CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

81-051/S-008

Trade Name:	Lortab Elixir
Generic Name:	Hydrocodone Bitartrate and Acetaminophen Elixir; 7.5mg/500mg per 15 mL
Sponsor:	Mikart, Inc.
Approval Date:	April 17, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

81-051/S-008

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Reviews / Information Included in this ANDA Review.

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CSO Labeling Review(s)	X
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

ANDA 81-051/S-008

APR 17 2001

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

Dear Madam:

This is in reference to your supplemental new drug application dated August 29, 1995, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug application for LORTAB® Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir), 7.5 mg/500 mg per 15 mL.

Reference is also made to our approvable letters dated July 22, 1997 and February 8, 1998, and to your amendments dated October 7, 1997, March 9, 1998 and April 10, 2001.

The supplemental application provides for revisions in the PRECAUTIONS (Pediatric Use subsection) and the DOSAGE AND ADMINISTRATION sections of the professional insert labeling. In addition, you have proposed a "Patient Information Leaflet" and carton labeling for the bottle of 473 mL.

We have completed the review of this supplemental application and it is approved. However, at the time of next printing we ask that you make the following revisions.

1. GENERAL

   Add the phrase "[see USP]" to the storage temperature statement.

2. PACKAGE INSERT LABELING

   a. OVERDOSAGE (Signs and Symptoms) – Second paragraph, second sentence:

      In adults, hepatic… [add a comma]

   b. DOSAGE AND ADMINISTRATION – Second paragraph, second sentence:

      …The total daily dosage for adults should not… [add "for adults"]

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

Please note that the changes approved in this supplement should be applied to your other applications for the different strengths of Hydrocodone Bitartrate and Acetaminophen Elixir, ANDAs 81-226 and 89-557. Please revise the package insert labeling accordingly and submit in final print as "Special Supplement – Changes Being Effected" in accordance with 21 CFR 314.70(c) to each of these approved applications.

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/

4/17/01

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

81-051/S-008

FINAL PRINTED LABELING

1003486

LORTAB® ELIXIR

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

7.5 mg/500 mg per 15 mL

Rev. IE 09/2000
P/N 1003486

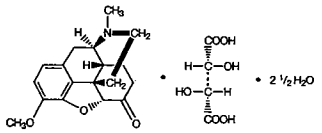
℞only
0540A00

DESCRIPTION

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

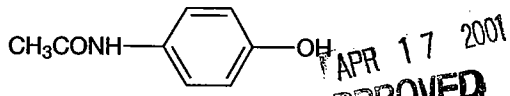
WARNING: May be habit forming (see PRECAUTIONS, Information for Patients, and DRUG ABUSE AND DEPENDENCE).

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:



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



APR 17 2001
APPROVED

$C_8H_9NO_2$ MW = 151.17

Lortab Elixir contains:	Per 5 mL	Per 15 mL
Hydrocodone Bitartrate	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 (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, acetaminophen, or any other component of this product.

WARNINGS

Respiratory Depression

At high doses or in ser
respiratory depression
Hydrocodone also affec
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Infants may have increa
opioids (see PRECAUTIO
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Head Injury and Increa

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Acute Abdominal Condi

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PRECAUTIONS

General

Special Risk Patients

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Cough Reflex

Hydrocodone suppresse
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Information for Patient

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Alcohol and other CNS
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prescribed.

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Laboratory Tests

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monitored with serial liv

Drug Interactions

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The use of MAO inhibito
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Drug/Laboratory Test In

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No adequate studies have
minophen has a potential

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Pregnancy

Teratogenic Effects

Pregnancy Category C

There are no adequate a
Elixir should be used du
potential risk to the fetu

Nonteratogenic Effects

Babies born to mothers

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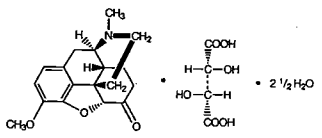

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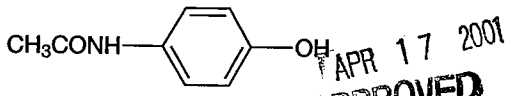

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INDICATIONS AND USAGE

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, acetaminophen, or any other component of this product.

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.

Infants may have increased sensitivity to the respiratory depressant effects of opioids (see PRECAUTIONS, Pediatric Use). If use of Lortab Elixir in such patients is contemplated, it should be administered cautiously, in substantially reduced initial doses, by personnel experienced in administering opioids to infants, and with intensive monitoring.

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 are 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. Such tasks should be avoided while taking this product.

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.

Physicians should instruct patients and caregivers to read the patient information leaflet, which appears as the last section of the labeling.

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-hydroxyindoleactic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies have been conducted in animals to determine whether hydrocodone has a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Hydrocodone has not demonstrated mutagenic potential using the Ames Salmonella-Microsomal Activation test, the Basc test on Drosophila germ cells, and the Micronucleus test on mouse bone marrow.

No adequate studies have been conducted in animals to determine whether acetaminophen has a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Acetaminophen has not demonstrated mutagenic potential using the Ames Salmonella-Microsomal Activation test, the Basc test on Drosophila germ cells, and the Micronucleus test on mouse bone marrow.

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. These signs usually appear during the first few days of life. 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

Narcotic analgesics cross the placental barrier. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. Narcotic analgesics should be avoided during labor if delivery of a premature infant is anticipated. If the mother has received narcotic analgesics during labor, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required (see OVERDOSAGE). The effect of hydrocodone, if any, on the later growth, development, and functional maturation of the child is unknown.

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 below the age of two years have not been established. Use of Lortab Elixir in the pediatric population is supported by the evidence from adequate and well controlled studies of hydrocodone and acetaminophen combination products in adults with additional data which support the development of metabolic pathways in children two years of age and over (see DOSAGE AND ADMINISTRATION for pediatric dosage information).

ADVERSE REACTIONS

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

Cardio-renal: Bradycardia, cardiac arrest, circulatory collapse, renal toxicity, renal tubular necrosis, hypotension.

Central Nervous System/Psychiatric: Anxiety, dizziness, drowsiness, dysphoria, euphoria, fear, general malaise, impairment of mental and physical performance, lethargy, light-headedness, mental clouding, mood changes, psychological dependence, sedation, somnolence progressing to stupor or coma.

Endocrine: Hypoglycemic coma.

Gastrointestinal System: Abdominal pain, constipation, gastric distress, heartburn, hepatic necrosis, hepatitis, occult blood loss, nausea, peptic ulcer, and vomiting.

Genitourinary System: Spasm of vesical sphincters, ureteral spasm, and urinary retention.

Hematologic: Agranulocytosis, hemolytic anemia, iron deficiency anemia, prolonged bleeding time, thrombocytopenia.

Hypersensitivity: Allergic reactions.

Musculoskeletal: Skeletal muscle flaccidity.

Respiratory Depression: Acute airway obstruction, apnea, dose-related respiratory depression (see OVERDOSAGE), shortness of breath.

Skin: Cold and clammy skin, diaphoresis, pruritus, rash.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Lortab Elixir (hydrocodone bitartrate and acetaminophen elixir) is classified as a Schedule III controlled substance.

Abuse and Dependence

Hydrocodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychological dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, this product should be prescribed and administered with caution appropriate to the use of other oral narcotic medications. However, psychological dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen elixir are 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

Toxicity from hydrocodone poisoning includes the opioid triad of loss of consciousness, pinpoint pupils, and respiratory depression (Cheyne-Stokes respiration, cyanosis, decrease in respiratory rate and/or tidal volume). Convulsions may occur.

The toxic dose of acetaminophen for adults is 10 grams. In adults hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams, or fatalities with less than 15 grams.

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

Other signs and symptoms of overdose of this product include bradycardia, cold and clammy skin, extreme somnolence progressing to stupor or coma, hypoglycemic coma, hypotension, renal tubular necrosis, skeletal muscle flaccidity, thrombocytopenia.

In severe overdosage, apnea; circulatory collapse; cardiac arrest; dose-dependent, potentially fatal hepatic necrosis; and death may occur.

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 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.

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 4 to 6 hours as needed for pain. The total daily dosage should not exceed 6 tablespoonfuls.

The usual dosages for children are given by the table below, and are to be given every 4 to 6 hours as needed for pain. These dosages correspond to an average individual dose of 0.27 mL/kg of Lortab Elixir (providing 0.135 mg/kg of hydrocodone bitartrate and 9 mg/kg of acetaminophen). Dosing should be based on weight whenever possible.

BODY WEIGHT	APPROXIMATE AGE	DOSE every 4 to 6 hours	MAXIMUM TOTAL DAILY DOSE (6 doses per day)
12 to 15 kg 27 to 34 lbs.	2 to 3 years	$\frac{3}{4}$ teaspoonful = 3.75 mL	$4\frac{1}{2}$ teaspoonfuls = 22.5 mL
16 to 22 kg 35 to 50 lbs.	4 to 6 years	1 teaspoonful = 5 mL	6 teaspoonfuls = 30 mL
23 to 31 kg 51 to 69 lbs.	7 to 9 years	$1\frac{1}{2}$ teaspoonfuls = 7.5 mL	9 teaspoonfuls = 45 mL
32 to 45 kg 70 to 100 lbs.	10 to 13 years	2 teaspoonfuls = 10 mL	12 teaspoonfuls = 60 mL
46 kg and up 101 lbs. and up	14 years to adult	1 Tablespoonful = 15 mL	6 Tablespoonfuls = 90 mL

The total daily dosage for children should not exceed 6 doses per day.

It is of utmost importance that the dose of Lortab Elixir be administered accu-

rately. A household teaspoon or tablespoon is not an adequate measuring device, especially when one-half or three-fourths of a teaspoonful is to be measured. Given the inexactitude of the household spoon measure and the possibility of using a tablespoon instead of a teaspoon, which could lead to overdosage, it is strongly recommended that care givers obtain and use a calibrated measuring device. Health care providers should recommend a dropper that can measure and deliver the prescribed dose accurately, and instruct care givers to use extreme caution in measuring the dosage.

HOW SUPPLIED

Lortab® Elixir (hydrocodone bitartrate and acetaminophen elixir) is a yellow-colored tropical fruit punch flavored liquid containing hydrocodone bitartrate 7.5 mg 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.

A Schedule CIII Narcotic.

ucb Pharma

Manufactured for
UCB Pharma, Inc.
Smyrna, GA 30080

Manufactured by
Mikart Inc.
Atlanta, GA 30318

Patient Information Leaflet

LORTAB® ELIXIR

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

7.5 mg/500 mg per 15 mL

C III

APPROVED
APR 17 2001

Summary

Lortab (pronounced LOR-tab) is used to relieve moderate to moderately severe pain. You should not take Lortab Elixir if you are allergic to hydrocodone or acetaminophen. The most common side effects of Lortab Elixir are abdominal pain, dizziness, drowsiness, light-headedness, nausea, shortness of breath, unusual tiredness, and vomiting. Take this medicine as directed by your doctor. Do not take more of it, do not take it more often, and do not take it for a longer time than your doctor ordered.

Uses

Lortab Elixir is an analgesic used to relieve moderate to moderately severe pain. Lortab Elixir is a combination product containing hydrocodone (hye-droe-KO-done) bitartrate and acetaminophen (a-seat-a-MIN-oh-fen). Hydrocodone is a narcotic pain reliever and a cough suppressant. Acetaminophen is a non-narcotic pain reliever and fever reducer. A narcotic analgesic and acetaminophen used together may provide better pain relief than either product used alone. If you have any questions, please call your doctor or pharmacist.

