# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 40-248

# APPROVAL LETTER

ANDA 40-248

APR 28 2000

UCB Pharma, Inc.
Attention: Mary Alonso
1950 Lake Park Drive
Smyrna, GA 30080

Dear Madam:

This is in reference to your abbreviated new drug application dated February 21, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/325 mg and 10 mg/325 mg.

Reference is also made to your amendments dated July 7, 1999, March 6, 2000, April 4, 2000, and April 13, 2000.

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. When used as recommended in the labeling, the drug product, Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/325 mg and 10 mg/ 325 mg, respectively, can be expected to have the same therapeutic effect as that of the listed drug product upon which the Agency relied as the basis of safety and effectiveness. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

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 which 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,

/S/

Gary Buehler 4/28/00
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 40-248

# Final Printed Labeling

laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

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

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

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

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

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

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

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

The toxic dose for adults for acetaminophen is 10 g.

## DOSAGE AND ADMINISTRATION

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

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

## HOW SUPPLIED

Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 10 mg/325 mg, contain hydrocodone bitartrate 10 mg and acetaminophen 325 mg. They are supplied as unscored, pastel yellow, capsule-shaped tablets, debossed ucb on one side and 940 on the other side, in containers of 100 tablets NDC 50474-940-01 and in hospital unit-dose packages of 100 tablets [4 x 25] NDC 50474-940-60.

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

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

℞ only.

A Schedule CIII Narcotic.

ucb Pharma

Manufactured for
**UCB Pharma, Inc.**
Smyrna, Georgia 30080

Manufactured by
**Mallinckrodt Inc.**
Hobart, New York 13788

Revised 2/98
P/N 1001645

49400298

# HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP 10 mg/325 mg

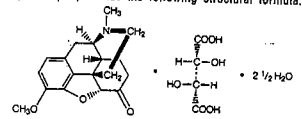
CIII

## DESCRIPTION

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

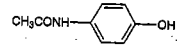
**WARNING: May be habit forming** (see PRECAUTIONS, Information for Patients, and DRUG ABUSE AND DEPENDENCE).

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:



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$ MW = 494.50

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



$C_8H_9NO_2$ MW = 151.17

Each pastel yellow tablet contains:

| | |
|---|---|
| Hydrocodone Bitartrate | 10 mg |
| Acetaminophen | 325 mg |

In addition, each tablet contains the following inactive ingredients: D&C Yellow No. 10, colloidal silicon dioxide, croscarmellose sodium, crospovidone, microcrystalline cellulose, povidone, pregelatinized starch, starch (corn), and stearic acid.

## 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.

COPY 9

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 tablets are indicated for the relief of moderate to moderately severe pain.

## CONTRAINDICATIONS

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

## WARNINGS

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

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

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

## PRECAUTIONS

**General:** Special Risk Patients: As with any narcotic analgesic agent, hydrocodone bitartrate and acetaminophen tablets 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 tablets 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; 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 tablets may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

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

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

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

**Pregnancy:**

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

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

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

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

**Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

## ADVERSE REACTIONS

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

Other adverse reactions include:

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

**Gastrointestinal System:** Prolonged administration of hydrocodone bitartrate and acetaminophen tablets may produce constipation.

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

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

**Dermatological:** Skin rash, pruritus.

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

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

## DRUG ABUSE AND DEPENDENCE

**Controlled Substance:** Hydrocodone bitartrate and acetaminophen tablets are 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 tablets 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:**

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

ucb Pharma

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NDC 50474-940-60

100 TABLETS (4 x 25)–Unit Dose

**USUAL DOSAGE:**
See package insert for complete dosage recommendations.

**STORAGE:** Store at controlled room temperature 15°-30°C (59°-86°F). Keep tablets in box to protect from light.

This unit-dose package is not child-resistant.

# HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP 10 mg/325 mg

℞ only

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FORM FDA 356H
STATEMENT OF CONFIDENTIALITY
CERTIFICATION OF
ATTACHMENT 1

laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

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

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

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

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

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

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

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

The toxic dose for adults for acetaminophen is 10 g.

## DOSAGE AND ADMINISTRATION

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

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

## HOW SUPPLIED

Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 7.5 mg/325 mg, contain hydrocodone bitartrate 7.5 mg and acetaminophen 325 mg. They are supplied as unscored, pastel blue; capsule-shaped tablets, debossed ucb on one side and 960 on the other side, in containers of 100 tablets NDC 50474-960-01 and in hospital unit-dose packages of 100 tablets [4 x 25] NDC 50474-960-60.

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

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

℞ only.

A Schedule CIII Narcotic.

ucb Pharma

Manufactured for
**UCB Pharma, Inc.**
Smyrna, Georgia 30080

Manufactured by
**Mallinckrodt Inc.**
Hobart, New York 13788

Revised 2/98
P/N 1001643

49600298

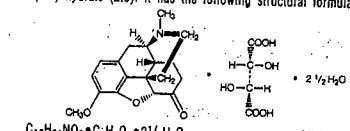
# HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP 7.5 mg/325 mg

## DESCRIPTION

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

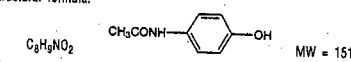
**WARNING: May be habit forming** (see PRECAUTIONS, Information for Patients, and DRUG ABUSE AND DEPENDENCE).

