USP 24.

Revised insert labeling may be submitted in an annual report provided all changes have been described in full.

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,

8/10/00

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 89-557/S-003
Division File
HFD-92

V:\FIRMSAM\MIKART\LTRS&REV\89557S03.AP.LABELING

ENDORSEMENTS: HFD-613/CPARK
HFD-613/CHoppes

8/10/00

Approval Letter - Single Supplement

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89-557/S-003

FINAL PRINTED LABELING

HYDROCODONE* BITARTRATE AND ACETAMINOPHEN ELIXIR

5 mg/500 mg per 15 mL

C III

Rx only

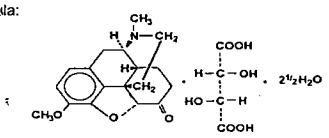
APPROVED AUG 14 2000

Code 539Z00
Rev. 06/00

DESCRIPTION:

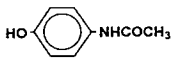
Hydrocodone bitartrate and acetaminophen is supplied in liquid form for oral administration.

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, 5 α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$ MW = 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:



$C_8H_9NO_2$ MW = 151.17

Hydrocodone bitartrate and acetaminophen elixir contains:

	Per 5 mL	Per 15 mL
Hydrocodone* Bitartrarate	1.67 mg	5 mg
(*Warning: May be habit forming)		
Acetaminophen	167 mg	500 mg
Alcohol	7.0 %	7.0 %

In addition, the liquid contains the following inactive ingredients: Citric acid, ethyl maltol, glycerin, methylparaben, propylene glycol, propylparaben, purified water, saccharin sodium, sorbitol solution, sucrose, D&C Yellow #10, FD&C Blue #1 and natural and artificial tropical fruit punch flavor.

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, 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-hydroxymetabolites.

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:

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, hydrocodone bitartrate and acetaminophen elixir should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function,

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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, hydrocodone bitartrate and acetaminophen 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 hydrocodone bitartrate and acetaminophen 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, 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. Hydrocodone bitartrate and acetaminophen 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 pediatric patients 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 nonambulatory 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 hydrocodone bitartrate and acetaminophen 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 brain stem respiratory centers (see OVERDOSAGE).

Dermatological: Skin rash, pruritus.

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: 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 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 endotracheal 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

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 endotracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

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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 or two tablespoonfuls (15 - 30 mL) every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablespoonfuls.

HOW SUPPLIED:

Hydrocodone bitartrate and acetaminophen elixir is a green, tropical fruit punch flavored liquid containing hydrocodone bitartrate 5 mg (* WARNING: May be habit forming) and acetaminophen 500 mg per 15 mL, with 7.0% alcohol, and is supplied in containers of 118 mL (4 fl oz), NDC 46672-578-04, in containers of 473 mL (16 fl oz), NDC 46672-578-16, and in containers of 3.785 L (1 gallon), NDC 46672-578-28.

Storage: Store at controlled room temperature, 15°C to 30°C (59°F to 86°F) (See USP).

Dispense in a tight, light-resistant container with a child-resistant closure.

Rx only

Manufactured by:
MIKART, INC.
Atlanta, GA 30318

Rev. 06/00

Code 539Z00

NDC 46672-578-01

C III

HYDROCODONE* BITARTRATE AND ACETAMINOPHEN ELIXIR
5 mg/500 mg per 15 mL

Contains:	Per 5 mL	Per 15 mL
Hydrocodone* Bitartrate	1.67 mg	5 mg
Acetaminophen	167 mg	500 mg
Alcohol	7.0%	7.0%

*WARNING: May be habit forming

Rx only

CONTENTS: 30 mL (1 fl oz)

APPROVED

AUG 14 2000

USUAL DOSAGE: See package insert for complete dosage recommendations.

WARNING: Keep this and all drugs out of the reach of children.