General Cautions

- Do not take this drug if you have allergies or unusual reactions to narcotic pain relievers or acetaminophen because it is likely that you may also be allergic to Lortab Elixir.
- This product may inhibit your mental and physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while you are taking this product.
- This medicine may not be right for you. Check with your doctor or pharmacist, if you:
  - are pregnant.
  - are nursing.
  - are taking other medications: narcotic pain relievers; allergy medicines; antidepressant medicines; acetaminophen-containing medicines or other medicines that cause central nervous system depression, including alcohol.
  - have other medical problems: a history of drug or alcohol abuse; recent head injury; emphysema, asthma, or other chronic lung disease; liver disease, kidney disease; underactive thyroid, Addison's disease, enlarged prostate or difficulty urinating.

Proper Use

Take this medicine as directed by your doctor. Do not share it with anyone else. This medicine can cause drug dependence and has the potential for abuse. Do not take more of it, do not take it more often, and do not take it for a longer time than your doctor ordered. If you think that this medicine is not working properly after taking it for some time, do not increase the dose. Check with your doctor or pharmacist.

Dosing

The dose of this medication will be different for different patients. Follow the directions provided by your doctor. The following information includes only the average doses of this medication. *If your dose is different, do not change doses unless your doctor tells you to do so.*

BODY WEIGHT	APPROXIMATE AGE	DOSE every 4 to 6 hours	MAXIMUM TOTAL DAILY DOSE (6 doses per day)
12 to 15 kg 27 to 34 lbs.	2 to 3 years	3/4 teaspoonful = 3.75 mL	4 1/2 teaspoonfuls = 22.5 mL
16 to 22 kg 35 to 50 lbs.	4 to 6 years	1 teaspoonful = 5 mL	6 teaspoonfuls = 30 mL
23 to 31 kg 51 to 69 lbs.	7 to 9 years	1 1/2 teaspoonfuls = 7.5 mL	9 teaspoonfuls = 45 mL
32 to 45 kg 70 to 100 lbs.	10 to 13 years	2 teaspoonfuls = 10 mL	12 teaspoonfuls = 60 mL
46 kg and up 101 lbs. and up	14 years to adult	1 Tablespoonful = 15 mL	6 Tablespoonfuls = 90 mL

It is very important that Lortab Elixir be dosed accurately. A household teaspoon or tablespoon is not an accurate measuring device, especially when one-half or three-fourths of a teaspoonful is to be measured.

Since a household teaspoon is not accurate and can be mixed-up with a tablespoon (which can cause overdosage), it is strongly recommended that you obtain and use a proper measuring device. Ask your doctor or pharmacist for help to find a dropper that can measure the needed dose properly and ask for help if you do not understand how to use the dropper.

Missed Dose

- To avoid a possible overdose, it is important that you do not take more than a single dosage at one time, or that you don't take doses at intervals less than 4 hours apart.
- If you miss taking a dose of Lortab Elixir, take it as soon as you remember. However, make sure to wait at least 4 hours before taking your next dose.
- If you missed taking a dose, and it is almost time for your next dose, skip the missed dose and take your medicine as scheduled.
- Do not double the prescribed dose.

Possible Side Effects

Side effects you may experience include abdominal pain, constipation, difficulty urinating, dizziness, drowsiness, fear, fuzzy thinking, general feeling of discomfort or illness, light-headedness, mood changes, nausea, nervousness, rash, shortness of breath, slower reactions, unusual tiredness, and vomiting.

Call your doctor if these effects continue or are bothersome.

Side effects not listed above may sometimes occur. If you notice any other effects, check with your doctor.

Storage

- Keep out of reach of children.
- Store at room temperature (protect from heat, do not refrigerate).
- Keep in original labeled bottle.
- Discard medicines that are old or no longer needed.

- Even a single overdose of this medicine may be a life-threatening situation. If you suspect that you or someone else may have taken more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately. This medicine was prescribed for your particular condition. Do not use it for another condition or give the drug to others.
- This leaflet provides a summary of information about Lortab Elixir. If you have any questions or concerns, or want more information about Lortab Elixir, contact your doctor or pharmacist. Your pharmacist also has a longer leaflet about Lortab Elixir that is written for health professionals that you can ask to read.

Prepared by UCB Pharma, Inc
Rev. IE 09/2000
P/N 1003486
0540A00

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Prepared by UCB Pharma, Inc
Rev. IE 09/2000
P/N 1003611
0540A00-P

ucb Pharma

1003611

LORTAB® ELIXIR
HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR
7.5 mg/500 mg per 15

Rev. IE 09/2000
P/N 1003611

Rx only
0540A00-P

LORTAB® ELIXIR C III

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

Patient Information Leaflet

APR 17 2001 APPROVED

Summary

Lortab (pronounced LOR-tab) is used to relieve moderate to moderately severe pain. You should not take Lortab Elixir if you are allergic to hydrocodone or acetaminophen. The most common side effects of Lortab Elixir are abdominal pain, dizziness, drowsiness, light-headedness, nausea, shortness of breath, unusual tiredness, and vomiting. Take this medicine as directed by your doctor. Do not take more of it, do not take it more often, and do not take it for a longer time than your doctor ordered.

Uses

Lortab Elixir is an analgesic used to relieve moderate to moderately severe pain. Lortab Elixir is a combination product containing hydrocodone (hye-droe-KO-done) bitartrate and acetaminophen (a-seat-a-MIN-oh-fen). Hydrocodone is a narcotic pain reliever and a cough suppressant. Acetaminophen is a non-narcotic pain reliever and fever reducer. A narcotic analgesic and acetaminophen used together may provide better pain relief than either product used alone. If you have any questions, please call your doctor or pharmacist.

General Cautions

- Do not take this drug if you have allergies or unusual reactions to narcotic pain relievers or acetaminophen because it is likely that you may also be allergic to Lortab Elixir.
- This product may inhibit your mental and physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while you are taking this product.
- This medicine may not be right for you. Check with your doctor or pharmacist, if you:
  - are pregnant.
  - are nursing.
  - are taking other medications: narcotic pain relievers; allergy medicines; antidepressant medicines; acetaminophen-containing medicines or other medicines that cause central nervous system depression, including alcohol.
  - have other medical problems: a history of drug or alcohol abuse; recent head injury; emphysema, asthma, or other chronic lung disease; liver disease, kidney disease; underactive thyroid, Addison's disease, enlarged prostate or difficulty urinating.

Proper Use

Take this medicine as directed by your doctor. Do not share it with anyone else. This medicine can cause drug dependence and has the potential for abuse. Do not take more of it, do not take it more often, and do not take it for a longer time than your doctor ordered. If you think that this medicine is not working properly after taking it for some time, do not increase the dose. Check with your doctor or pharmacist.

Dosing

The dose of this medication will be different for different patients. Follow the directions provided by your doctor. The following information includes only the average doses of this medication. *If your dose is different, do not change doses unless your doctor tells you to do so.*

BODY WEIGHT	APPROXIMATE AGE	DOSE every 4 to 6 hours	MAXIMUM TOTAL DAILY DOSE (6 doses per day)
12 to 15 kg 27 to 34 lbs.	2 to 3 years	3/4 teaspoonful = 3.75 mL	4 1/2 teaspoonfuls = 22.5 mL
16 to 22 kg 35 to 50 lbs.	4 to 6 years	1 teaspoonful = 5 mL	6 teaspoonfuls = 30 mL
23 to 31 kg 51 to 69 lbs.	7 to 9 years	1 1/2 teaspoonfuls = 7.5 mL	9 teaspoonfuls = 45 mL
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U.C.B.

2+19/64 x 2+15/16 x 7+5/8

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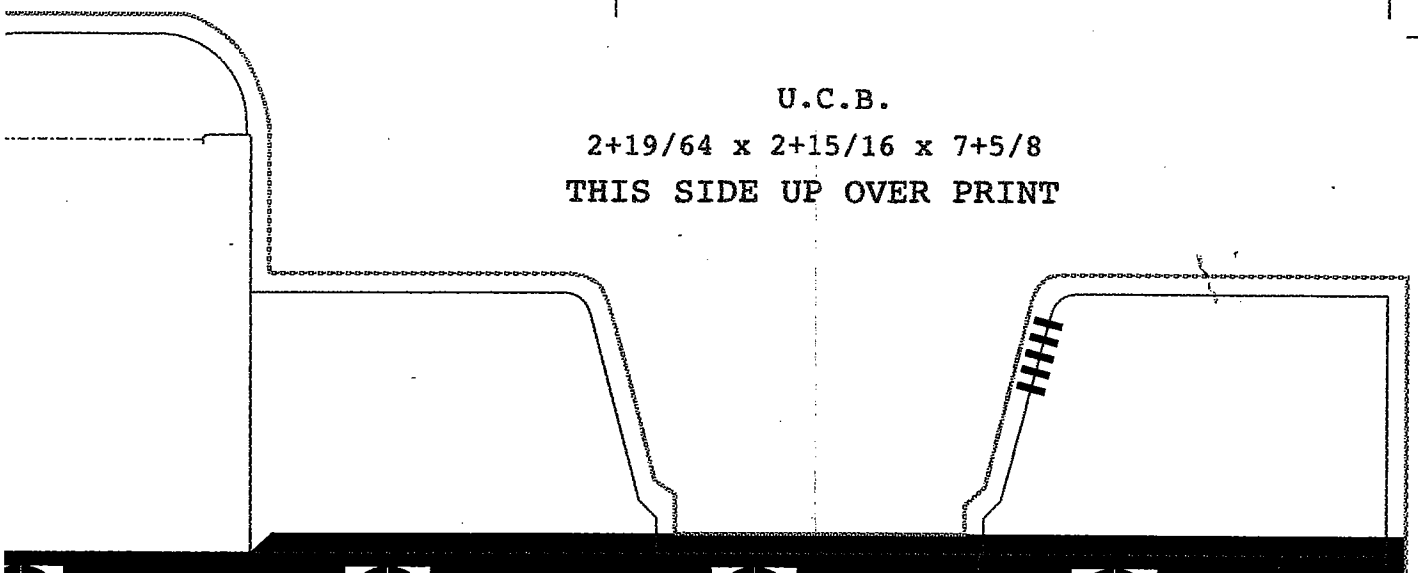


ucb Pharma

0474-909-16 1 Pint (473 mL)

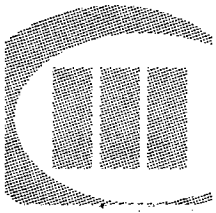
ORTAB® ELIXIR

OCODONE BITARTRATE

ACETAMINOPHEN ELIXIR

mg/500 mg per 15 mL

	Per 5 mL	Per 15 mL
s:		
idone		
trate.....2.5 mg		7.5 mg
nophen...167 mg		500 mg
.....7%		7%



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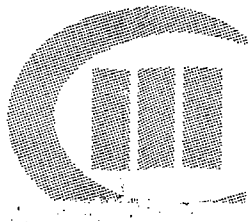
USUAL DOSAGE:
See package insert for complete dosage recommendations.

APR 17 2001 APPROVED

PHARMACIST:
Dispense in a tight, light-resistant container with a child-resistant closure.
Provide enclosed Patient Information Leaflet.

WARNING:
Keep this and all medications out of the reach of children.
May be habit forming.