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:



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2^1/_2H_2O$ MW = 494.50

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



$C_8H_9NO_2$ MW = 151.17

Each pastel blue tablet contains:

| | |
|---|---|
| Hydrocodone Bitartrate | 7.5 mg |
| Acetaminophen | 325 mg |

In addition, each tablet contains the following inactive ingredients: FD&C Blue No. 1, colloidal silicon dioxide, croscarmellose sodium, crospovidone, microcrystalline cellulose, povidone, pregelatinized starch, starch (corn), and stearic acid.

## 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 tablets are indicated for the relief of moderate to moderately severe pain.

## CONTRAINDICATIONS

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

## WARNINGS

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

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

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

## PRECAUTIONS

**General:** Special Risk Patients: As with any narcotic analgesic agent, hydrocodone bitartrate and acetaminophen tablets 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 tablets 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; 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 tablets may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

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

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

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

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

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

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

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

**Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

## ADVERSE REACTIONS

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

Other adverse reactions include:

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

**Gastrointestinal System:** Prolonged administration of hydrocodone bitartrate and acetaminophen tablets may produce constipation.

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

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

**Dermatological:** Skin rash, pruritus.

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

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

## DRUG ABUSE AND DEPENDENCE

**Controlled Substance:** Hydrocodone bitartrate and acetaminophen tablets are 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 tablets 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:**
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

**COPY 9**

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).

Lot No.:
Exp. Date:

Manufactured for
**UCB Pharma, Inc.**
Smyrna, GA 30080
**by Mallinckrodt Inc.**
Hobart, NY 13788

**NDC 50474-960-01** **100 TABLETS**

**HYDROCODONE BITARTRATE AND ACETAMINOPHEN**
**TABLETS USP**
5 mg/325 mg

Each oval blue [illegible] Hydrocodone Bitartrate [illegible] Acetaminophen [illegible] 5 mg/325 mg

**USUAL DOSAGE:** See package insert for complete dosage recommendations.

APPROVED

50474-960-01 1

Rev. 2[illegible]
1001642

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 40-248

# CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO.
1

2. ANDA
**40-248**

3. NAME AND ADDRESS OF APPLICANT
UCB Pharma, Inc.
Smyrna, GA

4. LEGAL BASIS FOR SUBMISSION
505(j)(2)(c)

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Hydrocodone Bitartrate and Acetaminophen

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

9. AMENDMENTS AND OTHER DATES

| UCB Pharma | FDA |
|---|---|
| **2/21/97*** (Original Filing) | **5/1/97** (Acknowledgement) |

10. PHARMACOLOGICAL CATEGORY
Analgesic, Antitussive, Antipyretic

11. Rx or OTC
Rx

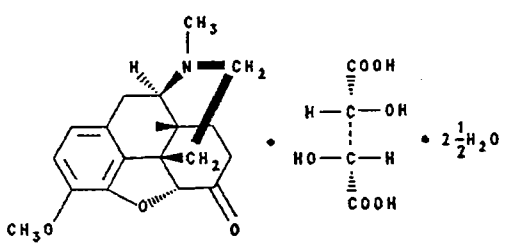
12. RELATED IND/NDA/DMF(s)
ANDA 88-058 Knoll (Vicodin® 5 mg/500 mg)
ANDA 40-134 UCB Pharma (7.5 mg/650 mg)

13. DOSAGE FORM
Tablets

14. POTENCY
7.5 mg/325 mg
10 mg/325 mg

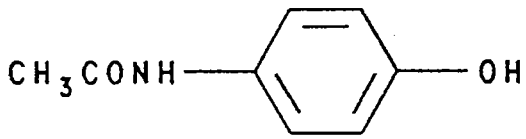
15. CHEMICAL NAME AND STRUCTURE
Hydrocodone Bitartrate: 4,5α-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5).

Hydrocodone Bitartrate USP
$C_{18}H_{21}NO_3 . C_4H_6O_6 . 2\frac{1}{2}H_2O$; M.W. = 494.50



4,5α-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). CAS [34195-34-1; 6190-38-1]

Acetaminophen USP
$C_8H_9NO_2$; M.W. = 151.17




4'-Hydroxyacetanilide. CAS [103-90-2]

16. RECORDS AND REPORTS
N/A

17. COMMENTS
The Original Filing of the ANDA dated **2/21/97**, was submitted based upon an ANDA Suitability Petition approved on **6/8/87**. As a consequence, the Agency determined that the reference drug product is suitable for submission as an ANDA. The petition states that these products are similar and related to the currently marketed Vicodin® brand tablet containing 5 mg/500 mg of the ds's.

