CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-418

APPROVAL LETTER

ANDA 40-418

JUN 27 2001

Mallinckrodt Inc.
Attention: Marianne Robb
675 McDonnell Blvd.
P.O. Box 5840
St. Louis, MO 63134-0840

Dear Madam:

This is in reference to your abbreviated new drug application dated June 30, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Hydrocodone Bitartrate and Acetaminophen Oral Solution, 7.5 mg/500 mg, respectively, per 15 mL.

Reference is also made to your amendments dated March 26 and May 14, 2001.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Hydrocodone Bitartrate and Acetaminophen Oral Solution, 7.5 mg/500 mg, respectively, per 15 mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Lortab® Elixir, 7.5 mg/500 mg, respectively, per 15 mL of Mikart Inc.).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Robert Lee Test/ for 6/27/2001

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-418

APPROVED DRAFT LABELING

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ORAL SOLUTION 7.5 mg/500 mg per 15 mL

Rx only

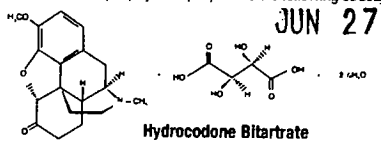
C III

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).

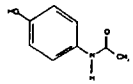
Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is: 4,5α-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:



Hydrocodone Bitartrate

$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$ MW=494.490

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:



$C_8H_9NO_2$ **Acetaminophen** MW = 151.16

HYDROCODONE BITARTRATE AND ACETAMINOPHEN oral solution contains:

	Per 5 mL	Per 15 mL
Hydrocodone Bitartrate, USP	2.5 mg	7.5 mg
Acetaminophen, USP	167 mg	500 mg

In addition, the liquid contains the following inactive ingredients: Citric Acid Anhydrous USP, Glycerin USP, Methylparaben NF, Polyethylene Glycol NF, Propylene Glycol USP, Propylparaben NF, Purified Water USP, Saccharin Sodium USP, Sodium Citrate Dihydrate USP, Sorbitol Solution NF, Sucrose NF, with D&C Yellow #10 as coloring and natural 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

Hydrocodone Bitartrate and Acetaminophen Oral Solution 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 Hydrocodone Bitartrate and Acetaminophen Oral Solution 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, Hydrocodone Bitartrate and Acetaminophen Oral Solution should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when Hydrocodone Bitartrate and Acetaminophen Oral Solution 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.

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 Oral Solution 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.

Pregnancy:

Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Hydrocodone Bitartrate and Acetaminophen Oral Solution 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 fews 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,

Patient Information Leaflet

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ORAL SOLUTION 7.5 mg/500 mg per 15 mL

Rx only

C III

Summary

Hydrocodone Bitartrate and Acetaminophen Oral Solution is used to relieve moderate to moderately severe pain. You should not take Hydrocodone Bitartrate and Acetaminophen Oral Solution if you are allergic to hydrocodone or acetaminophen. The most common side effects of Hydrocodone Bitartrate and Acetaminophen Oral Solution 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

Hydrocodone Bitartrate and Acetaminophen Oral Solution is an analgesic used to relieve moderate to moderately severe pain. Hydrocodone Bitartrate and Acetaminophen Oral Solution 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 Hydrocodone Bitartrate and Acetaminophen Oral Solution.
- 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	¾ teaspoonful = 3.75 mL	4½ 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	1½ 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 Hydrocodone Bitartrate and Acetaminophen Oral Solution 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 you doctor or pharmacist for help to find a dropper than 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 Hydrocodone Bitartrate and Acetaminophen Oral Solution, 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 Hydrocodone Bitartrate and Acetaminophen Oral Solution. If you have any questions or concerns, or want more information about Hydrocodone Bitartrate and Acetaminophen Oral Solution, contact your doctor or pharmacist. Your pharmacist also has a longer leaflet about Hydrocodone Bitartrate and Acetaminophen Oral Solution that is written for health professionals that you can ask to read.