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



ucb Pharma

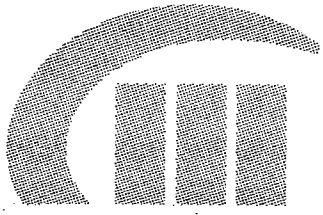
NDC 50474-909-16 1 Pint (473 mL)

LORTAB® ELIXIR

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

7.5 mg/500 mg per 15 mL

Contains:	Per 5 mL	Per 15 mL
Hydrocodone Bitartrate.....2.5 mg		7.5 mg
Acetaminophen...167 mg		500 mg
Alcohol 7%		7%



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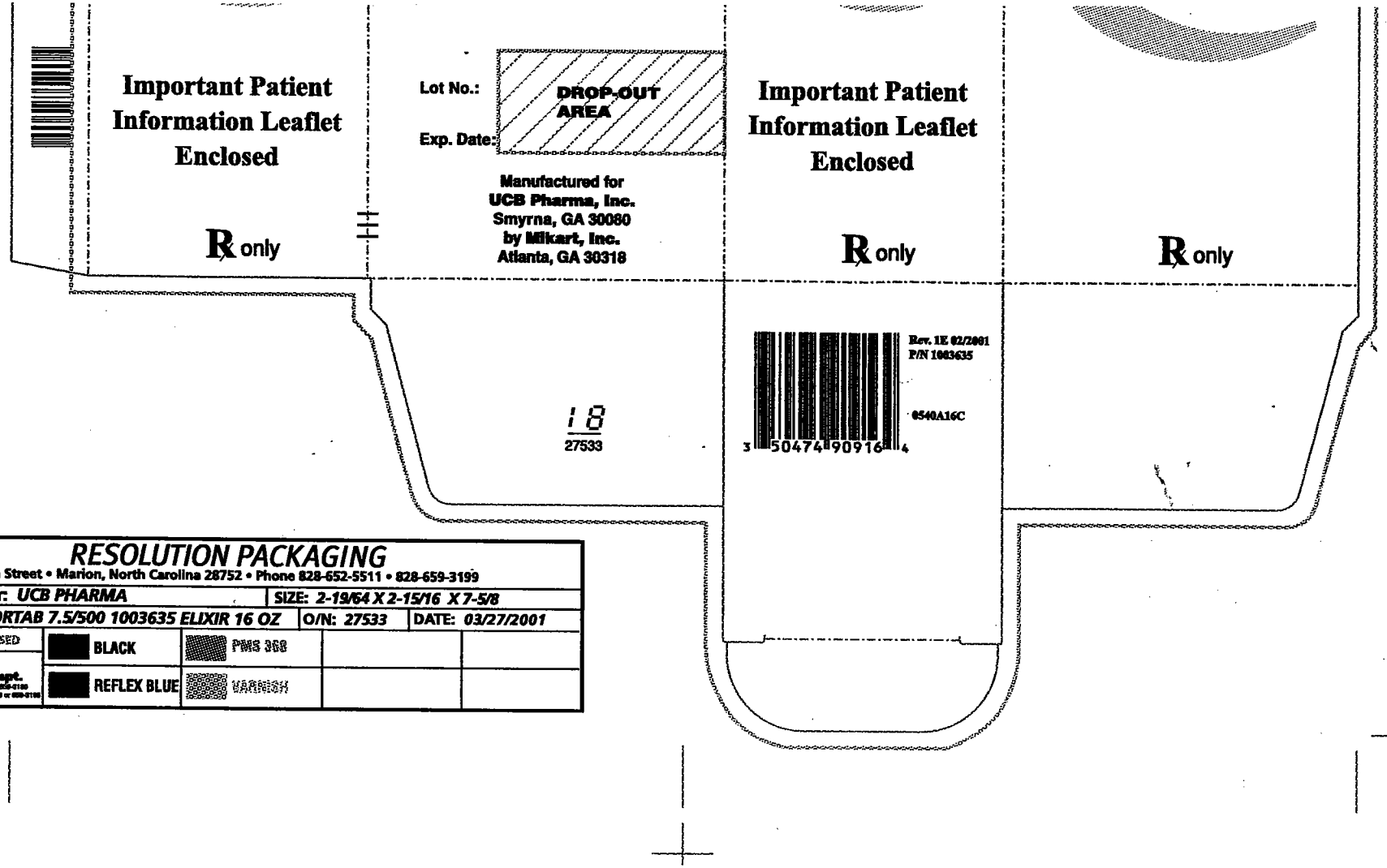

RESOLUTION PACKAGING				
33 Burgin Street • Marion, North Carolina 28752 • Phone 828-652-5511 • 828-659-3199				
Customer: *UCB PHARMA*		SIZE: *2-19/64 X 2-15/16 X 7-5/8*		
Item: *LORTAB 7.5/500 1003635 ELIXIR 16 OZ*		O/N: *27533*	DATE: *03/27/2001*	
COLORS USED	BLACK	PMS 368		
Graphics Dept.	REFLEX BLUE	VARNISH		

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

81-051/S-008

CSO LABELING REVIEW(S)

Clinical Review of ANDA 81-051
Labeling Consult from HFD-613
Second Copy

ANDA 81-051/S-008

Submission dates:	10/7/97 & 3/9/98
Consult date:	2/5/98
Review date:	8/24/00

Sponsor:

Mikart Inc.
1750 Chattahoochee Avenue, N.W.
Atlanta, Georgia 30318

Drug:

Lortab (hydrocodone bitartrate and acetaminophen elixir)
Elixir 7.5 mg/500 mg per 15 mL

Sponsor's Representative:

Cerie B. McDonald
Executive Vice-President
(404) 351-4510

Pharmacologic Category:

Opioid analgesic and antitussive/non-opiate, non-salicylate analgesic and antipyretic combination

Related Review:

Medical Officer's review dated 8/6/96 and Medical Team Leader's review dated 6/6/97, on the original 8/29/95 submission.

Submitted:

The original supplement dated 8/29/95 provided for proposed changes to the Pediatric Use subsection and Dosage and Information section in the package inert. This was consulted to HFD-550 2/26/96. The reviews dated 8/6/96 and 6/6/97 led to an approvable letter from HFD-613, Office of Generic Drugs, dated 7/22/97.

Mikart responded 10/7/97, and that amendment was consulted to HFD-550 on 2/5/98. While that consult has been pending, OGD sent Mikart another approvable letter dated 2/9/98. That letter informed Mikart that the 10/7/97 submission was under review with HFD-550 and it also provided Mikart with additional comments.

Mikart responded to the 2/9/98 letter on 3/9/98. That submission was provided to HFD-550 by fax. This review will look at both the 10/7/97 and 3/9/98 amendments.

Following is the labeling submitted by the company in the 10/7/97 amendment (there is no labeling in the 3/9/98 amendment). Reviewer recommended deletions are noted by ~~strikeout~~ and additions by double underline within the review.

LORTAB® Elixir CIII
HYDROCODONE± BITARTRATE AND ACETAMINOPHEN ELIXIR
7.5 mg/500 mg PER 15 ML

Reviewer's comments: *The approvable letter dated 2/9/98 stated that the statement _____ is no longer required. This is provided the habit forming characteristics of a drug product are adequately described in the Drug Abuse and Dependence section of the insert (see the Guidance for Industry, Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997-Elimination of Certain Labeling Requirements). Mikart's 3/9/98 amendment states that it will be deleted.*

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:

[STRUCTURE]

$C_{18}H_{21}N0_3 \bullet C_4H_6O_6 \bullet 2\ ½\ H_20$ 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:

[STRUCTURE]

$C_8H_9N0_2$ MW=151.16

Lortab Elixir contains:	Per 5 mL	Per 15 mL
Hydrocodone Bitartrate	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, methyl paraben, 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 (hydrocodone bitartrate and acetaminophen elixir) is indicated for the relief of moderate to moderately severe pain.

Reviewer's comments: *The established name should be in lower case letters.*

CONTRAINDICATIONS:
This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone, acetaminophen, or any other component of this product.

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.

Infants may have increased sensitivity to the respiratory depressant effects of opioids. (See PRECAUTIONS, Pediatric Use)

Reviewer's comments: *The paragraph above was added as requested in the 7/22/97 approvable letter. However, it conflicts with the precaution about safety and effectiveness in children less than 2 years of age. The second sentence should be deleted.*

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. Such tasks should be avoided while taking this product.

Reviewer's comments: *The Information for Patients was strengthened with wording from the same subsection in the Acetaminophen, Aspirin and Codeine Phosphate Labeling Guidance of December 1993.*

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 has a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Hydrocodone has not demonstrated mutagenic potential using the Ames Salmonella-Microsomal Activation test, the Basc test on Drosophila germ cells, and the Micronucleus test on mouse bone marrow.

No adequate studies have been conducted in animals to determine whether acetaminophen has a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Acetaminophen has not demonstrated mutagenic potential using the Ames Salmonella-Microsomal Activation test, the Basc test on Drosophila germ cells, and the Micronucleus test on mouse bone marrow.

Reviewer's comments: *The information above was taken from the 1993 Labeling Guidance. The information on the two active ingredients was separated because the studies would not have been done on a combination of the two.*

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. These signs usually appear during the first few days of life. 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.

Reviewer's comments: *The added sentence was taken from the 1993 Labeling Guidance. The rest of the paragraph is consistent with the wording in the Guidance.*

Labor and Delivery:

Narcotic analgesics cross the placental barrier. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. Narcotic analgesics should be avoided during labor if delivery of a premature infant is anticipated. If the mother has received narcotic analgesics during labor, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required (see OVERDOSAGE). The effect of hydrocodone, if any, on the later growth, development, and functional maturation of the child is unknown.

Reviewer's comments: *Revised according to the 1993 Labeling Guidance to make it stronger.*

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 below the age of two years have not been established. Use of Lortab Elixir in the pediatric population is supported by evidence from adequate and well-controlled studies of hydrocodone and acetaminophen combination products in adults with additional data which support the development of metabolic pathways in children two years of age and over. (See DOSAGE AND ADMINISTRATION for pediatric dosage information.)

Reviewer's comments: *The 7/22/97 approvable letter requested reducing the age limit in pediatric patients from 3 years to 2.*

ADVERSE REACTIONS (listed alphabetically, under each subsection)

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

Cardio-renal: Bradycardia, cardiac arrest, circulatory collapse, renal toxicity, renal tubular necrosis, hypotension.

Central Nervous System/Psychiatric: Anxiety, dizziness, drowsiness, dysphoria, euphoria, fear, general malaise, impairment of mental and physical performance, lethargy, light-headedness, mental clouding, mood changes, psychological dependence, sedation, somnolence progressing to stupor or coma.

Endocrine: Hypoglycemic coma.

Gastrointestinal System: Abdominal pain, constipation, gastric distress, heartburn, hepatic necrosis, hepatitis, occult blood loss, nausea, peptic ulcer, and vomiting.

Genitourinary System: Spasm of vesical sphincters, ureteral spasm, and urinary retention.

Hematologic: Agranulocytosis, hemolytic anemia, iron deficiency anemia, prolonged bleeding time, thrombocytopenia.

Hypersensitivity: Allergic reactions.

Musculoskeletal: Skeletal muscle flaccidity.

Respiratory Depression: Acute airway obstruction, apnea, dose-related respiratory depression (see OVERDOSAGE), shortness of breath.

Skin: Cold and clammy skin, diaphoresis, pruritus, rash.

Reviewer's comments: *The adverse reactions from hydrocodone and acetaminophen were combined, because these ingredients cannot be separated when one takes the drug product. Toxic effects from the Overdosage section were included as well.*

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Lortab Elixir (hydrocodone bitartrate and acetaminophen elixir) is classified as a Schedule III controlled substance.

Abuse and Dependence: Hydrocodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychological dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, this product should be prescribed and administered with caution appropriate to the use of other oral narcotic medications. However, psychological dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen elixir are used for a short time for the treatment of pain.

Reviewer's comments: *Added according to the 1993 Labeling Guidance.*

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:

Toxicity from hydrocodone poisoning includes the opioid triad of loss of consciousness, pinpoint pupils, and respiratory depression (Cheyne-Stokes respiration, cyanosis, decrease in respiratory rate and/or tidal volume). Convulsions may occur.

The toxic dose of acetaminophen for adults is 10 grams. In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams, or fatalities with less than 15 grams.

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

Other signs and symptoms of overdose of this product include bradycardia, cold and clammy skin, extreme somnolence progressing to stupor or coma, hypoglycemic coma, hypotension, renal tubular necrosis, skeletal muscle flaccidity, thrombocytopenia.