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable.

19. REVIEWER
Robert C. Permisohn
/S/

DATE COMPLETED
8/29/97
9/10/97

**Redacted** 32

**Page(s) of trade secret and /or confidential commercial information**

1. CHEMISTRY REVIEW NO.
2

2. ANDA
**40-248**

3. NAME AND ADDRESS OF APPLICANT
UCB Pharma, Inc.
Smyrna, GA

4. LEGAL BASIS FOR SUBMISSION
505(j)(2)(c)

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Hydrocodone Bitartrate and Acetaminophen

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

9. AMENDMENTS AND OTHER DATES

| UCB Pharma | FDA |
|---|---|
| **2/21/97** (Original Filing). | **5/1/97** (Acknowledgement). |
| | **9/29/97** (NA Major). |
| | **9/29/97** (Labels/Labeling). |
| **3/5/98 (Subject of this review).** | |
| **8/17/98 (Subject of this review).** | |

10. PHARMACOLOGICAL CATEGORY
Analgesic, Antitussive, Antipyretic

11. Rx or OTC
Rx

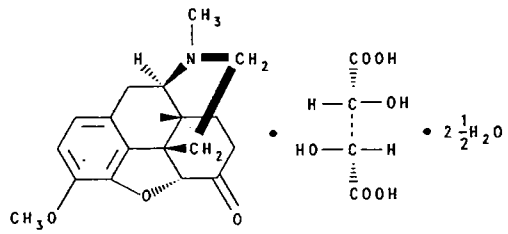
12. RELATED IND/NDA/DMF(s)
ANDA 88-058 Knoll (Vicodin® 5 mg/500 mg)
ANDA

13. DOSAGE FORM
Tablets

14. POTENCY
7.5 mg/325 mg
10 mg/325 mg

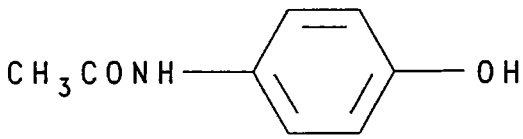
15. CHEMICAL NAME AND STRUCTURE
Hydrocodone Bitartrate: 4,5α-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5).

Hydrocodone Bitartrate USP
$C_{18}H_{21}NO_3 . C_4H_6O_6 . 2\frac{1}{2}H_2O$; M.W. = 494.50



4,5α-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). CAS [34195-34-1; 6190-38-1]

Acetaminophen USP
$C_8H_9NO_2$; M.W. = 151.17



4'-Hydroxyacetanilide. CAS [103-90-2]

16. RECORDS AND REPORTS
N/A

17. COMMENTS
The Original Filing of the ANDA dated **2/21/97**, was submitted based upon an ANDA Suitability Petition approved on **6/8/87**. As a consequence, the Agency determined that the reference drug product is suitable for submission as an ANDA. The petition states that these products are similar and related to the currently marketed Vicodin® brand tablet containing 5 mg/500 mg of the ds's.

**3/5/98, Amendment:** This responds to our deficiency letter (MAJOR FAX) dated **9/29/97**, addressing CMC information. The applicant pointed out that Mallinckrodt has purchased D. M. Graham Laboratories and Pharm Tech Packaging, and effective **7/1/97**, the name of both facilities became Mallinckrodt Chemical. The cited #'s in the review items #'s 20. *et al*, are from the MAJOR FAX, which are followed by the applicant's response.

In addition to responding to the deficiencies presented in the deficiency letter (MAJOR FAX) dated **9/29/97**, addressing CMC

information, the applicant was asked to note and acknowledge the following comments in their response:

1. The [redacted] procedures used for release and stability testing must be regarded as alternates to the compendium procedures for regulatory purposes.

**Applicant's response:** Agreed.

2. [redacted] validation protocols, as well as, cleaning validation summaries for the respective products that have been submitted will not be reviewed, since these fall within the purview of FDA field investigators.

**Applicant's response:** So acknowledged.

3. On p. 4 138, broad reference has been made to analytical controls which are general and appear to pertain to the entire product line. Only those items that are pertinent to these products should be included in submissions to this ANDA.

**Applicant's response:** Agreed.

4. The request for a waiver of *in vivo* bioequivalence study requirements is under review by the Division of Bioequivalence. The result of the review may be addressed in a separate communication.

**Applicant's response:** Understood.

5. The evaluation of compliance of all firms involved in the manufacture and testing of this drug product with the current good manufacturing practices regulations will be undertaken by our Office of Compliance. A satisfactory evaluation is required prior to approval of this application.

**Applicant's response:** So acknowledged.

6. Please provide any additional data for ongoing stability studies for the exhibit batches if available.

**Applicant's response:** The available stability data has been submitted (see item 29. of this review).

7. It is noted that on p. 9 002, a tentative expiration dating of 24 months for product in market packages stored at [redacted], has been proposed. This is not consistent with the stability protocol which requires the stability storage conditions to be

[redacted] In accordance with 21 CFR §211.137 and §211.166, the expiration dating period should be related to any storage conditions as determined by stability studies. In other words, the labeled storage condition of [redacted], must be supported by data for product kept at the stability storage condition of [redacted] and not vice versa.

