CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

81-051/S-006

Trade Name:	Lortab Elixir
Generic Name:	Hydrocodone Bitartrate and Acetaminophen Elixir; 7.5mg/500mg per 15 mL
Sponsor:	Mikart, Inc.
Approval Date:	June 8, 1995

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

81-051/S-006

CONTENTS

Reviews / Information Included in this ANDA Review.	
Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	
Medical Officer Review(s)	
Chemistry Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

81-051/S-006

APPROVAL LETTER

ANDA 81-051/S-006

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

JUN 8 1995

Dear Madam:

Reference is made to your supplemental new drug application dated March 10, 1995, submitted pursuant to Section 314.70(c) (Special Supplement - Changes Being Effected) of the Regulations, regarding your abbreviated new drug application for Lortab® Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir) 7.5 mg/500 mg per 15 mL.

The supplemental application provides for revised package insert labeling reflecting the addition of the gallon container size.

We have completed our review of this supplemental application and it is approved. Our letter of August 28, 1992, detailed the conditions relating to the approval of this abbreviated application.

However, at the time of next printing, revise your package insert labeling as follows:

OVERDOSAGE, Acetaminophen, third paragraph:

Insert a comma after "adults".

In addition, include the following revisions that were previously discussed in the March 10, 1995 telephone conversation between Anisa Dhalla of Mikart, Incorporated and Adolph Vezza of the FDA:

1. DRUG ABUSE AND DEPENDENCE

   Abuse and Dependence, second paragraph, second line- Delete the comma after "weeks".

2. PRECAUTIONS

   Pediatric Use - Replace "children" with "pediatric patients".

These minor editorial changes may be submitted in an annual report, provided they are described in full. [See 21 CFR 314.81 (b)(iii)]

The material submitted is being retained in our files.

Sincerely,

|S| for /

6-8-95

Yana Ruth Mille
Acting Director, Division of
Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 81-051/S-006
Dup/Division File
HFD-613/AVezza/C. Zimmermann/T. Phillips (no cc:)
HFD-600/RI |S| 6/7/95 |S| 6/7/95
Field Copy
HFD-82 |S| 6/8/95
6/5/95 81051.S06
F/T by fmf
Approval Letter

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

81-051/S-006

FINAL PRINTED LABELING

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 needed for pain. The total daily dosage should not exceed 6 tablespoonfuls.

HOW SUPPLIED

Lortab Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir, 7.5 mg/500 mg per 15 mL) is a yellow-colored, tropical fruit punch flavored liquid containing 7.5 mg hydrocodone* bitartrate (*Warning: May be habit forming) and 500 mg acetaminophen per 15 mL, with 7% alcohol. It is supplied in containers of 1 pint (473 mL), NDC 50474-909-16 and 1 gallon (3785 mL), NDC 50474-909-28.

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 III Narcotic.

APPROVED

JUN 8 1995

Manufactured for:
WHITBY PHARMACEUTICALS, INC.
Richmond, VA 23220

Manufactured by:
MIKART, INC.
Atlanta, GA 30318

Rev. 11/94
P/N 2H12020C
Code 540A00

LORTAB® ELIXIR

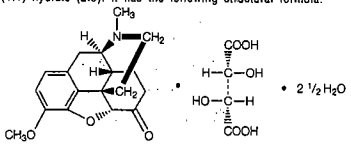
HYDROCODONE* BITARTRATE AND ACETAMINOPHEN ELIXIR
7.5 mg/500 mg per 15 mL

***Warning: May be habit forming.**

DESCRIPTION

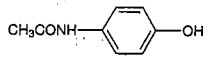
Hydrocodone bitartrate and acetaminophen is supplied in liquid form for oral administration.

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:



$C_{18}H_{21}NO_3 \bullet C_4H_6O_6 \bullet 2^1/_2H_2O$ 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 = 151.16

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, 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, 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

Lortab 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, 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 children have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are light-headedness, 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 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: Lortab Elixir (Hydrocodone* Bitartrate and Acetaminophen Elixir, 7.5 mg/500 mg per 15 mL) 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.

Original
81-051

LORTAB® ELIXIR

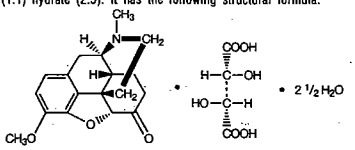
HYDROCODONE* BITARTRATE AND ACETAMINOPHEN ELIXIR
7.5 mg/500 mg per 15 mL

***Warning: May be habit forming.**

DESCRIPTION

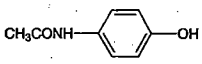
Hydrocodone bitartrate and acetaminophen is supplied in liquid form for oral administration.

