CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

81-051/S-001

Trade Name:	Lortab Elixir
Generic Name:	Hydrocodone Bitartrate and Acetaminophen Elixir; 7.5mg/500mg per 15 mL
Sponsor:	Mikart, Inc.
Approval Date:	January 29, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

81-051/S-001

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

81-051/S-001

APPROVAL LETTER

ANDA 81-051/S-001

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

JAN 2 9 1997

Dear Madam:

This is in reference to your supplemental new drug application dated August 3, 1994, 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 your amendment dated November 4, 1996.

The supplemental application provides for revised container labels (30 mL and 473 mL) and revised package insert labeling reflecting major changes throughout the text of the insert.

We have completed the review of this supplemental application and it is approved.

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

The material submitted is being retained in our files.

Sincerely yours,

/S/ for 1/29/97

Jerry Phillips
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-001

FINAL PRINTED LABELING

LORTAB® Elixir

HYDROCODONE* BITARTRATE AND ACETAMINOPHEN ELIXIR

7.5 mg/500 mg per 15 mL

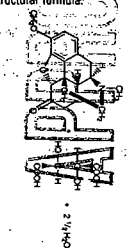
***Warning: May be habit forming.**

JAN 29 1997

DESCRIPTION:

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

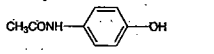
Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:



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

M.W. 494.50

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



$C_8H_9NO_2$ M.W. 151.17

Lortab Elixir contains:

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

In addition the liquid contains the following inactive ingredients: citric acid anhydrous, ethyl maltol, glycerin, 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-hydroxy-metabolites.

See OVERDOSAGE for toxicity information.

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

See OVERDOSAGE for toxicity information.

INDICATIONS AND USAGE:

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

CONTRAINDICATIONS:

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

WARNINGS:

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

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

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

PRECAUTIONS:

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

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

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

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

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

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

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

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

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

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

Pregnancy:

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

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all narcotics, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

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

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

ADVERSE REACTIONS:

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

Other adverse reactions include:

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

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

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

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

Dermatological: Skin rash, pruritis

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

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

DRUG ABUSE AND DEPENDENCE:

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

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

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

OVERDOSAGE:

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

Signs and Symptoms:

Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

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

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

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

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

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

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

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

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

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

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION:

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

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

HOW SUPPLIED:

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

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

CAUTION: Federal law prohibits dispensing without prescription.

A Schedule CIII Narcotic.

UCB Pharma

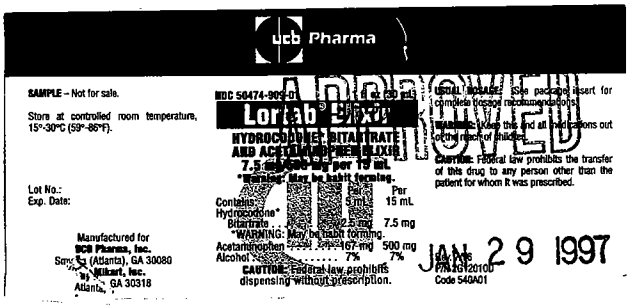
Manufactured For:
UCB PHARMA, INC.
Atlanta, GA 30080

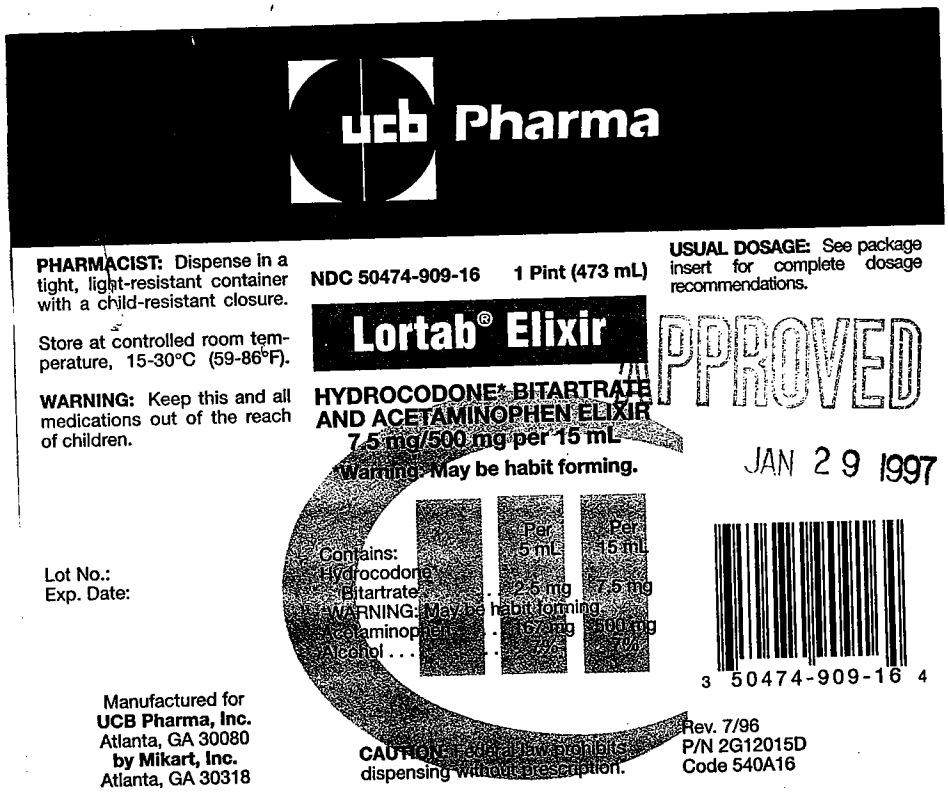
Manufactured By:
MIKART, INC.
Atlanta, GA 30318