**Applicant's response:** A corrected p. 9 002 which cites the stability storage condition of [redacted] has been submitted.

**8/17/98, Amendment:** This responds to our FAX dated **9/29/97**, addressing label/labeling issues. See item 32. of this review.

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable.

19. REVIEWER
Robert [redacted]sohn

DATE COMPLETED
11/30/98
12/31/98

APPEARS THIS WAY
ON ORIGINAL

**Redacted** 33

**Page(s) of trade secret and /or confidential commercial information**

1. CHEMISTRY REVIEW NO. 3

2. ANDA 40-248

3. NAME AND ADDRESS OF APPLICANT
UCB Pharma, Inc.
Attention: Mary D. Alonso
1950 Lake Park Drive
Smyrna, GA 30080

4. LEGAL BASIS FOR SUBMISSION
505(j)(2)(c)

The Original Filing of the ANDA dated 2/21/97 was submitted based upon an ANDA Suitability Petition approved on 6/8/87 under Docket Number 87 P-0129/CP. As a consequence, the Agency determined that the reference drug product is suitable for submission as an ANDA. The petition states that these products are similar and related to the currently marketed Vicodin® brand tablet containing 5 mg/500 mg of the Hydrocodone Bitartrate and Acetaminophen.

There are no current patents or exclusivities

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Hydrocodone Bitartrate and Acetaminophen Tablets, USP

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

9. AMENDMENTS AND OTHER DATES

| UCB Pharma | FDA |
|---|---|
| 2/21/97 - Original Filing | 5/1/97 - Acknowledgement |
| | 9/29/97 - Not Approvable, Major |
| | 9/29/97 - Labeling Deficiency |
| 3/5/98 - Amendment #1 | |
| 8/17/98 - Amendment #2 | |
| | 3/4/99 - Deficiency Letter #2 |
| | 3/23/99 - Fax, clarification |
| 7/7/99 - Amendment #3 | |

10. PHARMACOLOGICAL CATEGORY
Analgesic, Antitussive, Antipyretic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
ANDA 88-058 Knoll (Vicodin® 5 mg/500 mg)
ANDA [redacted]
DMF [redacted] - Hydrocodone Bitartrate USP, Mallinckrodt
DMF [redacted] - Acetaminophen [redacted]®, Mallinckrodt

DMF #
DMF #
DMF #
DMF #
DMF #
DMF #

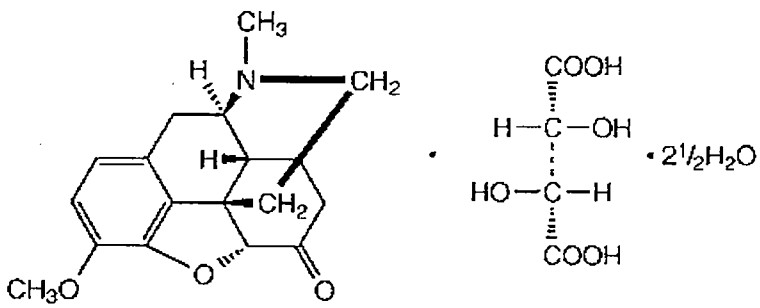
DMF #
DMF #
DMF #
DMF #
DMF #
DMF #

13. **DOSAGE FORM**
Tablets

14. **POTENCY**
7.5 mg/325 mg
10 mg/325 mg

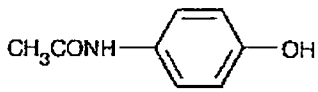
15. **CHEMICAL NAME AND STRUCTURE**

Hydrocodone Bitartrate USP
$C_{18}H_{21}NO_3 . C_4H_6O_6 . 2\frac{1}{2}H_2O$
M.W. = 494.50




Chemical Name: 4,5α-Epoxy-3-methoxy-17-methylmorphinan-6 one tartrate (1:1) hydrate (2:5).
CAS: 34195-34-1; 6190-38-1

Acetaminophen USP
$C_8H_9NO_2$
M.W.: 151.17




Chemical Name: 4'-hydroxyacetanilide,
CAS: 103-90-2

16. **RECORDS AND REPORTS**

8/31/97 - Chem. Review #1
2/21/97 - Bioequivalence waiver granted.
2/21/97 - Labeling Review #1
8/17/98 - Labeling Review #2
11/30/98 - Chem. Review #2
7/7/99 - Labeling Review #3, approved

17. **COMMENTS**

[ ]

Labeling was found satisfactory.

EER is acceptable.

DMF for drug substance hydrocodone bitartrate remains adequate, DMF for drug substance acetaminophen [redacted] also remains adequate.

Method validation was requested and found satisfactory.