Prepared by Mallinckrodt Inc.

tyco / Healthcare
Mallinckrodt
Rev. 050501

FPO
03751200
HYDROCODONE BITARTRATE AND ACETAMINOPHEN ORAL SOLUTION
7.5 mg/500 mg per 15 mL
Rx only

SPECIMEN

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 Hydrocodone Bitartrate and Acetaminophen Oral Solution in the pediatric population is supported by the evidence from adequate and well controlled studies of hydrcodone 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: Hydrocodone Bitartrate and Acetaminophen Oral Solution 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 oral solution 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:

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 (1g/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 four to six 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 Hydrocodone Bitartrate and Acetaminophen Oral Solution (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	4½ 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	1½ 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 Hydrocodone Bitartrate and Acetaminophen Oral Solution 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 than can measure and deliver the prescribed dose accurately, and instruct care givers to use extreme caution in measuring the dosage.

HOW SUPPLIED

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ORAL SOLUTION is a yellow-colored tropical fruit punch flavored liquid containing hydrocodone bitartrate 7.5 mg and acetaminophen 500 mg per 15 mL.

Bottles of 1 pint (473 mL)..... NDC No. 0406-0375-16

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

A Schedule CIII Narcotic.

Mallinckrodt Inc.
St. Louis, Missouri 63134, U.S.A.

SPECIMEN

tyco / Healthcare
Mallinckrodt
Rev. 050501

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-418

Bioequivalence Review(s)

Acetaminophen/Hydrocodone Bitartrate
Oral Solution, 500 mg/7.5 mg per 15 mL
ANDA # 40-418
Reviewer: Moheb H. Makary
W. 40418W.900

Mallinckrodt Inc.
St. Louis, MO
Submission Date:
September 15, 2000

Review of a Waiver Request

I. Objective:

The firm is requesting a waiver of *in vivo* bioequivalence study requirements for its drug product, Acetaminophen and Hydrocodone Oral Solution, 500 mg/7.5 mg per 15 mL. The reference listed drug is Lortab^{R} Elixir, 500 mg/7.5 mg per 15 mL (Mikart, NDA 81051, approved 8/28/92).

The drug product and the RLD are both opiate-containing analgesics indicated for the relief of moderate to moderately severe pain.

II. Formulations: (Not To Be Released Under FOI)

ACETAMINOPHEN & HYDROCODONE, Elixir (500 mg/7.5 mg) PER 15 mL		
INGREDIENT	TEST DRUG (Mallinckrodt)	LORTAB^{R} (Mikart)
Acetaminophen	500 mg	500 mg
Hydrocodone		
Alcohol		
Glycerin,		
Sorbitol Solution		
Propylene Glycol		
Natural Orange Flavoring		
Natural Pineapple Flavoring		
Polyethylene Glycol		
Sucrose,		
Ethyl Maltol		
Sodium Citrate Dihydrate USP		
FD&C Yellow #6		
FD&C Yellow #10		
Saccharin Sodium		
Methylparaben		
Propylparaben,		
Citric Acid,		

Glucose	---	
Tropical Fruit Flavor	---	
Purified Water		

Comments

1. The firm has met the criteria for waiver of the *in vivo* bioequivalence study requirements for its test product per 21 CFR 320.22 (b)(3), in that the product:

(i) Is an elixer (solubilized) dosage form.

(ii) Contains an active drug ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full new drug application.

(iii) Contains no inactive ingredient or other change in formulation from the listed reference drug product that may significantly affect absorption of the active drug ingredient.

2. The proposed test product contains Natural Orange Flavor and Natural Pineapple Flavor . These flavors are not included in the FDA Inactive Ingredient Guide (1996).

3. The levels of the Natural Orange and the Natural Pineapple Flavors in the final drug product are respectively.

4. In response to OGD's request, the manufacturer and supplier of the above flavors submitted the composition of the Natural Orange and the Natural Pineapple Flavors on June 19, 2001. Each component level is below in the final drug product. FEMA number was provided for each component. Please see attachment.