Manufactured by:
MIKART, INC.
Atlanta, GA 30318

Rev. 06/00

Code 539201

Lot No.:

Exp. Date:

PROFESSIONAL SAMPLE

STORAGE: Store at controlled room temperature, 15°C to 30°C (59°F to 86°F) (see USP).

NDC 46672-578-01

C III

HYDROCODONE* BITARTRATE AND ACETAMINOPHEN ELIXIR
5 mg/500 mg per 15 mL

Contains:	Per 5 mL	Per 15 mL
Hydrocodone* Bitartrate	1.67 mg	5 mg
Acetaminophen	167 mg	500 mg
Alcohol	7.0%	7.0%

*WARNING: May be habit forming

Rx only

CONTENTS: 30 mL (1 fl oz)

AUG 14 2000

AUG 14 2000

USUAL DOSAGE: See package insert for complete dosage recommendations.

WARNING: Keep this and all drugs out of the reach of children.

Manufactured by:
MIKART, INC.
Atlanta, GA 30318

Rev. 06/00

Code 539201

Lot No.:

Exp. Date:

PROFESSIONAL SAMPLE

STORAGE: Store at controlled room temperature, 15°C to 30°C (59°F to 86°F) (see USP).

JUN 19 2000 0002

Lot No.:

Exp. Date:

PHARMACIST: Dispense in a tight, light-resistant container with a child-resistant closure.

STORAGE: Store at controlled room temperature, 15°C to 30°C (59°F to 86°F) (See USP).

C III

NDC 46672-578-04

HYDROCODONE* BITARTRATE AND ACETAMINOPHEN ELIXIR

5 mg/500 mg per 15 mL

Contains:	Per 5 mL	Per 15 mL
Hydrocodone* Bitartrate	1.67 mg	5 mg
Acetaminophen	167 mg	500 mg
Alcohol	7.0 %	7.0 %

*(**WARNING:** May be habit forming)

Rx only

CONTENTS: 118 mL (4 fl oz)

USUAL DOSAGE: See package insert for complete dosage recommendations.

WARNING: Keep this and all drugs out of the reach of children.

Manufactured by:
MIKART, INC.
Atlanta, GA 30318

Rev. 06/00

Code 539Z04

Lot No.:

Exp. Date:

PHARMACIST: Dispense in a tight, light-resistant container with a child-resistant closure.

STORAGE: Store at controlled room temperature, 15°C to 30°C (59°F to 86°F) (See USP).

C III

NDC 46672-578-04

HYDROCODONE* BITARTRATE AND ACETAMINOPHEN ELIXIR

5 mg/500 mg per 15 mL

Contains:	Per 5 mL	Per 15 mL
Hydrocodone* Bitartrate	1.67 mg	5 mg
Acetaminophen	167 mg	500 mg
Alcohol	7.0 %	7.0 %

*(**WARNING:** May be habit forming)

Rx only

CONTENTS: 118 mL (4 fl oz)

USUAL DOSAGE: See package insert for complete dosage recommendations.

WARNING: Keep this and all drugs out of the reach of children.

Manufactured by:
MIKART, INC.
Atlanta, GA 30318

Rev. 06/00

Code 539Z04

NDC 46672-578-16

HYDROCODONE* BITARTRATE AND ACETAMINOPHEN ELIXIR
5 mg/500 mg per 15 mL

C III

Contains:	Per 5 mL	Per 15 mL
Hydrocodone* Bitartrate	1.67 mg	5 mg
Acetaminophen	167 mg	500 mg
Alcohol	7.0 %	7.0 %

*WARNING: May be habit forming

Rx only

CONTENTS: 473 mL (16 fl oz)

Lot No.:

Exp. Date:

PHARMACIST: Dispense in a tight, light-resistant container with a child-resistant closure.

STORAGE: Store at controlled room temperature, 15°C to 30°C (59°F to 86°F) (see USP).

USUAL DOSAGE: See package insert for complete dosage recommendations.

WARNING: Keep this and all drugs out of the reach of children.