18. **CONCLUSIONS AND RECOMMENDATIONS**

Not Approvable - Minor

19. **REVIEWER** Tao-Chin L. Wang **DATE COMPLETED** 12/17/99

**Redacted** 28

**Page(s) of trade secret and /or confidential commercial information**

1. **CHEMISTRY REVIEW NO.** 4

2. **ANDA** 40-248

3. **NAME AND ADDRESS OF APPLICANT**
UCB Pharma, Inc.
Attention: Mary D. Alonso
1950 Lake Park Drive
Smyrna, GA 30080

4. **LEGAL BASIS FOR SUBMISSION**
505(j)(2)(c)

The Original Filing of the ANDA dated 2/21/97 was submitted based upon an ANDA Suitability Petition approved on 6/8/87 under Docket Number 87 P-0129/CP. As a consequence, the Agency determined that the reference drug product is suitable for submission as an ANDA. The petition states that these products are similar and related to the currently marketed Vicodin® brand tablet containing 5 mg/500 mg of the Hydrocodone Bitartrate and Acetaminophen.

There are no current patents or exclusivities.

5. **SUPPLEMENT(s)**
N/A

6. **PROPRIETARY NAME**
N/A

7. **NONPROPRIETARY NAME**
Hydrocodone Bitartrate and Acetaminophen Tablets, USP

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

9. **AMENDMENTS AND OTHER DATES**

| UCB Pharma | FDA |
|---|---|
| 2/21/97 - Original Filing | 5/1/97 - Acknowledgement |
| | 9/29/97 - Not Approvable, Major |
| | 9/29/97 - Labeling Deficiency |
| 3/5/98 - Amendment #1 | |
| 8/17/98 - Amendment #2 | |
| | 3/4/99 - Deficiency Letter #2 |
| | 3/23/99 - Fax, clarification |
| 7/7/99 - Amendment #3 | |
| | 2/7/00 - Fax, Deficiency Letter |
| 3/6/00 - Amendment #4 | |

10. **PHARMACOLOGICAL CATEGORY**
Analgesic, Antitussive, Antipyretic

11. **Rx or OTC**
Rx

12. **RELATED IND/NDA/DMF(s)**
ANDA 88-058 Knoll (Vicodin® 5 mg/500 mg)
ANDA —
DMF # — Hydrocodone Bitartrate USP, Mallinckrodt
DMF # — Acetaminophen — Mallinckrodt
DMF # —
DMF # —
DMF # —
DMF # —

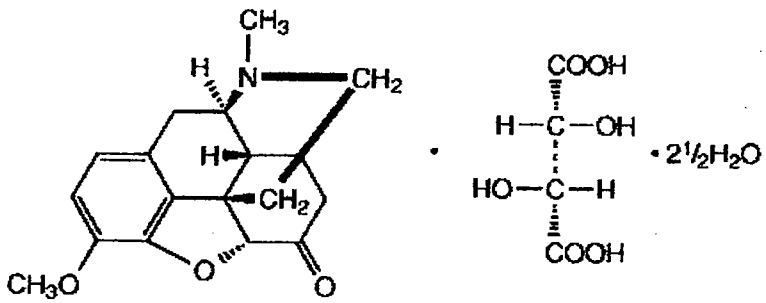
DMF #
DMF #
DMF #
DMF #
DMF #
DMF #
DMF #
DMF

13. **DOSAGE FORM**
Tablets

14. **POTENCY**
7.5 mg/325 mg
10 mg/325 mg

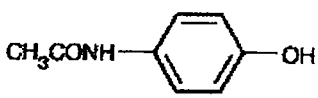
15. **CHEMICAL NAME AND STRUCTURE**

Hydrocodone Bitartrate USP
$C_{18}H_{21}NO_3.C_4H_6O_6.2H_2O$
M.W. = 494.50



Chemical Name: 4,5α-Epoxy-3-methoxy-17-methylmorphinan-6 one tartrate (1:1) hydrate (2:5).
CAS: 34195-34-1; 6190-38-1

Acetaminophen USP
$C_8H_9NO_2$
M.W.: 151.17



Chemical Name: 4'-hydroxyacetanilide,
CAS: 103-90-2

16. **RECORDS AND REPORTS**
8/31/97 - Chem. Review #1
2/21/97 - Bioequivalence waiver granted.
2/21/97 - Labeling Review #1
8/17/98 - Labeling Review #2
11/30/98 - Chem. Review #2

7/7/99 - Labeling Review #3, approved
12/17/99 - Chem. Review #3

17. **COMMENTS**

[redacted]

(3/21/00).

EER is acceptable.

DMF for drug substance hydrocodone bitartrate is adequate; DMF for drug substance acetaminophen [redacted] is adequate.

Method validation was requested and found satisfactory.