III. Recommendation:

The Division of Bioequivalence agrees that the information submitted by Mallinckrodt, Inc., demonstrates that Acetaminophen/Hydrocodone Bitartrate Oral Solution, 500 mg/7.5 mg per 15 mL, falls under 21 CFR section 320.22 (b) (3) of the Bioavailability/Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study for the test product is granted. From the Bioequivalence point of view, the Division of Bioequivalence deems the test solution formulation to be bioequivalent to

Lortab[R] Elixir (Acetaminophen/Hydrocodone Bitartrate), 500 mg/7.5 mg per 15 mL, manufactured by

The firm should be informed of the above recommendation.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

BDAVIT 4/13/01

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT Barbara M. Davit Date: 6/20/01

Concur: Dale P. Conner Date: 6/20/01
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-418 APPLICANT: Mallinckrodt, Inc.

DRUG PRODUCT: Acetaminophen/Hydrocodone Bitartrate Oral Solution, 500 mg/7.5 mg per 15 mL

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-418 APPLICANT: Mallinckrodt, Inc.

DRUG PRODUCT: Acetaminophen/Hydrocodone Bitartrate Oral Solution, 500 mg/7.5 mg per 15 mL

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-418

ADMINISTRATIVE DOCUMENTS

DIVISION REVIEW SUMMARY

ANDA: 40-418
DRUG PRODUCT: Hydrocodone Bitartrate and Acetaminophen
DOSAGE FORM: Oral Solution
STRENGTH: 500mg/15mL; 7.5mg/15mL

FIRM: Mallinckrodt Inc.
Attention: Marianne Robb
P.O. Box 5840
675 McDonnell Blvd.
St Louis, MO 63134-0840

cGMP STATUS/EIR UPDATE STATUS
Establishment inspection was found acceptable on 30-OCT-2000. Mallinckrodt cGMP certification letter is provided on pages 286-287.

BIO STUDY
Bio waiver was granted on 20-JUN-2001.

VALIDATION
Analytical methods were validated by the Northeast Regional Laboratory on ---Pending---.

DRUG SUBSTANCE TESTS and SPECIFICATIONS

Tests and Specifications for Hydrocodone Bitartrate USP (Lot No. 1582A49643) (pages 063-064):

Tests	Specifications

Page(s) 4

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Test	Specification

LABELING
Labeling Branch approval was granted.

STERILIZATION VALIDATION
N/A

SIZE OF BIO/STABILITY BATCHES (FIRM'S SOURCE OF NDS OK?)
Manufacturing Yield: (page 371)

Packaging Yield: bottles (98.4%)
(pages 058 and 468)

Hydrocodone Bitartrate USP:
The firm references DMF owned by Mallinckrodt (LOA page 065). The DMF was found satisfactory by GXS on 11-AUG-2000. cGMP Certification is provided on page 066.

Acetaminophen USP:
The firm references DMF owned by Mallinckrodt (LOA page 107). The DMF was found satisfactory by GXS on 03-MAY-2000.

PROPOSED PRODUCTION BATCH

The scale of the Demonstration Batch supports the proposed Production Batch scale.

RECOMMENDATION:
Recommend approval of generic drug product Hydrocodone Bitartrate and Acetaminophen Oral Solution, 500mg/15mL and 7.5mg/15mL

SIGNATURES: DATE:

Dominick Roselle D Roselle 5/21/01

Glen Smith
Team Leader

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-418

CORRESPONDENCE

MALLINCKRODT

Mallinckrodt Inc. 675 McDonnell Boulevard PO Box 5840 St. Louis MO 63134 Phone: 314.654.2000 www.mallinckrodt.com

AMENDMENT TO A PENDING APPLICATION
LABELING AMENDMENT

May 14, 2001

N/AF

ORIG AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: ANDA 40-418: Hydrocodone Bitartrate and Acetaminophen Oral Solution (7.5 mg/500 mg per 15 mL)

Dear Madame or Sir:

Mallinckrodt hereby submits the following Labeling amendment to the above referenced ANDA in response to a May 2, 2001 facsimile deficiency. This amendment to a pending application consists of one volume. An archival copy is being filed in a blue folder and a technical copy is being filed in a red folder.

For more detailed information on the organization of this application, please refer to the "Executive Summary" which is included following the Table of Contents.

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. If there are any questions concerning this information, please contact myself or James F. Baker, Ph.D. at (314) 654-5729.

Sincerely,

Marianne Robb

Marianne Robb
Manager, Regulatory Submissions
Phone: (314) 654-6258
Fax: (314) 654-6496

MAR 14 2001

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-418 APPLICANT: Mallinckrodt Inc.