In severe overdosage, apnea; circulatory collapse; cardiac arrest; dose-dependent, potentially fatal hepatic necrosis; and death may occur.

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 [redacted] -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.

[redacted]

Reviewer's comments: *The sentence above was moved up so that it would appear with the other statement on acetaminophen toxicity.*

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 dosage for adults is one tablespoonful every 4 to 6 hours as needed for pain. The total daily dosage for adults should not exceed 6 tablespoonfuls.

The usual dosages for children are given by the table below, and are to be given every 4 to 6 hours as needed for pain. These dosages correspond to an average individual dose of 0.27 mL/kg of Lortab Elixir (providing 0.135 mg/kg of hydrocodone bitartrate and 9 mg/kg of acetaminophen). Dosing should be based on weight whenever possible.

BODY WEIGHT	APPROXIMATE AGE	DOSE Every 4 to 6 hours	MAXIMUM TOTAL DAILY DOSE (6 doses per day)
12 to 15 kg 27 to 34 lbs.	2 to 3 years	¾ teaspoonful =3.75 mL	4 ½ teaspoonfuls =22.5 mL
16 to 22 kg 35 to 50 lbs.	4 to 6 years	1 teaspoonful =5 mL	6 teaspoonfuls =30 mL
23 to 31 kg 51 to 69 lbs.	7 to 9 years	1 ½ teaspoonfuls =7.5 mL	9 teaspoonfuls =45 mL
32 to 45 kg 70 to 100 lbs.	10 to 13 years	2 teaspoonfuls =10 mL	12 teaspoonfuls =60 mL
46 kg and up 101 lbs. and up	14 years to adult	1 Tablespoonful =15 mL	6 Tablespoonfuls =90 mL

The total daily dosage for children should not exceed 6 doses per day.

It is of utmost importance that the dose of Lortab Elixir be administered accurately. A household teaspoon or tablespoon is not an adequate measuring device, especially when one-half or three-fourths of a teaspoonful is to be measured. Given the inexactitude of the household spoon measure and the possibility of using a tablespoon instead of a teaspoon, which could lead to overdosage, we strongly recommend that care givers obtain and use a calibrated measuring device. Health care providers should recommend a dropper that can measure and deliver the prescribed dose accurately, and instruct care givers to use extreme caution in measuring the dosage.

Reviewer's comments: *The dosing chart was added as requested. It is recommended that weight in pounds be included as well. Mikart also agreed to the recommendation that the maximum pediatric dosing be 6 doses per day.*

The approvable letter dated 7/22/97 stated in issue #5:

'It is of utmost importance that the dose of Lortab Elixir be administered as prescribed. The measure "teaspoonful" is not an adequate measuring device, especially when one-half of a teaspoonful should be measured. Given the inexactitude of the

teaspoonful measure and the possibility of using a tablespoon instead of a teaspoon, which could lead to overdosage and all its life-threatening consequences, we strongly urge you to provide an adequate measuring device with the bottle of Lortab Elixir. We recommend a dropper that can measure and deliver 2.5 and 5 mL of Lortab Elixir. The proper use of the dropper should be in the "Patient's Information" leaflet that comes with the Lortab Elixir package.'

The last paragraph above was added by Mikart in response to this. It should be revised as above to emphasize the difference between kitchen spoons and a measuring device.

HOW SUPPLIED

Lortab® Elixir (hydrocodone bitartrate and acetaminophen elixir) is a yellow-colored, tropical fruit punch flavored liquid containing 7.5 mg hydrocodone* bitartrate (~~[redacted]~~) and 500 mg acetaminophen 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.
~~[redacted]~~ Rx only.
Caution: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.
A Schedule CIII Narcotic

Reviewer's comments: *The approvable letter dated 2/9/98 stated that as a result of the FDA Modernization Act of 1997, the statement* ~~[redacted]~~ *will be replaced by "Rx only." Mikart's 3/9/98 amendment states that it will be revised.*

The caution statement on the transfer of the drug to any other person is required per 21 CFR 290.5.

Manufactured for
UCB PHARMA, INC.
Atlanta, GA 30080
Manufactured by:
Mikart, Inc.
Atlanta, GA 30318

Reviewer's comments: *In the 3/9/98 amendment, Mikart states that UCB Pharma, Inc., the distributor of Lortab Elixir, will provide physicians with measuring spoons, to be handed out with Patient Information Leaflets, included in the 10/7/97 response to the 7/22/97 approvable letter, and intended by Mikart to be promotional pieces and not part of the professional labeling. It is recommended that the information in the leaflet be attached to the package insert. It is not, however, considered a Patient Package Insert, and therefore need not be referred to in the Precautions section [21 CFR 201.57(f)(2)]. It is reviewed below.*

Prescription Drug Information

LORTAB® Elixir CIII

hydrocodone* bitartrate and acetaminopher elixir), 7.5 mg/500 mg/15 mL.

Summary

Lortab (pronounced LOR-tab) is used to relieve moderate to moderately severe pain. You should not take Lortab Elixir if you are allergic to hydrocodone or acetaminophen. The most common side effects of Lortab Elixir are abdominal pain, dizziness, drowsiness, light-headedness, , nausea, shortness of breath, unusual tiredness, and vomiting. Take this medicine as directed by your doctor. Do not take more of it, do not take it more often, and do not take it for a longer time than your doctor ordered.

Uses

Lortab Elixir is an analgesic used to relieve moderate to moderately severe pain. Lortab Elixir is a combination product containing hydrocodone (hye-droe-KO-done) bitartrate and acetaminophen (a-seat-a-MIN-oh-fen). Hydrocodone is a narcotic pain reliever and cough suppressant. Acetaminophen is a non-narcotic pain reliever and fever reducer. A narcotic analgesic and acetaminophen used together may provide better pain relief than either product used alone.

If you have any questions, please call your doctor or pharmacist.

General Cautions

- Do not take this drug if you have allergies or unusual reactions to narcotic pain relievers or acetaminophen because it is likely that you may also be allergic to Lortab Elixir.
- This product may inhibit your mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while you are taking this product.

This medicine may not be right for you. Check with your doctor or pharmacist, if you:

- are pregnant.
- are nursing.
- are taking other medications: narcotic pain relievers; allergy medicines; antidepressant medicines; acetaminophen-containing medicines or other medicines that cause central nervous system depression, including alcohol.
- have other medical problems: a history of drug or alcohol abuse; recent head injury; emphysema, asthma, or other chronic lung disease; liver disease, kidney disease; underactive thyroid, Addison's disease, enlarged prostate or difficulty urinating.

Proper Use

Take this medicine as directed by your doctor. Do not share it with anyone else. This medicine can cause drug dependence and has the potential for abuse. Do not take more of it, do not take it more often, and do not take it for longer time than your doctor ordered. If you think that this medicine is not working properly after taking it for some time, do not increase the dose. Check with your doctor or pharmacist.

Dosing

The dose of this medication will be different for different patients. Follow the directions provided by your doctor. The following information includes only the average doses of this medication. *If your dose is different, do not change doses unless your doctor tells you to do so.*

BODY WEIGHT	APPROXIMATE AGE	DOSE Every 4 to 6 hours	MAXIMUM TOTAL DAILY DOSE (6 doses per day)
12 to 15 kg 27 to 34 lbs.	2 to 3 years	¾ teaspoonful =3.75 mL	4 ½ teaspoonfuls =22.5 mL
16 to 22 kg 35 to 50 lbs.	4 to 6 years	1 teaspoonful =5 mL	6 teaspoonfuls =30 mL
23 to 31 kg 51 to 69 lbs.	7 to 9 years	1 ½ teaspoonfuls =7.5 mL	9 teaspoonfuls =45 mL
32 to 45 kg 70 to 100 lbs.	10 to 13 years	2 teaspoonfuls =10 mL	12 teaspoonfuls =60 mL
46 kg and up 101 lbs. and up	14 years to adult	1 Tablespoonful =15 mL	6 Tablespoonfuls =90 mL

Reviewer's comments: *The weights in pounds were revised, so that all weights are accounted for, and children with the in-between weights will get the lower dose.*

It is very important that Lortab Elixir be dosed accurately. A household teaspoon or tablespoon is not an accurate measuring device, especially when one-half or three-fourths of a teaspoonful is to be measured.

Since a household teaspoon is not accurate and can be mixed-up with a tablespoon (which can cause overdosage), it is strongly recommended that you obtain and use a proper measuring device. Ask your doctor or pharmacist for help to find a dropper that can measure the needed dose properly and ask for help if you do not understand how to use the dropper.

Missed Dose

- To avoid a possible overdose, it is important that you do not take more than a single dosage at one time, or that you do not take doses at intervals less than 4 hours apart.
- If you miss taking a dose of Lortab Elixir, take it as soon as you remember. However, make sure to wait at least 4 hours before taking your next dose.
- If you missed taking a dose, and it is almost time for your next dose, skip the missed dose and take your medicine as scheduled.
- Do not take double the prescribed dose.

Possible Side Effects

[redacted]

Side effects you may experience include abdominal pain, constipation, difficulty urinating, dizziness, drowsiness, fear, fuzzy thinking, general feeling of discomfort or illness, light-headedness, mood changes, nausea, nervousness, rash, shortness of breath, slower reactions, unusual tiredness, and vomiting.

Call your doctor if these effects continue or are bothersome.

Side effects not listed above may sometimes occur. If you notice any other effects, check with your doctor.

Storage

- Keep out of reach of children
- Store at room temperature (protect from heat, do not refrigerate)
- Keep in original labeled bottle
- Discard medicines that are old or no longer needed

Even a single overdose of this medicine may be a life-threatening situation. If you suspect that you or someone else may have taken more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately. This medicine was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

This leaflet provides a summary of information about Lortab Elixir. If you have any questions or concerns, or want more information about Lortab Elixir, contact your doctor or pharmacist. Your pharmacist also has a longer leaflet about Lortab Elixir that is written for health professionals that you can ask to read.

Prepared by UCB Pharma, Inc.

Recommendations: The labeling should be revised as indicated above for the supplement to be approved. Mikart should be encouraged to make the Patient Information Leaflet part of the package insert rather than just a promotional piece.

While it is helpful if calibrated measuring spoons are provided with prescriptions of this product, either by the physician or pharmacist, there is not sufficient justification at this time to require it and it is unlikely that all patients would receive them unless Mikart changes the distribution size and includes spoons as part of the packaging.

Joanne M. Holmes

Wiley A. Chambers, M.D.

cc:
ANDA 81-051
HFD-550/Div Dir/Midthun (first copy signed by K. Midthun, 8/00)
HFD-550/Dep Dir/Chambers
HFD-550/Med TL/Goldkind
HFD-550/Clin Rev/Holmes
HFD-550/SCSO/Vaccari
HFD-613/OGD

81051s8.doc

cc: ANDA 81-051/S-008
Division File
HFD-92

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

Approval Letter - Single Supplement

FOR THE RECORD

Background on 81-051/S-008 (Pediatric supplement and proposal for Patient Information Labeling)

1. The firm has submitted pediatric supplement on August 29, 1995.

2. Sent consult to the DAAOPD (HFD-550) on 2/26/96.

3. Consult responses were received. (consult dated 8/6/96 and 6/6/97).

4. Issued an approvable letter to the firm on 7/22/97 based on the consult responses mentioned above.

5. The firm has responded on 10/7/97 to the Agency's letter dated 7/22/97. In this amendment, the firm has proposed a patient information leaflet.

6. Second consult was sent to the DAAOPD on 2/5/98 regarding this patient information leaflet.

7. OGD sent another approvable letter to the firm on 2/9/98 informing that their proposal is under review by the DAAOPD.

8. Mikart responded on 3/9/98 to the letter dated 2/9/98. The firm's submission dated 3/9/98 was faxed to the HFD-550 on March, 1998.