18. **CONCLUSIONS AND RECOMMENDATIONS**
Not Approvable - Minor

19. **REVIEWER** Tao-Chin L. Wang

**DATE COMPLETED** 3/20/2000

APPEARS THIS WAY
ON ORIGINAL

**Redacted** 22

**Page(s) of trade secret and /or confidential commercial information**

1. **CHEMISTRY REVIEW NO.** 5

2. **ANDA** 40-248

3. **NAME AND ADDRESS OF APPLICANT**
UCB Pharma, Inc.
Attention: Mary D. Alonso
1950 Lake Park Drive
Smyrna, GA 30080

4. **LEGAL BASIS FOR SUBMISSION**
505(j)(2)(c)

The Original Filing of the ANDA dated 2/21/97 was submitted based upon an ANDA Suitability Petition approved on 6/8/87 under Docket Number 87 P-0129/CP. As a consequence, the Agency determined that the reference drug product is suitable for submission as an ANDA. The petition states that these products are similar and related to the currently marketed Vicodin® brand tablet containing 5 mg/500 mg of the Hydrocodone Bitartrate and Acetaminophen.

There are no current patents or exclusivities.

5. **SUPPLEMENT(s)**
N/A

6. **PROPRIETARY NAME**
N/A

7. **NONPROPRIETARY NAME**
Hydrocodone Bitartrate and Acetaminophen Tablets, USP

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

9. **AMENDMENTS AND OTHER DATES**

| UCB Pharma | FDA |
|---|---|
| 2/21/97 - Original Filing | 5/1/97 - Acknowledgement |
| | 9/29/97 - Not Approvable, Major |
| | 9/29/97 - Labeling Deficiency |
| 3/5/98 - Amendment #1 | |
| 8/17/98 - Amendment #2 | |
| | 3/4/99 - Deficiency Letter #2 |
| | 3/23/99 - Fax, clarification |
| 7/7/99 - Amendment #3 | |
| | 2/7/00 - Fax, Deficiency Letter |
| 3/6/00 - Amendment #4 | |
| | 4/5/00 - Telecon |
| 4/13/00 - Amendment #5 | |

10. **PHARMACOLOGICAL CATEGORY**
Analgesic, Antitussive, Antipyretic

11. **Rx or OTC**
Rx

12. **RELATED IND/NDA/DMF(s)**
ANDA 88-058 Knoll (Vicodin® 5 mg/500 mg)
ANDA
DMF # — - Hydrocodone Bitartrate USP, Mallinckrodt
DMF # — - Acetaminophen ( ), Mallinckrodt
DMF #

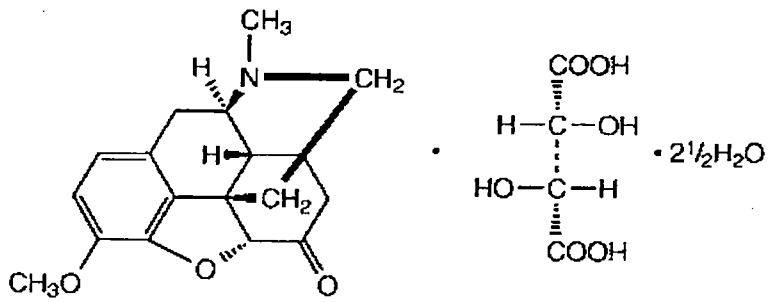
DMF #
DMF #
DMF #
DMF #
DMF #
DMF #
DMF #
DMF #
DMF #
DMF #
DMF #

13. **DOSAGE FORM**
Tablets

14. **POTENCY**
7.5 mg/325 mg
10 mg/325 mg

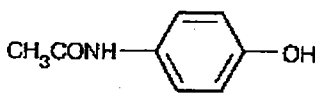
15. **CHEMICAL NAME AND STRUCTURE**

Hydrocodone Bitartrate USP
$C_{18}H_{21}NO_3.C_4H_6O_6.2H_2O$
M.W. = 494.50




Chemical Name: 4,5α-Epoxy-3-methoxy-17-methylmorphinan-6 one tartrate (1:1) hydrate (2:5).
CAS: 34195-34-1; 6190-38-1

Acetaminophen USP
$C_8H_9NO_2$
M.W.: 151.17




Chemical Name: 4'-hydroxyacetanilide,
CAS: 103-90-2

16. **RECORDS AND REPORTS**
8/31/97 - Chem. Review #1
2/21/97 - Bioequivalence waiver granted.

2/21/97 - Labeling Review #1
8/17/98 - Labeling Review #2
11/30/98 - Chem. Review #2
7/7/99 - Labeling Review #3, approved
12/17/99 - Chem. Review #3
3/20/00 - Chem. Review #4
4/7/00 - Labeling Review #4, approved

17. **COMMENTS**

Labeling is acceptable (4/10/00).

Bioequivalence waiver was granted (1/26/98).

EER is acceptable (2/23/00).

DMF for the drug substance hydrocodone bitartrate is adequate (2/25/00); DMF for the drug substance acetaminophen is adequate (3/20/00).

Method validation was requested and found satisfactory (7/23/97).