APPROVED
AUG 14 2000

Manufactured by:
MIKART, INC.
Atlanta, GA 30318

Rev. 06/00

Code 539Z16

NDC 46672-578-16

HYDROCODONE* BITARTRATE AND ACETAMINOPHEN ELIXIR
5 mg/500 mg per 15 mL

C III

Contains:	Per 5 mL	Per 15 mL
Hydrocodone* Bitartrate	1.67 mg	5 mg
Acetaminophen	167 mg	500 mg
Alcohol	7.0 %	7.0 %

*WARNING: May be habit forming

Rx only

CONTENTS: 473 mL (16 fl oz)

Lot No.:

Exp. Date:

PHARMACIST: Dispense in a tight, light-resistant container with a child-resistant closure.

STORAGE: Store at controlled room temperature, 15°C to 30°C (59°F to 86°F) (see USP).

USUAL DOSAGE: See package insert for complete dosage recommendations.

WARNING: Keep this and all drugs out of the reach of children.

APPROVED
AUG 14 2000

Manufactured by:
MIKART, INC.
Atlanta, GA 30318

Rev. 06/00

Code 539Z16

NDC 46672-578-28

HYDROCODONE* BITARTRATE AND ACETAMINOPHEN ELIXIR
5 mg/500 mg per 15 mL

Contains:	Per 5 mL	Per 15 mL
Hydrocodone* Bitartrate	1.67 mg	5 mg
Acetaminophen	167 mg	500 mg
Alcohol	7.0 %	7.0 %

*(**WARNING:** May be habit forming)

Rx only

CONTENTS: 3.785 L (1 Gallon)

Lot No.:

Exp. Date:

PHARMACIST: Dispense in a tight, light-resistant container with a child-resistant closure.

STORAGE: Store at controlled room temperature, 15°C to 30°C (59°F to 86°F) (See USP).

USUAL DOSAGE: See package insert for complete dosage recommendations.

WARNING: Keep this and all drugs out of the reach of children.

APPROVED
AUG 14 2000

Manufactured by:
MIKART, INC.
Atlanta, GA 30318

Rev. 06/00

Code 539Z28

NDC 46672-578-28

HYDROCODONE* BITARTRATE AND ACETAMINOPHEN ELIXIR
5 mg/500 mg per 15 mL

Contains:	Per 5 mL	Per 15 mL
Hydrocodone* Bitartrate	1.67 mg	5 mg
Acetaminophen	167 mg	500 mg
Alcohol	7.0 %	7.0 %

*(**WARNING:** May be habit forming)

Rx only

CONTENTS: 3.785 L (1 Gallon)

Lot No.:

Exp. Date:

PHARMACIST: Dispense in a tight, light-resistant container with a child-resistant closure.

STORAGE: Store at controlled room temperature, 15°C to 30°C (59°F to 86°F) (See USP).

USUAL DOSAGE: See package insert for complete dosage recommendations.

WARNING: Keep this and all drugs out of the reach of children.

APPROVED
AUG 14 2000

Manufactured by:
MIKART, INC.
Atlanta, GA 30318

Rev. 06/00

Code 539Z28

JUN 19 2000 0014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89-557/S-003

CORRESPONDENCE

Mikart

SL - 003/AL
NDA SUPP AMEND

June 19, 2000

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 89-557 Amendment to Supplemental Application S-003
Hydrocodone Bitartrate and Acetaminophen Elixir 5 mg/500 mg per 15 mL

Dear Mr. Sporn:

Mikart has received your letter dated June 3, 1999 regarding the above supplemental application. We have made the requested minor revisions and are submitting 12 copies of final printed labeling. Three copies of each type are mounted on the attached pages. The remaining 9 copies of each are in the enclosed envelope.

Please note that Mikart has elected to retain the "Warning: May be habit forming" statement, as was determined to be acceptable in the GUIDANCE FOR INDUSTRY entitled "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 - Elimination of Certain Labeling Requirements."