9. On May 27, 1999 & March 30, 2000, we faxed all materials associated with these consults to DAAOPD as a reminder.

10. We have received a letter from Mikart on 1/20/00 complaining about this long-overdue supplement.

11. We have received the response to this consult electronically on 8/25/00.

12. Prepared a letter to the sponsor on 8/29/00 based on the review by HFD-550, which addressed both the 10/7/97 and 3/9/98 amendments.
13. We issued an approval letter in April, 2001.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

81-051/S-008

MEDICAL OFFICER REVIEW(S)

MEDICAL TEAM LEADER REVIEW

ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG PRODUCTS DIVISION -- HFD-550

ANDA #:	**81-051, SL008**
SUBMISSION DATE:	Sept. 1, 1995.
TYPE:	Pediatric Labeling Supplement
REVIEW DATE:	May 30, 1997.
REVIEWER:	John Hyde, Ph.D., M.D.
NAME:	**LORTAB ELIXIR** (hydrocodone bitartrate and acetaminophen elixir, 7.5/500 mg per 15 mL)
APPLICANT:	Mikart, Inc.
PHARMACOLOGIC CATEGORY:	Opioid/Non-opioid Combination Analgesic.
PROPOSED INDICATIONS:	Moderate to moderately severe pain.
DOSAGE FORM & ROUTE:	Elixir, oral.
RELATED REVIEWS:	Medical Officer Review of 8/6/96
CSO:	C. Koerner
MATERIALS REVIEWED:	Volumes 7.1-7.3, containing labeling proposal and copies of references.

RESUME:

Background

Agency Policies Regarding Acetaminophen (APAP) and Hydrocodone Bitartrate (HCB) Dosing

Dosing recommendations for acetaminophen (APAP) for adults and children 2 years and older appear in the Tentative Final Monograph for Internal Analgesics (TFM). The adult maximum individual dose for q4h dosing is 650 mg, corresponding to 9.3 mg/kg @ 70 kg, or 13 mg/kg @ 50 kg (the small adult). The maximum total daily adult dose is 4000 mg, permitting up to 6 of the above single doses. The 4000 mg daily limit corresponds to a per-weight daily limit of 57 mg/kg @ 70 kg, or 80 mg/kg @ 50 kg.

For children, the TFM dosing is given by age, but it corresponds to about 11 to 15 mg/kg for an individual dose. The maximum daily dose limit is five doses, but a daily maximum is also given for each age range as a specified amount that corresponds roughly to 75 mg/kg. Note that as q4h divided doses (up to 6 doses per day), the daily limit would be attained with six individual doses of 12.5 mg/kg, the middle of the recommended range for an individual dose.

The FDA's substitution policy for hydrocodone bitartrate (HCB) states that HCB may be substituted for codeine at a ratio of 1 mg HCB for 6 mg codeine. As a consequence, the maximum adult dosing of HCB is 10 mg every 4 to 6 hours, with the maximum total daily adult dose of HCB being 60 mg. There is no recommended pediatric dosing.

Current Product

LORTAB Elixir is indicated for moderate to moderately severe pain. It contains 167 mg acetaminophen (APAP) and 2.5 hydrocodone bitartrate (HCB) per 5 mL (~1 teaspoonful), so the ratio of HCB:APAP is 1:67. The recommended adult dosing is 15 mL (~ 1 tablespoonful) every 4 to 6 hours, up to 6 times/day. This provides 500 mg APAP and 7.5 mg HCB per dose, and a daily maximum of 3000 mg APAP and 45 mg HCB. Expressed as per-weight dosing for a small (50 kg) adult, the individual dose is 0.15 mg/kg HCB and 10 mg/kg APAP, while the maximum daily dose is 0.9 mg/kg HCB and 60 mg/kg APAP. It is noteworthy that the individual dose and daily totals for both components are very close to 75% of the maximum recommendations for each of the components:

Table 1: Adult Dosing of LORTAB Elixir vs. Its Components

	Individual Dose (mg)		Max Daily Dose (mg)	
	APAP	HCB	APAP	HCB
Max Recomended for Individual Component (with q 4 hour Dosing)	650	10	4000	60
Amount Provided with the Recommended LORTAB Dosing	500	7.5	3000	45
LORTAB Dosing as % of Max Component Recommendation	77%	75%	75%	75%

Similar Products

Hydrocodone is not presently marketed alone. It appears in combination with APAP in analgesics or with decongestants or antihistamines in antitussive preparations. The most similar product listed in the 1997 PDR is actually Tylenol with Codeine Elixir, each 5 mL of which contains 120 mg APAP and 12 mg codeine (equivalent 2 mg HCB). The indication however is for mild to moderate pain. The recommended dosing is:

Adults:	15 mL q4h prn (equivalent to 6 mg HCB/360 mg APAP per dose with implied daily maximum of 36/1960).
Children 7-12	10 mL 3-4 times/day (equivalent to 4 mg HCB/240 mg APAP per dose, with daily maximum of 16/960).
Children 3-6	5 mL 3-4 times/day (equivalent to 2 mg HCB/120 mg APAP per dose, with daily maximum of 8/480).

Pediatric Dosing Information

The submission included 68 supporting documents, mainly journal articles, some book chapters, some practice guidelines, and a copy of the suitability petition ruling for this ANDA. Of these, 26 directly mentioned pediatric analgesia, although not all had dosing recommendations. There were no articles with primary pediatric pharmacokinetic data, and only two presented clinical data: a 1977 report by Farb *et. al.* of an uncontrolled study of APAP and codeine in post-tonsillectomy pain, and a 1993 report by Schachtal using APAP in sore throat. The applicant's list of references is appended. In the following, the documents are referred to only by (lead) author and year.

Acetaminophen (APAP)

Dosing of 10 to 15 mg/kg to be given q4h was almost universally the recommendation for oral dosing, although the American Pain Society '89 recommended only 10 to 12 mg/kg q4h. There were very few explicit recommendations for a maximum daily dose. The Gaukroger '91 article noted that APAP up to 65 mg/kg/day had no significant side effects.

Hydrocodone Bitartrate (HCB)

For HCB, dosing recommendations were sparse and less consistent. The Agency for Health Care Policy and Research (AHCPR) '92 recommended 0.2 mg/kg q3 to 4h, with no daily limit specified--it could therefore implied to be 1.6 mg/kg/day. In Morrow '87 the recommendation is 0.6 mg/kg/day divided into 3 or 4 doses, implying individual doses of 0.15 to 0.2 mg/kg q6 to 8h. This is a much lower daily dose than that implied by the AHCPR '92, and it is the same daily dose recommended for HCB used as an antitussive. Jacox '94 recommended 0.2 mg/kg q3-4h for moderate to severe cancer pain, similar to the AHCPR recommendations. Ready '92 recommended a maintenance dose of 0.07 to 0.15 mg/kg q4-6h for acute pain.

More data are available for codeine, for which the recommended dosing is quite commonly cited as 0.5 to 1.0 mg/kg q4h. No daily maximum is given; the implied maximum with q4h dosing is 6 mg/day. Using the ratio of 1:6 from the FDA substitution policy, the codeine recommendations translate to HCB recommendations of 0.083 to 0.167 mg/kg for an individual dose of HCB, with an implied daily limit of 1.0 mg/kg/day. Application of the above pediatric dosing produces the adult HCB dosing of the Substitution Policy Memo when applied to a 60 kg adult.

The '91 article by Berde and the '91 article by Mahan have some information on pediatric PK/PD for opioids. They note that premature infants and term newborns less than about 1 month have reduced opioid clearance. Also infants younger than 3 to 6 months are more susceptible to respiratory depression than adults, but that above that age metabolism (normalized to body weight) and PD are like that of adults. The conclusions are based on extrapolation from morphine to the other opioids. The articles contain no primary data, but cite articles not included in the submission. The AHCPR

Medical Review pg 4

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pages of trade secret and /or confidential commercial information

The applicant did not provide clear explanation for the 4 dose limitation. It does not appear in the literature other than the Morrow '87 article. It is however the same as the regimen for Tylenol with Codeine Elixir.

DISCUSSION:

Individual Dose Size

This reviewer decided to analyze the dosing recommendation in the following way: The LORTAB adult dosing provides 75% of the maximum recommended dosing for each of its components. This nicely reflects the philosophy that combination products should offer the possibility of achieving acceptable efficacy with less than maximal doses of each component, which should improve tolerability. Using the same ratio for the pediatric dosing, q4h target dosing for APAP should be 12.5 x 75% = 9.375 mg/kg; this would be provided by **0.28** mL/kg of elixir. For HCB the q4h target dosing would be 0.167 x 75% = 0.125 mg/kg; provided by **0.25** mL/kg of elixir. This suggests a compromise dose of **0.26 to 0.27** mL/kg elixir. With this as a guide, and with some manual adjustment to fit the vagaries of discrete dosing and age ranges, the reviewer produced the following recommend dosing table, in which the dose comes out most closely corresponding to 0.27 mL/kg:

Table 3: Reviewer's Modified LORTAB Dosing

weight range in kg	approx. age range (yrs)	Total mL	Total mg APAP	Total mg HCB	APAP mg/kg			HCB mg/kg		
					min	max	avg	min	max	avg
12 - 15	2 - 3	3.8	125	1.9	8.4	10.4	9.3	0.125	0.156	0.140
16 - 22	4 - 6	5	167	2.5	7.6	10.4	8.9	0.114	0.156	0.133
23 - 31	7 - 9	7.5	251	3.8	8.1	10.9	9.4	0.121	0.163	0.140
32 - 45	10 - 13	10	334	5.0	7.4	10.4	8.8	0.111	0.156	0.131
46 -	14-adult	15	501	7.5	# # #	10.9	# # #	# # # #	0.163	# # # #
Averages for Weights 12 - 45:							9.02			0.135

It is notable that this table is very similar to the applicant's (Table 2), although slightly more conservative in a few cases. It also fills in the gaps in the applicant's ranges, and provides for reduced dosing for small 3 year olds as well as including age 2 years in the age range.

The average dose in Table 3 is a little under the target for APAP and a little over the target for HCB, but this is inherent in the combination found in LORTAB: Adult dosing has a HCB:APAP ratio of 10:650 = 1:65, close to the ratio of 1:67 found in LORTAB. However, the pediatric recommendations tend to be a little heavier on APAP, with a ratio of 0.167:12.5 = 1:75. Thus any pediatric dosing with this product will have to be a little lighter on APAP, or a little heavier on HCB, or both.

Total Daily Dose

The applicant's recommended dosing is 3 to 4 times per day. The following table shows the total daily dose of the applicant proposed dosing at 4 times per day, as well as the total when given 5 or 6 times per day:

Table 4: Total Daily LORTAB Doses Using Multiples of Applicant's Proposed Individual Doses

A similar table using the reviewer's modification of the dosing schedule is given below:

Table 5: Total Daily LORTAB Doses Using Multiples of Reviewer's Modified Individual Doses

weight range in kg	approx. age range (yrs)	Single Dose (mL)	mg/kg in 4 doses				mg/kg in 5 doses				mg/kg in 6 doses			
			avg		max		avg		max		avg		max	
			APAP	HCB	APAP	HCB	APAP	HCB	APAP	HCB	APAP	HCB	APAP	HCB
12 - 15	2 - 3	3.75	37	0.56	42	0.63	47	0.70	52	0.78	56	0.84	63	0.94
16 - 22	4 - 6	5	36	0.53	42	0.63	44	0.67	52	0.78	53	0.80	63	0.94
23 - 31	7 - 9	7.5	37	0.56	44	0.65	47	0.70	54	0.82	56	0.84	65	0.98
32 - 45	10 - 13	10	35	0.53	42	0.63	44	0.66	52	0.78	53	0.79	63	0.94
46 -	14-adult	15	# #	# # #	44	0.65	# #	# # #	54	0.82	# #	# # #	65	0.98

This proposed dosing at 6 tablets per day yields, on average, just under 75% of the recommended maximum daily APAP dose, and lightly over (~82%) that fraction of the maximum daily HCB dose. A situation very similar to how the recommended LORTAB adult daily dosing related to the maximum adult dosing for its components. Even at the maximum (for the lowest weight in each range) the daily dose is below the maximum for each of its components.