18. **CONCLUSIONS AND RECOMMENDATIONS**
Approvable

19. **REVIEWER** Tao-Chin L. Wang
**DATE COMPLETED** 4/17/2000

**Redacted** 24

**Page(s) of trade secret and /or confidential commercial information**

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 40-248

# BIOEQUIVALENCE REVIEW

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA/AADA: 40-248 APPLICANT:UCB PHARM

DRUG PRODUCT: Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/325 mg and 10 mg/325 mg

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in U.S.P. 23.

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,

/S/

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

T.M

# OFFICE OF GENERIC DRUGS
# DIVISION OF BIOEQUIVALENCE

ANDA/~~AADA~~ # 40248 SPONSOR: UCB Pharma.
DRUG: Hydrocodone Bitartrate & Acetaminophen
DOSAGE FORM: Tablets
STRENGTH(s): 7.5 mg/325 mg & 10 mg/325 mg.
TYPE OF STUDY: Single/~~Multiple~~ ~~Fasting~~/Fed
STUDY SITE:

STUDY SUMMARY:

N/A

DISSOLUTION:
Acceptable

PRIMARY REVIEWER: A P Patel BRANCH: 3
INITIAL: /S/ DATE: 6/25/97

BRANCH CHIEF: Dr. R. M. Mhatre, Ph. D. BRANCH: 3
INITIAL: /S/ DATE: 6/30/97

DIRECTOR
DIVISION OF BIOEQUIVALENCE
INITIAL: DATE: 1/26/98

DIRECTOR
OFFICE OF GENERIC DRUGS
INITIAL: DATE:

CC: ANDA 40-248
ANDA DUPLICATE
DIVISION FILE
BIO DRUG FILE
FIELD COPY
HFD-650 PATEL

X:NEW\FIRMSNZ\UCBPHARM\40248W.297

BIOEQUIVALENCY - ACCEPTABLE

1. **FASTING STUDY** (STF)

   Clinical: _____
   Analytical: _____

   Strengths: _____

   **Outcome: AC IC UN NC**

2. **FOOD STUDY** (STP)

   Clinical: _____
   Analytical: _____

   Strengths: _____

   **Outcome: AC IC UN NC**

3. **MULTIPLE DOSE STUDY** (STM)

   Clinical: _____
   Analytical: _____

   Strengths: _____

   **Outcome: AC IC UN NC**

4. **DISSOLUTION DATA** (DIS)

   All Strengths

   **Outcome: AC IC UN NC**

5. **STUDY AMENDMENT** (STA)

   Strengths: _____
   **Outcome: AC IC UN NC**

6. **WAIVER** (WAI)

   Strengths: _____

   **Outcome: AC IC UN NC**

(7.) **DISSOLUTION WAIVER** (DIW)

   Strengths: 7.5/325MG AND 10/325MG
   **Outcome: AC IC UN NC** Acceptable

8. **OTHER** (OTH) _____

   Strengths: _____

   **Outcome: AC IC UN NC**

9. **OTHER OPTIONS** (less common):
   a. Protocol (PRO)
   b. Protocol Amendment (PRA)
   c. Protocol/Dissolution (PRD)

   Strengths: _____
   d. Special Dosage (STS)
   e. Study/Dissolution (STD)
   f. Bio study (STU)

   **Outcome: AC IC UN NC**

Outcome Decisions:Acceptable
**AC** - Acceptable
**NC** - No Action

**UN** - Unacceptable (fatal flaw)
**IC** - Incomplete

Hydrocodone Bitartrate and Acetaminophen Tablets
7.5 mg/ 325 mg and 10 mg/325 mg
ANDA # 40-248
Reviewer: A.P. Patel
File: x:\wpfile\biofinal\40248w.297

UCB Pharma, Inc.
Smyrna, GA
Submission Date:
Feb. 21, 1997

Review of Dissolution Data and Waiver Request

I. Introduction:

Hydrocodone bitartrate is a phenanthrene-derivative opiate agonist that is used as an antitussive and an analgesic agent. Acetaminophen is a synthetic non-opiate derivative of p-aminophenol which produces analgesia and antipyresis.

II. Objective:

The firm has submitted dissolution data in support of a request for a bioequivalence study waiver as provided for under 21 CFR 320.22(c) for its hydrocodone bitartrate/acetaminophen, 7.5mg/325mg and 10mg/ 325mg tablets manufactured by UCB, Inc. The listed drug is Vicodin® Tablets (hydrocodone bitartrate and acetaminophen tablets, 5mg/500mg) manufactured and distributed by Knoll Pharmaceuticals, Inc.

This ANDA was submitted based on an approved ANDA suitability petition under 314.93. The petition was filed under Section 505 (j)(2)(c) of the Act where the Agency determined that the referenced product was suitable for submission as an ANDA. The petition was approved on June 8, 1987, under Docket Number 87 P-0129/CP. The reason for the petition was a new strength.