DRUG PRODUCT: Hydrocodone Bitartrate and Acetaminophen Oral Solution 500mg/15mL; 7.5mg/15mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. For Step 7b, page 9 of your Blank Batch Record

2.

3. For Step 11f, page 12 of the BBR. we recommend

4. For the addition of

5. For the addition of Sucrose NF, Step 18d, page 18

6. Please specify the maximum time allowed from the start of mixing to final packaging.

7. Your Release and Stability Specification for p-

8. Your Stability Protocol includes an intermediate condition for testing at 30°C/60% RH to be performed when significant changes are observed at accelerated conditions. This testing condition is part of a draft guidance and should not be adopted at this time. Please modify your stability protocol to delete the intermediate condition and resubmit the protocol for review.

9. Please provide any additional Stability Data accrued to date.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

A Methods Validation package was sent to the Northeast Regional Laboratory, please provide samples when requested.

Sincerely yours,

for Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

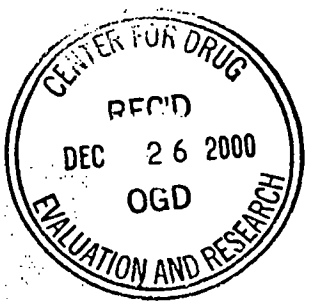
MALLINCKRODT

Mallinckrodt Inc. 675 McDonnell Boulevard PO Box 5840 St. Louis MO 63134 Phone: 314.654.2000 www.mallinckrodt.com

AMENDMENT TO A PENDING APPLICATION
CMC AMENDMENT/FINAL PRINTED LABELING

NDA ORIG AMENDMENT
N/AC

December 22, 2000



Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: ANDA 40-418: Hydrocodone Bitartrate and Acetaminophen Oral Solution (7.5 mg/500 mg per 15 mL)

Dear Madame or Sir:

Mallinckrodt hereby submits the following Chemistry, Manufacturing, and Controls amendment and Final Printed Labeling for the above referenced application.

This amendment to a pending application consists of one volume. An archival copy is being filed in a blue folder and a technical copy is being filed in a red folder. Twelve copies of Final Printed Labeling are being filed in a separate blue folder.

This also certifies that, per 21 C.F.R. §314.440 (a)(4) and concurrently with the filing of this amendment, true copies of the technical sections of the amendment were sent to the local district offices. These "field" copies are contained in maroon folders. For more detailed information on the organization of this application, please refer to the "Summary" which is included following the Table of Contents.

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. If there are any questions concerning this information, please contact myself or James F. Baker, Ph.D. at (314) 654-5729.

Sincerely,

Marianne Robb

Marianne Robb
Manager, Regulatory Submissions
Phone: (314) 654-6258
Fax: (314) 654-6496

MALLINCKRODT

Mallinckrodt Inc. 675 McDonnell Boulevard PO Box 5840 St. Louis MO 63134 Phone: 314.654.2000 www.mallinckrodt.com

CMC ELECTRONIC SUBMISSION ESD

July 27, 2000

NEW CORRESP
NC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: ANDA 40-418 for Hydrocodone Bitartrate and Acetaminophen Oral Solution (7.5 mg/500 mg per 15 mL)

Dear Madame or Sir:

On June 30, 2000 pursuant to Section 505 (j) of the Food, Drug and Cosmetic Act, Mallinckrodt Inc. Submitted an ANDA for Hydrocodone Bitartrate and Acetaminophen Oral Solution (7.5 mg/500 mg per 15 mL), a Schedule III prescription drug indicated for the treatment of moderate to moderately severe pain.

The purpose of this submission is to provide the Agency with a copy of the CMC Electronic submission ESD and companion document for the above referenced application. The Chemistry, Manufacturing, and Control information is provided in a blue archival folder with the proposed text for the proposed draft package insert in WordPerfect 6.1 format on two 3.5" diskettes. The CMC Electronic Submission ESD is provided on compact discs and the companion document is provided on 3.5" diskettes.

The information contained on the compact discs and the 3.5" diskettes is the same as that contained in the paper copy.