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:



$C_{18}H_{21}NO_3 \bullet C_4H_6O_6 \bullet 2\frac{1}{2}H_2O$ 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 = 151.16

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, FD&C Red #40, 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.

JUN 8 1995

APPROVED

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with complete 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

Lortab 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.

JUN 8 1995

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 not 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.

APPROVED

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 children have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are light-headedness, 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 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: Lortab Elixir (Hydrocodone* Bitartrate and Acetaminophen Elixir, 7.5 mg/500 mg per 15 mL) 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 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 needed for pain. The total daily dosage should not exceed 6 tablespoonfuls.

HOW SUPPLIED

Lortab Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir, 7.5 mg/500 mg per 15 mL) is a yellow-colored, tropical fruit punch flavored liquid containing 7.5 mg hydrocodone* bitartrate (*Warning: May be habit forming) and 500 mg acetaminophen per 15 mL, with 7% alcohol. It is supplied in containers of 1 pint (473 mL), NDC 50474-909-16 and 1 gallon (3785 mL), NDC 50474-909-28.

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 III Narcotic.

Manufactured for:
WHITBY PHARMACEUTICALS, INC.
Richmond VA 23220

Manufactured by:
MIKART, INC.
Atlanta, GA 30318

Rev. 11/94
P/N 2H12020C
Code 540A00

APPROVED
APR 8 1995
APPROVED

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

81-051/S-006

CORRESPONDENCE

ANDA 81-051/S-006

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

JUN 8 1995

Dear Madam:

Reference is made to your supplemental new drug application dated March 10, 1995, submitted pursuant to Section 314.70(c) (Special Supplement - Changes Being Effected) of the Regulations, regarding your abbreviated new drug application for Lortab® Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir) 7.5 mg/500 mg per 15 mL.

The supplemental application provides for revised package insert labeling reflecting the addition of the gallon container size.

We have completed our review of this supplemental application and it is approved. Our letter of August 28, 1992, detailed the conditions relating to the approval of this abbreviated application.

However, at the time of next printing, revise your package insert labeling as follows:

OVERDOSAGE, Acetaminophen, third paragraph:

Insert a comma after "adults".

In addition, include the following revisions that were previously discussed in the March 10, 1995 telephone conversation between Anisa Dhalla of Mikart, Incorporated and Adolph Vezza of the FDA:

1. DRUG ABUSE AND DEPENDENCE

   Abuse and Dependence, second paragraph, second line- Delete the ——— after "weeks".

2. PRECAUTIONS

   Pediatric Use - Replace " ——— " with "pediatric patients".

These minor editorial changes may be submitted in an annual report, provided they are described in full. [See 21 CFR 314.81 (b)(iii)]

The material submitted is being retained in our files.

Sincerely,

/S/ for /

6-8-95

Yana Ruth Mille
Acting Director, Division of
Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 81-051/S-006
Dup/Division File
HFD-613/AVezza/CZimmermann/JPhillips (no cc:)
HFD-600/RF /S/ 6/7/95 /S/ 6/7/95
Field Copy
HFD-82 /S/ 6/8/95
6/5/95 81051.S06
F/T by fmf
Approval Letter

MIKART, INC.
PHARMACEUTICAL MANUFACTURERS

PI approved (c S-001 changes) model 4/94 Guidance

March 10, 1995

Mr. Douglas L. Sporn, Acting 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-006
NDA SUPPL. FOR Lab. Revision
SL-006/AI

Re: ANDA 81-051 Lortab Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir 7.5 mg/500 mg per 15 mL)
Supplement to an approved application
CHANGES BEING EFFECTED

Dear Mr. Sporn:

Mikart intends to introduce customer labeling in the gallon packaging size for the above application. Since customer labeling has not been printed previously for this packaging size, Mikart has created the package insert adding this packaging size and its corresponding NDC number following the 4/94 FDA Labeling Guidance for Hydrocodone Bitartrate and Acetaminophen.

— had before per cutdeep

This package insert will be used for the gallon packaging size effective March 20, 1995. As per the telephone conversation with Mr. Adolph Vezza on March 10, 1995, the following two corrections will be made at next reprint. The comma in the insert "Drug Abuse and Dependence" section that was included after the word "weeks" in the phrase "... ..." will be removed, and the word "[redacted]" will be changed to "pediatric patients" in the insert "Precautions" section. The label for the gallon packaging size was submitted in a supplement to the application dated January 25, 1995. Mikart has proposed a revised insert for the product based on the new FDA Labeling Guidance in a supplement dated August 3, 1994. Three copies of final printed labeling are attached. Nine additional copies are enclosed.

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

Sincerely,

Judy H. Howard for

Cerie B. McDonald
Executive Vice-President

CBM/jas
Enc.

RECEIVED
MAR 13 1995
GENERIC DRUGS

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