Revised 2/96
Code 540A00
P/N 2H12020E

000 8

NOV 04 1996


ucb Pharma
SAMPLE – Not for sale.
Store at controlled room temperature, 15°-30°C (59°-86°F).
Lot No.:
Exp. Date:
Manufactured for
UCB Pharma, Inc.
Atlanta, GA 30080
by Mikart, Inc.
Atlanta, GA 30318
NDC 50474-909-01
Lortab® Elixir
HYDROCODONE* BITARTRATE AND ACETAMINOPHEN ELIXIR
7.5 mg/500 mg per 15 mL
*Warning: May be habit forming.
Per 15 mL
Contains:
Hydrocodone* Bitartrate 7.5 mg
*WARNING: May be habit forming.
Acetaminophen 500 mg
Alcohol 7%
CAUTION: Federal law prohibits dispensing without prescription.
USUAL DOSAGE: See package insert for complete dosage recommendations.
WARNING: Keep this and all medications out of the reach of children.
CAUTION: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.
APPROVED
JAN 29 1997
Rev. 7/96
P/N 2G12010
Code 540A01


ucb Pharma
PHARMACIST: Dispense in a tight, light-resistant container with a child-resistant closure.
Store at controlled room temperature, 15-30°C (59-86°F).
WARNING: Keep this and all medications out of the reach of children.
NDC 50474-909-16 1 Pint (473 mL)
Lortab® Elixir
HYDROCODONE* BITARTRATE AND ACETAMINOPHEN ELIXIR
7.5 mg/500 mg per 15 mL
*Warning: May be habit forming.
USUAL DOSAGE: See package insert for complete dosage recommendations.
APPROVED
JAN 29 1997
Per 5 mL
Per 15 mL
Contains:
Hydrocodone* Bitartrate 2.5 mg 7.5 mg
*WARNING: May be habit forming.
Acetaminophen 167 mg 500 mg
Alcohol 7% 7%
Lot No.:
Exp. Date:
3 50474-909-16 4
Manufactured for
UCB Pharma, Inc.
Atlanta, GA 30080
by Mikart, Inc.
Atlanta, GA 30318
CAUTION: Federal law prohibits dispensing without prescription.
Rev. 7/96
P/N 2G12015D
Code 540A16

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

81-051/S-001

CORRESPONDENCE

MIKART, INC.
PHARMACEUTICAL MANUFACTURERS

NDA SUPPL AMENDMENT
5L004 AL

November 4, 1996

FPL sent fax to 11/8/96

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-001

Dear Mr. Sporn:

Mikart has received your letter of June 8, 1995 regarding the above supplemental application. We have made the requested revisions and are now submitting 12 copies of final printed container and insert labeling, three of which are mounted. The nine other copies are included separately. Please note that additional minor editorial changes have been made as directed in the Office's letters for other similar applications, in order to provide uniformity for the Lortab® product line.

With the submission of this information, there are no longer any outstanding deficiencies, and we respectfully request that the supplemental application be approved. Thank you for your cooperation in the review of this material.

Sincerely,

Cerie B. McDonald
Executive Vice-President

CBM/sw

Enc.

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

ANDA 81-051/S-001

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

JUN 8 1995

Dear Madam:

Reference is made to your supplemental new drug application dated August 3, 1994, submitted pursuant to Section 314.70 of the Regulations, regarding your abbreviated new drug application for Lortab® Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir) 7.5 mg/500 mg per 15 mL.

The supplemental application provides for revised container labels (30 mL and 473 mL) and revised package insert labeling reflecting major changes throughout the text of the insert.

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 you revise the following:

1. CONTAINER LABELS

   a. Delete the statement "[redacted]" that appears directly under the "USUAL DOSAGE" statement. This is duplicate information that is stated in the "USUAL DOSAGE" statement.

   b. Increase the print size on the 30 mL container label. It is blurred and very difficult to read.

2. INSERT

   Please revise the insert labeling as directed in the approval letter for Supplement-006.

Please prepare and submit final printed labels and labeling as an amendment to this approved application.

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

Sincerely,

/S/ for 6-8-95

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

cc: ANDA 81-051/S-001
HFD-613/AVezza/CZimmermann/JPhillips (no cc:)
Dup/Division File /S/ 6/6/95
HFD-600/RF /S/ 6/6/95
Field Copy
6/5/95 81051.S01
Approvable

/S/ 6/8/95

APPEARS THIS WAY
ON ORIGINAL

MIKART, INC.
PHARMACEUTICAL MANUFACTURERS

NDA NO. _____ REF NO. SL-001
NDA SUPPL FOR Labeling Revision
DRAFT

August 3, 1994

approvable letter
dated 3/10/95
PI satisfactory & changes
made 4/94 Labeling
Guidance
/S/

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

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

Dear Mr. Sporn:

Mikart has received the Labeling Guidance, revised 12/93, concerning the above application. As per your request dated Febraury 24, 1994, the labeling has been revised in accordance with this guidance. Four copies of draft labeling are attached.

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

Sincerely,

Cerie B. McDonald
Executive Vice-President

CBM/js

Enc.

RECEIVED
AUG 0 8 1994
GENERIC DRUGS

ORIGINAL

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