In the event review of the paper submission is initiated before the electronic submission is received and processed, it is Mallinckrodt's understanding the review will be completed using the hard copy only.

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. If there are any questions concerning this information, please contact myself or Dr. James Baker, Assistant Director, regulatory Affairs at (314) 654-5729.

Sincerely,

Marianne Robb
Manager, Regulatory Affairs
Phone: (314) 654-6258
Fax: (314) 654-6496

MALLINCKRODT

Mallinckrodt Inc. 675 McDonnell Boulevard Phone: 314.654.2000
PO Box 5840 www.mallinckrodt.com
St. Louis MO 63134

AMENDMENT TO A PENDING APPLICATION
CMC AMENDMENT/FINAL PRINTED LABELING

December 22, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: ANDA 40-418: Hydrocodone Bitartrate and Acetaminophen Oral Solution (7.5 mg/500 mg per 15 mL)

Dear Madame or Sir:

Mallinckrodt hereby submits the following Chemistry, Manufacturing, and Controls amendment and Final Printed Labeling for the above referenced application.

This amendment to a pending application consists of one volume. An archival copy is being filed in a blue folder and a technical copy is being filed in a red folder. Twelve copies of Final Printed Labeling are being filed in a separate blue folder.

This also certifies that, per 21 C.F.R. §314.440 (a)(4) and concurrently with the filing of this amendment, true copies of the technical sections of the amendment were sent to the local district offices. These "field" copies are contained in maroon folders. For more detailed information on the organization of this application, please refer to the "Summary" which is included following the Table of Contents.

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. If there are any questions concerning this information, please contact myself or James F. Baker, Ph.D. at (314) 654-5729.

Sincerely,

Marianne Robb
Manager, Regulatory Submissions
Phone: (314) 654-6258
Fax: (314) 654-6496

ANDA 40-418

Mallinckrodt Inc.
Attention: Marianne Robb
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, MO 63134-0840

OCT 26 2000

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the refuse to receive letter dated August 23, 2000 and your correspondence dated September 15, 2000.

NAME OF DRUG: Hydrocodone Bitartrate and Acetaminophen Oral Solution, 7.5 mg/500 mg per 15 mL

DATE OF APPLICATION: June 30, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: September 18, 2000

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Jeen Min
Project Manager
(301) 827-5849

Sincerely yours,

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

MALLINCKRODT

Mallinckrodt Inc. 675 McDonnell Boulevard
P.O. Box 5840
St. Louis, MO 63134
Phone: 314-654-2000
www.mallinckrodt.com

AMENDMENT TO A PENDING APPLICATION

September 15, 2000

NDA ORIG AMENDMENT
N/AC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: ANDA 40-418: Hydrocodone Bitartrate and Acetaminophen Oral Solution (7.5 mg/500 mg per 15 mL)

Dear Madame or Sir:

Mallinckrodt Inc. hereby submits this amendment to ANDA 40-418 in response to an FDA correspondence dated August 23, 2000. This ANDA is for Hydrocodone Bitartrate and Acetaminophen Oral Solution (7.5 mg/500 mg per 15 mL), a Schedule III prescription drug indicated for the treatment of moderate to moderately severe pain. Hydrocodone Bitartrate and Acetaminophen Oral Solution (7.5 mg/500 mg per 15 mL) will be manufactured, processed, packaged, labeled, and tested for release and stability by Mallinckrodt Inc. at Mallinckrodt's facility in Hobart, New York. The packaged product will be held and distributed by Mallinckrodt Inc. at Mallinckrodt & Second Streets in St. Louis, Missouri.

This amendment consists of one (1) volume. An archival copy is being filed in blue folders and a technical review copy is being filed in red folders. For more detailed information on the organization of this amendment, please refer to "Summary" which is included immediately following the Table of Contents.

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. For additional information, my phone numbers are 314-654-6258 (phone) or 314-654-6496 (fax) or call Dr. James F. Baker, Assistant Director, Regulatory Affairs at 314-654-5729.