A recurring theme in many of the more recent pediatric pain management articles was the problem of undertreatment of pain in children. Since the duration of action of the components is around 4 hours or so, limiting dosing to no more often than 6 hours may make the drug less than fully effective in relieving pain for many children. This reviewer feels the dosing should be allowed at least 5 times per day, which would allow dosing q4h while awake; a maximum of 6 times per day would be the preferred maximum.

Youngest Age

No clear reason was given for restricting the age to 3 years and up. The references indirectly indicate that opioid metabolism and pharmacodynamic response are similar to adults at ages above about 6 months. The AHCPR modified its dosing recommendations for opioids only for ages up to 6 months, but did recommend that opioids be given to infants by trained personnel in settings with monitoring capability. Since the TFM APAP recommendations go down to age 2, it would be reasonable for these recommendations to go that low as well. That would provide complete dosing information for "children" (generally considered to be age 2 years and up). Expressing dosing in mL/kg would provide at least some guidance to physicians who need to treat younger patients. Even if the labeling avoids explicit recommendations below a certain age, use in very young patients could be reasonably anticipated given that the product has pediatric labeling. Thus there should be verbiage in the **WARNINGS-Respiratory Depression** section describing the need for caution, initial dose reduction, and monitoring, if use is contemplated in infants up to 6 months.

CONCLUSIONS:

This submission contains neither pediatric PK data nor pediatric clinical study data. Nevertheless, there is enough experience with the components or closely related compounds, so that rational dosing recommendations can be made.

Acetaminophen dosing recommendations are given in the TFM and they agree closely with the weight-base pediatric recommendations in the literature. Codeine dosing recommendations appear well established, and an application of the HCB substitution policy produces HCB doses between the most and least conservative recommendations. The proposed dose also makes sense as an extrapolation of the adult dose. A slight modification of the applicant's proposal is recommended, since it completes the weight ranges. A recommended per-weight dosing should be part of the dosing description, but presentation as a table is helpful as well.

There is no bright line for setting the lowest age for giving dosing recommendations. The TFM APAP dosing goes down to 2 years, and it appears that the response to opioids can be extrapolated down to about 6 months. Since "children" is commonly considered to go down to age 2 years (cf. Pediatric Final Rule), age 2 years would be a reasonable breakpoint. At the same time, there should be a warning about the special risks of use in young infants, since the existence of pediatric labeling could be expected to generate additional usage that extrapolates somewhat beyond the recommendations.

The daily limit of 4 doses seems unnecessarily conservative in view of recent articles pointing out the undertreatment of pain in children. The

references provided in the submission give support for dosing every 4 to 6 hours, and imply less restrictive total daily dosing. It seems that the maximum should be at least five doses, and a cap of six doses per day is reasonable.

Certain sections of the proposed labeling do not precisely conform to the OGD labeling guidance for APAP/codeine solutions and suspensions, although most of the sections should equally apply to this APAP/HCB combination. This reviewer will defer to OGD policy for maintaining consistency regarding those other aspects of the labeling.

RECOMMENDATIONS:

1. In the **Respiratory Depression** section under **WARNINGS**, the following sentences should be added:

Infants [redacted] may have increased sensitivity to the respiratory depressant effects of opioids. If use of LORTAB Elixir in such patients is contemplated, it should be administered cautiously, in substantially reduced initial doses, by personnel experienced in administering opioids to infants, and with intensive monitoring.

2. The **DOSAGE AND ADMINISTRATION** section should be revised to be substantially equivalent to the following:

Dosage should be adjusted according to [redacted] 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 dosage for adults is one tablespoonful every 4 to 6 hours as needed for pain. The total daily dosage for adults should not exceed 6 tablespoonfuls.

The usual dosages for children are given by the table below, and are to be given every 4 to 6 hours as needed for pain. These dosages correspond to an average individual dose of 0.27 mL/kg of LORTAB elixir (providing 0.135 mg/kg of hydrocodone bitartrate and 9 mg/kg of acetaminophen). Dosing should be based on weight whenever possible.

BODY WEIGHT	APPROXIMATE AGE	DOSE Every 4 to 6 Hours	MAXIMUM TOTAL DAILY DOSE (6 Doses per Day)
12 to 15 kg	2 to 3 years	3/4 teaspoonful = 3.75 mL	4 1/2 teaspoonfuls = 22.5 mL
16 to 22 kg	4 to 6 years	1 teaspoonful = 5 mL	6 teaspoonfuls = 30 mL
23 to 31 kg	7 to 9 years	1 1/2 teaspoonfuls = 7.5 mL	9 teaspoonfuls = 45 mL
32 to 45 kg	10 to 13 years	2 teaspoonfuls = 10 mL	12 teaspoonfuls = 60 mL
46 kg and up	14 years to adult	1 Tablespoonful = 15 mL	6 Tablespoonfuls = 90 mL

The total daily dosage for children should not exceed 6 doses per day.

3. The age limit cited in the **Pediatric Use** section should be reduced from __ years to 2 years.

Orig ANDA # 81-051
HFD-550/Div File
HFD-550/CSO/Koerner
HFD-550/MO/JHyde
WAC 6/26/97

6-6-97
John E. Hyde, Ph.D., M.D.

APPEARS THIS WAY
ON ORIGINAL

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

81-051/S-008

ADMINISTRATIVE DOCUMENTS

Out JUN 26 1997

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

HFD-550

REQUEST FOR CONSULTATION

HFD-613

TO (Division/Office)	FROM:
Susan Schmidt - Ophthalmic Drug Products	Div of Labeling - Program Support, Adolphe Legros, 594-0365

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
2-26-96		81-051/S-008	SUPPLEMENT	8-29-95

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Hydrocodone Bitartrate + Acetaminophen Elixir	HIGH	Analgesic	4-15-95

NAME OF FIRM

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☑ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER (Specify below)

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL– BIOPHARMACEUTICS
- ☐ IN–VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS (Attach additional sheets if necessary)

Mikart has supplied data to support their proposed changes to the Pediatric use AND DOSAGE AND ADMINISTRATION SECTION subsection in the professional insert for ANDA 81-051 LORTAB® Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir). They are referencing the final rule published in the Federal Register on December 13, 1994 amending 21 CFR 201.57 to provide for revisions for the "Pediatric Use" subsection of prescription drug labeling.

NC 3-4-96

/S/ HFD 613 594-0365

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one) ☐ MAIL ☑ HAND COURIER

SIGNATURE OF DELIVERER

FORM FDA 2301 (7/92)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

81-051/S-008

CORRESPONDENCE

Mikart

SL-008/AL

NDA SUPP AMEND

April 10, 2001

Mr. William Peter Rickman, Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2, Room 294 (HFD-630)
7500 Standish Place
Rockville, MD 20855

Reference: ANDA #81-051/S-008
LORTAB®ELIXIR (Hydrocodone Bitartrate and Acetaminophen Elixir 7.5 mg/500 mg per 15 mL)

Dear Mr. Rickman:

Reference is made to Mikart's Supplemental New Drug Application, ANDA #81-051/S-008, LORTAB®Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir, 7.5 mg/500 mg per 15 mL), submitted on August 29, 1995 providing for revisions on the labeling to include pediatric use information. This supplement provided for changes in the labeling to include pediatric dosing information. Reference is also made to approvable letters from your office dated July 22, 1997 and September 6, 2000, outlining certain changes to be submitted as an amendment to this supplemental application.

All changes requested in the September 6, 2000 approvable letter have been implemented. Herewith submitted, are side-by-side comparisons of the Insert and the Patient Information Leaflet as well as twelve copies of the Final Printed Labeling with the changes requested. Additionally, Mikart, Inc. is proposing the addition of a carton for the product to accommodate the packaging of a sufficient number of Patient Information Leaflets with each trade size package to allow distribution of a leaflet with each prescription dispensed. Final Printed Labeling is also enclosed for your review.

If you have any questions regarding this application, please contact me at (404) 351-4510.

Sincerely,

Gary Haught for
CERIE B. MCDONALD

Cerie B. McDonald
President

CBM:gmh

CENTER FOR DRUG
APR 1 1 2001
EVALUATION AND RESEARCH

Mikart, Inc. • Pharmaceutical Manufacturer
1750 Chattahoochee Avenue • Atlanta, Georgia 3031
404-351-4510 • Fax 404-350-043

ANDA 81-051/S-008

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

AUG 30 2000

Dear Madam:

This is in reference to your supplemental new drug application dated August 29, 1995, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug application for LORTAB® Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir), 7.5 mg/500 mg per 15 mL.

Reference is also made to our approvable letters dated July 22, 1997 and February 8, 1998, and to your amendments dated October 7, 1997 and March 9, 1998.

The supplemental application provides for revisions in the PRECAUTIONS (Pediatric Use subsection) and the DOSAGE AND ADMINISTRATION sections of the professional insert labeling. In addition, you have proposed a "Patient Information Leaflet" entitled "Prescription Drug Information" in this supplement.

The Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products has completed the review of this supplemental application and has found it approvable. However, before the supplemental application may be approved, it is necessary that you submit final printed labeling as an amendment to this supplemental application with the following changes. Please be advised that this letter supercedes the comments forwarded to you in our approvable letter dated July 22, 1997.

1. INSERT

   a. General

      i. Please note that USAN names are common nouns and should be treated as such in the text of labeling (*i.e.*, lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the package insert.

      ii. As a result of the FDA Modernization Act of 1997 the following revisions are indicated as stated in our letter of February 9, 1998.

A) The statement "[redacted]" is no longer required by the regulations. You may delete this statement throughout your labels and labeling.

B) The "[redacted]" statement is to be replaced by the symbol "Rx Only" throughout your labels and labeling.

b. CONTRAINDICATIONS – Revise to read as follows:

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone, acetaminophen, or any other component of this product.

c. WARNINGS (Respiratory Depression) – Second paragraph:

Infants may have increased sensitivity to the respiratory depressant effects of opioids. (See PRECAUTIONS, Pediatric Use)

d. PRECAUTIONS

i. Information for Patients

A) First paragraph:

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. Such tasks should be avoided while taking this product.

B) See comment (b) under "Patient Information Leaflet" below.

ii. Carcinogenesis, Mutagenesis, Impairment of Fertility – Revise this subsection to read as follows:

No adequate studies have been conducted in animals to determine whether hydrocodone has a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Hydrocodone has not demonstrated mutagenic potential using the Ames Salmonella-Microsomal Activation test, the Basc test on Drosophila germ cells, and the Micronucleus test on mouse bone marrow.

No adequate studies have been conducted in animals to determine whether acetaminophen has a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Acetaminophen has not demonstrated mutagenic potential using the Ames Salmonella-Microsomal Activation test, the Basc test on Drosophila germ cells, and the Micronucleus test on mouse bone marrow.

iii. Pregnancy (*Nonteratogenic Effects*) – Include the following statement as the new third sentence.

...and fever. These signs usually appear during the first few days of life. The intensity...

iv. Labor and Delivery – Revise this subsection to read as follows:

Narcotic analgesics cross the placental barrier. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. Narcotic analgesics should be avoided during labor if delivery of a premature infant is anticipated. If the mother has received narcotic analgesics during labor, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required (see OVERDOSAGE). The effect of hydrocodone, if any, on the later growth, development, and functional maturation of the child is unknown.

e. ADVERSE REACTIONS (listed alphabetically, under each subsection) – Revise this section to read as follows:

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

Cardio-renal: Bradycardia, cardiac arrest, circulatory collapse, renal toxicity, renal tubular necrosis, hypotension.