Thank you for your cooperation in the review and approval of this material. Should you require any additional information, please do not hesitate to contact me.

Sincerely,

Cerie B. McDonald,
President

CBM/jhh

Enclosures: Final printed labeling

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JUN 23 2000
OGD

Mikart, Inc. • Pharmaceutical Manufacturers
1750 Chattahoochee Avenue • Atlanta, Georgia 30318
404-351-4510 • Fax 404-350-0432

ANDA 89-557/S-003

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

JUN - 3 1999

Dear Madam:

This is in reference to your supplemental new drug application dated October 29, 1997, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug application for Hydrocodone Bitartrate and Acetaminophen Elixir, 5 mg/500 mg per 15 mL.

The supplemental application provides for revisions to the container labels and insert labeling to be in conformance with the April 1994 Labeling Guidance for Hydrocodone Bitartrate and Acetaminophen Tablets USP.

We have completed the review of this supplemental application and it is approvable. However, before the supplemental application may be approved, it is necessary that you make the following revisions:

1. GENERAL COMMENTS

   a. Revise your storage temperature recommendations throughout your labels and labeling as follows:

      Store at controlled room temperature 15°-30°C (59°-86°F) (see USP).

   b. As a result of the FDA Modernization Act of 1997, the statement "CAUTION: Federal law ..." must be replaced with the symbol "Rx only" throughout your labels and labeling. Place the symbol on the main panel of the container labels and immediately beneath the title on the insert labeling. We refer you to the Guidance For Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements ...", at the internet site: http//www.fda.gov/cder/guidance/index.htm for guidance.

c. The FDA Modernization Act of 1997 has deleted the requirement for the presence of the statement "WARNING: May be habit-forming." Throughout the labels and labeling of scheduled drugs. You may remove this statement and accompanying asterisk from your labels and labeling.

2. CONTAINER 30 mL, 118 mL, 473 mL, 3.785 L

See GENERAL COMMENTS above.

3. INSERT

a. GENERAL COMMENT

There is no need to capitalize the established name throughout the text of the insert unless required by sentence structure.

b. DESCRIPTION

First sentence - "is supplied" rather than ~~~~

c. HOW SUPPLIED

i. See GENERAL COMMENTS above.

ii. "118 mL (4 fl oz)"; "473 mL (16 fl oz)"; "3.785 L (1 gallon)"

Prepare and submit 12 copies of final printed container labels and insert labeling as an amendment to this supplemental application.

The changes provided for in this supplemental application may not be initiated until you have been notified in writing that the supplemental application is approved.

Sincerely yours,

6/3/99

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Mikart

October 29, 1997

Approvable letter
drafted 6/1/99
G. Vegas

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

NDA NO. _____ REF NO SL-003
NDA SUPPL FOR Label Rev.

Re: ANDA 89-557
Hydrocodone Bitartrate and Acetaminophen Elixir 5mg/500mg per 15mL
SUPPLEMENT TO AN APPROVED APPLICATION

Dear Mr. Sporn:

Enclosed please find 4 copies of draft container and insert labeling for Hydrocodone Bitartrate and Acetaminophen Elixir 5mg/500mg per 15mL, which has been revised in accordance with the 04/94 labeling guidance.

In addition to the above, the Pediatric Use subsection of the outsert labeling has been revised in accordance with the 12/13/94 Federal Register in that the word "children" has been replaced with "pediatric patients". We have also changed the molecular weight of Acetaminophen from 151.16 to 151.17, in accordance with USP 23/ NF 18.

Thank you for your cooperation in the review of this material. Should you need additional information, please do not hesitate to contact us.

Sincerely,

Cerie B. McDonald
Executive Vice-President

CBM/lac

RECEIVED
NOV 6 1997
GENERIC DRUGS

Mikart, Inc. • Pharmaceutical Manufacturers
1750 Chattahoochee Avenue • Atlanta, Georgia 30318
404-351-4510 • Fax 404-350-0432