Sincerely,

Marianne Robb
Manager, Regulatory Affairs

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 40-418

3. NAME AND ADDRESS OF APPLICANT
Mallinckrodt Inc.
Attention: Marianne Robb
P.O. Box 5840
675 McDonnell Blvd.
St Louis, MO 63134-0840

4. LEGAL BASIS FOR SUBMISSION
RLD: Hydrocodone Bitartrate and Acetaminophen
Dosage Form: Oral Elixir
Manufacturer: Mikart
ANDA: 81-051
Approval Date: Aug 28, 1992

Patents: There are no unexpired patents for this product.
Exclusivity: There is no exclusivity for this product.

Patent and Exclusivity Statements are provided on page 010.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME
Hydrocodone Bitartrate and Acetaminophen Oral Solution

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:

30-JUN-2000:	Original Application
27-JUL-2000:	CMC Electronic Submission
15-SEP-2000:	Amendment
22-DEC-2000:	Amendment
26-MAR-2001:	Minor Amendment

FDA:

23-AUG-2000:	Refuse to File Letter
26-OCT-2000:	Acknowledgement Letter
14-MAR-2001:	Minor Deficiency Letter

10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

USP

13. DOSAGE FORM
Oral Solution

14. POTENCIES
500mg/15mL; 7.5mg/15mL

15. CHEMICAL NAME AND STRUCTURE
Hydrocodone Bitartrate:
$C_{18}H_{21}NO_3 - C_4H_6O_6 - 2½ H_2O$; MW=494.490

Acetaminophen:
$C_8H_9NO_2$; MW =151.16

16. RECORDS AND REPORTS
FDA memo dated 23-OCT-2000 requesting pharm/tox consult during chemistry review (Vol. 2.1)
1st Labeling Review (Vol. 2.1)
2nd Labeling Review (Vol. 2.1)
1st Chemistry Review (Vol. 2.1)
Pharm/Tox consult conclusion

17. COMMENTS
-EER Found Acceptable.
-Bio Waiver was granted.
-Labeling Review was found satisfactory.
-MV samples were sent to the Northeast Regional Lab.
- Refuse to file letter issued due to FDA concerns about the inactive ingredient, PEG 1450, exceeding the maximum concentration previously approved by the Agency in an oral dosage form. A detailed response from the firm appears in Vol. 2.1.
-The pharm/Tox consult concluded that the PEG 1450 inactive was acceptable at the proposed level.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend Approval

19. REVIEWER:
D. Roselle, Ph.D.

DATE COMPLETED:
18-APR-2001

Page(s) 23

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

chem Rev. 2

4/18/01

MALLINCKRODT

Mallinckrodt Inc. 675 McDonnell Boulevard PO Box 5840 St. Louis MO 63134 Phone: 314.654.2000 www.mallinckrodt.com

MINOR AMENDMENT TO A PENDING APPLICATION
CMC AMENDMENT

March 26, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: ANDA 40-418: Hydrocodone Bitartrate and Acetaminophen Oral Solution (7.5 mg/500 mg per 15 mL)

Dear Madame or Sir:

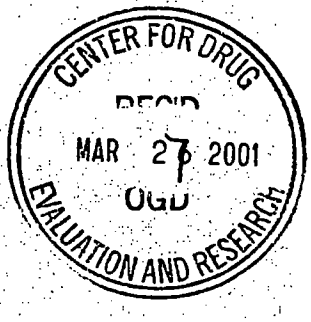
Mallinckrodt hereby submits the following Chemistry, Manufacturing, and Controls amendment to the above referenced ANDA in response to a March 14, 2001 facsimile deficiency. This amendment to a pending application consists of one volume. An archival copy is being filed in a blue folder and a technical copy is being filed in a red folder.

This also certifies that, per 21 C.F.R. §314.440 (a)(4) and concurrently with the filing of this amendment, true copies of the technical sections of the amendment were sent to the local district offices. These "field" copies are contained in maroon folders. For more detailed information on the organization of this application, please refer to the "Executive Summary" which is included following the Table of Contents.

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. If there are any questions concerning this information, please contact myself or James F. Baker, Ph.D. at (314) 654-5729.