Central Nervous System/Psychiatric: Anxiety, dizziness, drowsiness, dysphoria, euphoria, fear, general malaise, impairment of mental and physical performance, lethargy, light-headedness, mental clouding, mood changes, psychological dependence, sedation, somnolence progressing to stupor or coma.

Endocrine: Hypoglycemic coma.

Gastrointestinal System: Abdominal pain, constipation, gastric distress, heartburn, hepatic necrosis, hepatitis, occult blood loss, nausea, peptic ulcer, and vomiting.

Genitourinary System: Spasm of vesical sphincters, ureteral spasm, and urinary retention.

Hematologic: Agranulocytosis, hemolytic anemia, iron deficiency anemia,

prolonged bleeding time, thrombocytopenia.

Hypersensitivity: Allergic reactions.

Musculoskeletal: Skeletal muscle flaccidity.

Respiratory Depression: Acute airway obstruction, apnea, dose-related respiratory depression (see OVERDOSAGE), shortness of breath.

Skin: Cold and clammy skin, diaphoresis, pruritus, rash.

f. DRUG ABUSE AND DEPENDENCE (Abuse and Dependence) – Revise the first paragraph to read as follows:

Hydrocodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychological dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, this product should be prescribed and administered with caution appropriate to the use of other oral narcotic medications. However, psychological dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen elixir are used for a short time for the treatment of pain.

g. OVERDOSAGE

i. Signs and Symptoms - Revise this subsection to read as follows:

Toxicity from hydrocodone poisoning includes the opioid triad of loss of consciousness, pinpoint pupils, and respiratory depression (Cheyne-Stokes respiration, cyanosis, decrease in respiratory rate and/or tidal volume). Convulsions may occur.

The toxic dose of acetaminophen for adults is 10 grams. In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams, or fatalities with less than 15 grams.

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

Other signs and symptoms of overdose of this product include bradycardia, cold and clammy skin, extreme somnolence progressing to stupor or coma, hypoglycemic coma, hypotension, renal tubular necrosis, skeletal muscle flaccidity, thrombocytopenia.

In severe overdosage, apnea; circulatory collapse; cardiac arrest; dose-dependent, potentially fatal hepatic necrosis; and death may occur.

ii. Treatment

A) Second paragraph, second sentence – Revise to read:

... Vomiting should be induced with syrup of ipecac,... [delete
]

B) Delete the last sentence '

h. DOSAGE AND ADMINISTRATION

i. Table – Revise to read as follows. Please note that weights in lbs were added to the table.

BODY WEIGHT	APPROXIMATE AGE	DOSE Every 4 to 6 hours	MAXIMUM TOTAL DAILY DOSE (6 doses per day)
12 to 15 kg 27 to 34 lbs.	2 to 3 years	¾ teaspoonful =3.75 mL	4 ½ teaspoonfuls =22.5 mL
16 to 22 kg 35 to 50 lbs.	4 to 6 years	1 teaspoonful =5 mL	6 teaspoonfuls =30 mL
23 to 31 kg 51 to 69 lbs.	7 to 9 years	1 ½ teaspoonfuls =7.5 mL	9 teaspoonfuls =45 mL
32 to 45 kg 70 to 100 lbs.	10 to 13 years	2 teaspoonfuls =10 mL	12 teaspoonfuls =60 mL
46 kg and up 101 lbs. and up	14 years to adult	1 Tablespoonful =15 mL	6 Tablespoonfuls =90 mL

ii. Fifth paragraph:

It is of utmost importance that the dose of Lortab Elixir be administered accurately. A household teaspoon or tablespoon is not an adequate measuring device, especially when one-half or three-fourths of a teaspoonful is to be measured. Given the inexactitude of the household spoon measure and the possibility of using a tablespoon instead of a teaspoon, which could lead to overdosage, it is strongly recommended that care givers obtain and use a calibrated measuring device. Health care providers should recommend a dropper that can measure and deliver the prescribed dose accurately, and instruct care givers to use extreme caution in measuring the dosage.

i. HOW SUPPLIED

Add "[see USP]" to the storage temperature statement.

2. PATIENT INFORMATION LEAFLET (Prescription Drug Information)

a. See general comment (a)(i) under INSERT.

b. We acknowledge that it is not your intention to have a patient information leaflet accompany the drug product when it is shipped to the pharmacy or physician. However, we note that it is in contrary to your position stated in your letter of October 7, 1997, in which you stated that "UCB Pharma, Inc., the distributor of Lortab Elixir, will provide Patient Information Leaflets to physicians and pharmacists to hand out to the patient at the time the prescription is written and at the time of dispensing.". We strongly recommend that you provide this patient information leaflet as a labeling piece for our approval and for distribution to patients rather than as promotional material. Please note that if you elect to submit this as patient information, it must be referenced in the "Information for Patients" subsection of the PRECAUTIONS section of the insert and the entire text of the leaflet must appear at the end of the professional package insert labeling. We direct you to 21 CFR 201.57(f)(2) for further guidance.

c. Summary – Revise to read as follows:

Lortab (pronounced LOR-tab) is used to relieve moderate to moderately severe pain. You should not take Lortab Elixir if you are allergic to hydrocodone or acetaminophen. The most common side effects of Lortab Elixir are abdominal pain, dizziness, drowsiness, light-headedness, nausea, shortness of breath, unusual tiredness, and vomiting. Take this medicine as directed by your doctor. Do not take more of it, do not take it more often, and do not take it for a longer time than your doctor ordered.

d. Uses

Lortab Elixir is an analgesic used to relieve moderate to moderately severe pain. Lortab Elixir is a combination product containing hydrocodone (hye-droe-KO-done) bitartrate and acetaminophen (a-seat-a-MIN-oh-fen). Hydrocodone is a narcotic pain reliever and cough suppressant. Acetaminophen is a non-narcotic pain reliever and fever reducer. A narcotic analgesic and acetaminophen used together may provide better pain relief than either product used alone. If you have any questions, please call your doctor or pharmacist.

e. General Cautions

i. Add the following as the second bullet.

- This product may inhibit your mental or physical abilities required for the performance of potentially hazardous tasks such as driving a

car or operating machinery. Such tasks should be avoided while you are taking this product.

ii. Add period to read "are pregnant." and "are nursing.".

f. Proper Use – Add the following as the new second and third sentences:

... doctor. Do not share it with anyone else. This medicine can cause drug dependence and has the potential for abuse. Do not take ...

g. Dosing

i. Table - Revise the weights in lbs in the first column as follows:

BODY WEIGHT	APPROXIMATE AGE	DOSE Every 4 to 6 hours	MAXIMUM TOTAL DAILY DOSE (6 doses per day)
12 to 15 kg 27 to 34 lbs.	2 to 3 years	¾ teaspoonful =3.75 mL	4 ½ teaspoonfuls =22.5 mL
16 to 22 kg 35 to 50 lbs.	4 to 6 years	1 teaspoonful =5 mL	6 teaspoonfuls =30 mL
23 to 31 kg 51 to 69 lbs.	7 to 9 years	1 ½ teaspoonfuls =7.5 mL	9 teaspoonfuls =45 mL
32 to 45 kg 70 to 100 lbs.	10 to 13 years	2 teaspoonfuls =10 mL	12 teaspoonfuls =60 mL
46 kg and up 101 lbs. and up	14 years to adult	1 Tablespoonful =15 mL	6 Tablespoonfuls =90 mL

ii. Second paragraph:

It is very important that Lortab Elixir be dosed accurately. A household teaspoon or tablespoon is not an accurate measuring device, especially when one-half or three-fourths of a teaspoonful is to be measured.

iii. Last paragraph, First sentence:

Since a household teaspoon is not accurate ... [add "household"]

h. Missed Dose – Revise to read as follows:

- To avoid a possible overdose, it is important that you do not take more than a single dosage at one time, or that you do not take doses at intervals less than 4 hours apart.
- If you miss taking a dose of Lortab Elixir, take it as soon as you remember. However, make sure to wait at least 4 hours before taking your next dose.
- If you missed taking a dose, and it is almost time for your next dose, skip the missed dose and take your medicine as scheduled.

- Do not take double the prescribed dose.

i. Possible Side Effects – Revise to read as follows:

Side effects you may experience include abdominal pain, constipation, difficulty urinating, dizziness, drowsiness, fear, fuzzy thinking, general feeling of discomfort or illness, light-headedness, mood changes, nausea, nervousness, rash, shortness of breath, slower reactions, unusual tiredness, and vomiting.

Call your doctor if these effects continue or are bothersome.

Side effects not listed above may sometimes occur. If you notice any other effects, check with your doctor.

j. Penultimate paragraph immediately following "Storage" subsection – Revise to read as follows:

Even a single overdose of this medicine may be a life-threatening situation. If you suspect that you or someone else may have taken more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately. This medicine was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

3. DOSING CARD and PharmAlert

We acknowledge that you will submit these promotional materials to our Division of Drug Marketing, Advertising, and Communications (DDMAC) at the time of initial use, as required in 21 CFR 314.81(b)(3).

4. MEASURING SPOON

We acknowledge that the measuring spoons, which is to provided to the physician in a separate box, will be submitted to DDMAC at the time of their initial dissemination. While it is helpful if calibrated measuring spoons are provided with prescriptions of this product, either by the physician or pharmacist, there is not sufficient justification at this time to require it and it is unlikely that all patients would receive them unless you change the distribution size and include spoons as part of the packaging.

Prepare and submit 12 copies of final printed package insert labeling and the Patient Information Leaflet (if you choose – see comment 2b) as an amendment to this supplement.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison with your last submission with all differences annotated and explained.

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,

/S/ 8/30/00

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

APPEARS THIS WAY
ON ORIGINAL

Mikart

March 9, 1998

SUPPL AMENDEMENT
SL-008 AL

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
AMENDMENT TO SUPPLEMENTAL APPLICATION S-008

Dear Mr. Sporn:

Mikart has received your letter dated February 9, 1998. In conjunction with the distributor of this product, UCB Pharma, we would like to respond now to the issues raised. We have used the outline of your letter to organize our response.

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

Cerie B. McDonald
Executive Vice-President

RECEIVED
MAR 13 1998
GENERIC DRUGS

CBM/sw

Enc.

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

ANDA 81-051/S-008

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

FEB 9 1998

Dear Madam:

This is in reference to your supplemental new drug application dated August 29, 1995, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug application for LORTAB® Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir), 7.5 mg/500 mg per 15 mL.

Reference is also made to our approvable letter dated July 22, 1997, and to your amendment dated October 7, 1997.

The supplemental application provides for revisions in the PRECAUTIONS (Pediatric Use subsection) and the DOSAGE AND ADMINISTRATION sections of the professional insert labeling.

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

1. INSERT

   We note you have submitted a draft patient information leaflet. If it is your intention to have a patient information leaflet accompany the drug product when it is dispensed this must be referenced in the Information for Patients subsection of the PRECAUTIONS section of the insert and also the entire text of the leaflet must appear at the very end of the professional package insert labeling. We direct you to 21 CFR 201.57(f)(2) for further guidance.

2. PATIENT INFORMATION LEAFLET

   The information contained in this leaflet is a new presentation for the labeling of this drug product and as such is not part of the approved labeling. This

labeling, along with your proposed package insert labeling as amended, will be consulted to the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products for their review and comment. We will notify you of their comments when they are available. We will not take further action on this supplement until we receive their response.

3. DOSING CARD and PharmAlert

We consider these labeling pieces advertising, educational, or promotional in nature and do not review them for approval.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 and a copy of the product's current professional labeling at the time of their initial use.