Sincerely,

Marianne Robb
Manager, Regulatory Submissions
Phone: (314) 654-6258
Fax: (314) 654-6496



ANDA 40-418

Mallinckrodt Inc.
Attention: Marianne Robb
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, MO 63134-0840

AUG 23 2000

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated June 30, 2000, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Oral Solution, 7.5 mg/500 mg per 15 mL.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to receive this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

The concentration of the inactive ingredient, Polyethylene Glycol in your proposed product exceeds the maximum concentration of this inactive ingredient previously approved by the Agency in an oral dosage form. Please provide additional justification to demonstrate safety such as examples of approved drug products administered by the same route of administration which contain this inactive ingredient in the same concentration range. The information to demonstrate safety should include, but is not limited to examples of approved drug products administered by the same route of administration which contain the same inactive ingredients and that are within the same concentration range.

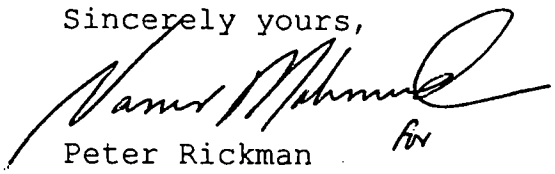
You have failed to provide a Form 356h listing the correct established name of your proposed product. You indicate that the established name of your product is "Hydrocodone Bitartrate and Acetaminophen Tablets, USP". Please provide a revised Form 356h with an original signature indicating the correct established name of the drug product.

Thus, it will not be received as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Upon receipt of this communication, you may either amend your application to correct the deficiencies or withdraw your application under 21 CFR 314.99. If you have any questions please call:

Emily Thomas
Project Manager
(301) 827-5862

Sincerely yours,



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

ANDA 40-418
cc:

Endorsement:

9
10

40-418

MALLINCKRODT

Mallinckrodt Inc. 675 McDonnell Boulevard PO Box 5840 St. Louis MO 63134 314.654.2000 www.mallinckrodt.com

ORIGINAL APPLICATION

June 30, 2000

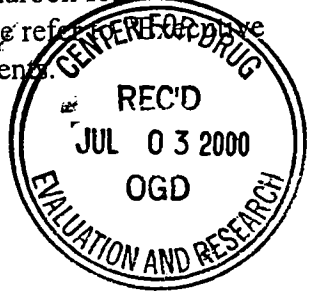
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: ORIGINAL SUBMISSION:
Hydrocodone Bitartrate and Acetaminophen Oral Solution
(7.5 mg/500 mg per 15 mL)

Dear Madame or Sir:

Mallinckrodt Inc. hereby submits this Abbreviated New Drug Application under 21 C.F.R. § 314.92(a)(1). This ANDA is for Hydrocodone Bitartrate and Acetaminophen Oral Solution (7.5 mg/500 mg per 15 mL), a Schedule III prescription drug indicated for the treatment of moderate to moderately severe pain. Hydrocodone Bitartrate and Acetaminophen Oral Solution (7.5 mg/500 mg per 15 mL) will be manufactured, processed, packaged, labeled, and tested for release and stability by Mallinckrodt Inc. at Mallinckrodt's facility in Hobart, New York. The packaged product will be held and distributed by Mallinckrodt Inc. at Mallinckrodt & Second Streets in St. Louis, Missouri.

This original application consists of two (2) volumes. An archival copy is being filed in blue folders and a technical review copy is being filed in red folders. A separate copy of the bioequivalence section is being submitted in an orange folder. This also certifies that, per 21 C.F.R. §314.440(a)(4) and concurrently with the filing of this ANDA, true copies of the technical sections of the ANDA were sent to the Branch Office in Maplewood, MO and the District Office in Buffalo, NY. These "field copies" are contained in maroon folders. For more detailed information on the organization of this application, please refer to the "Table of Contents Summary" which is included immediately following the Table of Contents.



In addition, it is Mallinckrodt's intention that an electronic submission will arrive within 30 days of this paper application. In the event review of the paper submission is initiated before the electronic submission is received and processed, it is Mallinckrodt's understanding the review will be completed using the hard copy only.

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. For additional information, my phone numbers are 314-654-6258 (phone) or 314-654-6496 (fax) or call Dr. James F. Baker, Assistant Director, Regulatory Affairs at 314-654-5729.

Sincerely,

/Marianne Robb

Marianne Robb
Manager, Regulatory Affairs