4. MEASURING SPOON

a. Your measuring spoon sample was damaged in the U.S. mail.

b. How will the spoon accompany the product? We note you have indicated that you will provide physicians with these measuring spoons. Is it your intent to supply spoons with the pint bottle or with the physician samples?

5. LABELS AND LABELING

As a result of the FDA Modernization Act of 1997 the following revisions must be made:

a. The statement [redacted]." is no longer required by the regulations. Please delete wherever it appears throughout your labels and labeling.

b. The [redacted]' statement is to be replaced by the symbol "℞" wherever it appears throughout your labels and labeling.

Revised labels and labeling to be in accord with the FDA Modernization Act of 1997 may be submitted in an annual report, provided that the changes are described in full.

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,

/S/ for 2/9/98

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

cc: ANDA 81-051/S-008
Division File
HFD-600/Reading File
HFD-610/JPhillips
Field Copy
aev/2/5/98|X:\NEW\FIRMSAM\MIKART\LTRS&REV\81051S08.CO2
APPROVABLE LETTER - CONSULT

Endorsements:
HFD-613/AVezza /S/ 2/9/98
HFD-613/CHoppes

APPEARS THIS WAY
ON ORIGINAL

Mikart

October 7, 1997

Dr. Jerry Phillips, Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2, Room 204 (HFD-630)
7500 Standish Place
Rockville, Maryland 20855

NDA SUPP AMEND
SL-008/AL

RE: ANDA#81-051/S-008
Lortab® Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir)

Dear Sir:

Reference is made to Mikart, Inc.'s Supplemental New Drug Application #81-051/S-008 for Lortab® Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir), submitted August 29,1995. Reference is also made to an approvable letter from your office dated July 22, 1997, outlining certain changes to be submitted as an amendment to this supplemental application.

Herewith submitted, in duplicate, is Mikart,Inc.'s response and twelve copies of the Final Printed Labeling with the changes requested.

If you have any questions regarding this application, please contact the undersigned at (404) 351-4510 or by facsimile at (404) 350-0432

Sincerely,

Cerie B. McDonald
Executive Vice-President

RECEIVED
OCT 15 1997
GENERIC DRUGS

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

ANDA 81-051/S-008

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

JUL 22 1997

Dear Madam:

This is in reference to your supplemental new drug application dated August 29, 1995, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug application for LORTAB® Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir).

The supplemental application provides for revisions in the PRECAUTIONS (Pediatric Use subsection) and the DOSAGE AND ADMINISTRATION sections of the professional insert labeling.

The Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products has completed the review of this supplemental application and has found it approvable. However, before the supplemental application may be approved, it is necessary that you submit final printed labeling as an amendment to this supplemental application with the following changes:

1. WARNINGS, Respiratory Depression - Add the following:

   Infants ——————————— may have increased sensitivity to the respiratory depressant effects of opioids. If use of LORTAB® Elixir in such patients is contemplated, it should be administered cautiously, in substantially reduced initial doses, by personnel experienced in administering opioids to infants, and with intensive monitoring.

2. DOSAGE AND ADMINISTRATION - Revise this section as follows:

   Dosage should be adjusted according to the 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 dosage for adults is one tablespoonful every 4 to 6 hours as needed for pain. The total daily dosage for adults should not exceed 6 tablespoonfuls.

The usual dosages for children are given by the table below, and are to be given every 4 to 6 hours as needed for pain. These dosages correspond to an average individual dose of 0.27 mL/kg of LORTAB elixir (providing 0.135 mg/kg of hydrocodone bitartrate and 9 mg/kg of acetaminophen). Dosing should be based on weight whenever possible.

BODY WEIGHT	APPROXIMATE AGE	DOSE Every 4 to 6 Hours	MAXIMUM TOTAL DAILY DOSE (6 Doses per Day)
12 to 15 kg	2 to 3 years	3/4 teaspoonful = 3.75 mL	4½ teaspoonfuls = 22.5 mL
16 to 22 kg	4 to 6 years	1 teaspoonful = 5 mL	6 teaspoonfuls = 30 mL
23 to 31 kg	7 to 9 years	1 ½ teaspoonfuls = 7.5 mL	9 teaspoonfuls = 45 mL
32 to 45 kg	10 to 13 years	2 teaspoonfuls = 10 mL	12 teaspoonfuls = 60 mL
46 kg and up	14 years to adult	1 Tablespoonful = 15 mL	6 Tablespoonfuls = 90 mL

The total daily dosage for children should not exceed 6 doses per day.

3. PRECAUTIONS, Pediatric Use - Decrease the age limit cited from ~~~~ to 2 years.

4. NOTE: If you are reluctant to accept a maximum pediatric dosing of 6 doses per day,

5.

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,

/S/ for 7/22/97

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

cc: ANDA 81-051/S-008
Division File
HFD-600/Reading File
HFD-610/JPhillips
njg/7/17/97/X:\NEW\FIRMSAM\MIKART\LTRS&REV\81051S08.AEL
APPROVABLE LETTER - SINGLE SUPPLEMENT

Endorsement:
HFD-613/AVezza /S/ 7/17/97
HFD-613/JGrace

ANDA 81-051/S-008

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

FEB 29 1996

Dear Madam:

This is in reference to your supplemental new drug application dated August 29, 1995, submitted pursuant to 21 CFR 201.57 regarding your abbreviated new drug application for LORTAB® Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir).

The supplemental application provides for revisions in the PRECAUTIONS (Pediatric Use subsection) and the DOSAGE AND ADMINISTRATION sections of the professional insert labeling.

We have reviewed the labeling submitted and have the following comments:

> The proposed insert labeling and supportive data have been forwarded to the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products (HFD-550) for their review and comment. We will not take further action on this supplement until we receive their response. We will inform you of their comments when they are available.

The material submitted is being retained in our files.

Sincerely Yours,

/S/ 2/28/96

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

cc: ANDA 81-051/S-008 /S/ 2/28/96
Dup/Division File
HFD-613/AVezza/JGrace (no cc:)
HFD-600/RF /S/ - 2/28/96
FIELD COPY
aev 2/26/96/ x:\...\mikart\ltrs&rev\81051S08.CON
Letter Out - Consult

Orig Approvable letter drafted 7/16/97 A Vezza

BIOAVAILABILITY

MIKART, INC.

PHARMACEUTICAL MANUFACTURERS

letter out to firm - submission sent out for consult A. Vezza 2/29/96

NDA NO. SLOO8

NDA SUPPL FOR Label rev

August 29, 1995

Office for Generic Drugs
Center of Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II, HFD 660
7500 Standish Place, Room 150
Rockville, Maryland 20857

RECEIVED

SEP 0 1 1995

GENERIC DRUGS

Re: ANDA # 81-051 LORTAB ELIXIR (Hydrocodone Bitartrate and Acetaminophen Elixir, 7.5/500 mg/per 15 mL)

Gentlemen:

Reference is made to MIKART, INC. ANDA # 81-051 for LORTAB ELIX-IR(Hydrocodone Bitartrate and Acetaminophen Elixir, 7.5\500 mg per 15 ml), indicated for the relief of moderate to moderately severe pain. LORTAB ELIXIR is manufactured by MIKART and distributed by WHITBY PHARMACEUTICALS, INC. Reference is also made to final rule published in the Federal Register on December 13, 1994 amending 21 CFR 201.57 to provide for revisions for the "Pediatric Use" subsection of prescription drug labeling.

Pursuant to 201.57(f)(d), MIKART herewith requests a waiver from conducting clinical trials in pediatric patients, because sufficient historical and scientific data already exists to support a pediatric labeling recommendation for LORTAB ELIXIR. Under §201.57(f)(d), the need for such studies may be waived where other data can satisfy the requirements. §201.57(f)(9)(iv) describes more fully how the agency would determine that data from adequate and well-controlled studies with adult subjects could provide substantial evidence of effectiveness in children. This subsection specifically states, "*FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. The additional information supporting pediatric use must ordinarily include data on the pharmacokinetics of the drug in the pediatric population for determination of appropriate dosage.*

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

Other information, such as data from pharmacodynamic studies of the drug in the pediatric population, data from other studies supporting the safety or effectiveness of the drug in pediatric patients, pertinent premarketing or postmarket in studies or experience, may be necessary to show that the drug can be used safely and effectively in pediatric patients....."

Herewith submitted is information to support this labeling change, which provides evidence that the management of pain and the effects of analgesics are sufficiently similar in children and adults to permit extrapolation. Combinations of hydrocodone bitartrate with acetaminophen have been shown in many controlled clinical trials to be safe and effective in the treatment of moderate to moderately severe pain in adult patients and are marketed by numerous pharmaceutical manufacturers. There is a general consensus of expert opinion, reflected in the pediatric literature, that the analgesic effect of acetaminophen and opioids(including hydrocodone) is sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. There is likewise a general consensus of expert opinion, reflected in the pediatric literature, excluding neonates and young infants, that adverse effects of opioids(including hydrocodone) are sufficiently similar in the pediatric and adult populations to permit extrapolation from adult experience to pediatric patients.

Other supporting information includes postmarketing experience with a similar acetaminophen and hydrocodone bitartrate combination product, LORTAB LIQUID (Hydrocodone*Bitartrate and Acetaminophen Elixir). (Warning: May be habit forming) marketed by RUSS PHARMACEUTICALS, INC. from January 1984 until April 1993. The formulation had a ratio of hydrocodone bitartrate and acetaminophen of 2.5/120 mg per 5 ml and the prescribing information for pediatric use was as follows:

"...1 tsp for children 3-6 years, 3 or 4 times daily; 2 tsp for children 7-12 years, 3-4 times daily; and for children under 3 years: safe dose has not yet been established."

Historical data from LORTAB LIQUID or LORTAB ELIXIR revealed no adverse events reports in the pediatric population attributed to either of these products over almost 10 years. LORTAB LIQUID was marketed about seven years with pediatric labeling and, to the best of our knowledge, no adverse event reports from pediatric use were reported either to the manufacturer or the distributor.

Furthermore, acetaminophen, as a single entity and as a constituent of combination products including a combination with codeine, is currently the most extensively used pediatric analgesic in the United States. Hydrocodone, the other constituent of LORTAB ELIXIR, is a close congener of codeine and is 6 times as potent. It is labeled for pediatric use as an antitussive in other formulations, and it is recognized in compendia and in the medical .pa
literature as a useful analgesic for the treatment of pain in children.

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

Combinations of concomitant administration of opioid analgesics with acetaminophen or nonsteroidal anti-inflammatory drugs (peripheral analgesics) are used primarily when peripheral analgesics alone are inadequate for pain management. The rationale for such combined therapy is the enhancement of analgesia by combining two analgesics with different mechanisms of action. Combinations of hydrocodone bitartrate with acetaminophen have been shown in many controlled clinical trials to be safe and effective in the treatment of moderate to moderately severe pain in adult patients and are marketed by numerous pharmaceutical manufacturers.

Like adults patients, pediatric patients experience pain due to trauma, surgical procedures and medical conditions. As reflected in the literature, there in a growing awareness and concern in the pediatric community that children with pain do not receive optimal analgesic therapy.

Whitby Pharmaceutical, Inc., the distributor for Lortab Elixir, receives approximately 3 calls per week from physicians and pharmacists requesting information on the appropriate pediatric dosing information for LORTAB ELIXIR.

Herewith submitted is a supplement with revised labeling providing for the addition of dosing recommendations for pediatric patients, ages 3-12 years. Labeling of the above mentioned product has been reviewed and the revisions are in accordance with 201.57(f)(9)(iv) is supportable.

We trust this information is sufficient for the agency to determine that LORTAB ELIXIR can be safely and effectively used in pediatric patients based on our recommended doses. Should you require additional information, please feel free to contact me.

Sincerely,

Cerie B. McDonald
Executive Vice-President

CBM/ec

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