III. **Comments:**

The Firm contends that their drug product meets the criteria for waiver under the CFR 320.22 (c), the test drug product:

> 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.
>
> Acetaminophen/Hydrocodone Bitartrate Tablets are coded AA on various strengths in the "Orange Book".
>
> *In vivo* bioequivalence is satisfied for dosage forms with AA code by an acceptable dissolution study. Active ingredients in the test tablets meet the "Q" specifications.

For a comparison of test and reference product formulations and dissolution test results, please see table 1 and table 2, respectively.

IV. Deficiencies: None

V. Recommendations:

1. The dissolution testing conducted by UCB Pharma Inc. on its Hydrocodone Bitartrate/Acetaminophen, 7.5mg/325mg and 10mg/325mg Tablet strengths are acceptable. The waiver of the in vivo bioequivalence study requirements is granted for the test product Hydrocodone Bitartrate/Acetaminophen 7.5mg/325mg and 10mg/325mg Tablet strengths based on 21 CFR 320.22 (c).

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of phosphate buffer pH 5.8, at 37°C using USP XXIII apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than 80% of the labeled amount of both acetaminophen and hydrocodone bitartrate in the dosage form are dissolved in 30 minutes.

The firm should be informed of the above recommendations.

/S/ 6/25/97

A.P.Patel
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE /S/ Date: 6/30/97
Ramakant M. Mhatre, Ph.D.
Chief, Branch III
Division of Bioequivalence

Concur: /S/ Date: 11/14/97

Nicholas M. Fleischer, Ph.D.
Director
Division of Bioequivalence

cc: ANDA# 40-248 (Original, Duplicate), HFD 650 (Director), HFD-658 (A.P.Patel), Drug File, Division File.

**Formulation: (Not to be released through FOI)**

UCB Pharma, Inc. Hydrocodone Bitartrate and Acetaminophen (7.5mg/325mg and 10mg/325mg) tablets.

**Table 1**

| Ingredients | mg per tablet (7.5mg/325mg) | mg per tablet (10mg/325mg) |
|---|---|---|
| Hydrocodone Bitartrate USP | 7.5 | 10.0 |
| Acetaminophen USP | | |
| Microcrystalline Cellulose, NF | | |
| Colloidal Silicon Dioxide, NF | | |
| Croscarmellose Sodium, NF | | |
| Stearic Acid | | |
| Starch, NF ( cornstarch) | | |
| FD&C Blue #1 lake | | |
| D&C Yellow #10 lake | | |
| Total | 499.4 | 501.9 |

This formulation obtained from manufacturing form chart.

APPEARS THIS WAY
ON ORIGINAL

**Dissolution Testing:**

The following USP 23 conditions were used:

Apparatus: 2 (paddle) at 50 RPM
Medium: 900 mL phosphate buffer pH 5.8
Specifications: NLT 80% (Q) in 30 minutes for both active ingredients
Test product: Hydrocodone Bitartrate/Acetaminophen 7.5mg/325mg Tablets
lot #:EXPT9636 Exp. Date: N/A

Hydrocodone Bitartrate/Acetaminophen 10mg/325mg Tablets
lot #:EXPT9635 Exp. Date: N/A

Reference product: Knoll's 5mg/500mg Vicodin® Tablets
lot #10760115 Exp. Date: 3/99

**Table 2**

| Time (min) | 7.5mg Hydrocodone Bitartrate Test Mean | %CV | Reference Mean | %CV | 325mg Acetaminophen Test Mean | %CV | Reference Mean | %CV |
|---|---|---|---|---|---|---|---|---|
| 10 | 102.8 | 1.4 | 90.5 | 7.4 | 97.7 | 1.9 | 64.8 | 12.6 |
| 20 | 101.8 | 1.2 | 95.6 | 3.8 | 97.2 | 1.6 | 72.2 | 9.7 |
| **30** | **100.8** | **1.3** | **96.7** | **2.3** | **96.2** | **1.3** | **75.5** | **8.6** |
| 45 | 99.5 | 1.3 | 97.1 | 1.8 | 95.4 | 0.9 | 79.3 | 8.3 |

| Time (min) | 10mg Hydrocodone Bitartrate Test Mean | %CV | Reference Mean | %CV | 325mg Acetaminophen Test Mean | %CV | Reference Mean | %CV |
|---|---|---|---|---|---|---|---|---|
| 10 | 102.4 | 1.7 | 90.5 | 7.4 | 99.3 | 1.7 | 64.8 | 12.6 |
| 20 | 101.4 | 1.7 | 95.6 | 3.8 | 99.0 | 1.9 | 72.2 | 9.7 |
| **30** | **100.4** | **1.8** | **96.7** | **2.3** | **97.4** | **1.8** | **75.5** | **8.6** |
| 45 | 99.2 | 1.8 | 97.1 | 1.8 | 96.9 | 1.7 | 79.3 | 8.3 |

Active ingredients in the test tablets meet the "Q" specifications, NLT 80% dissolved in 30 minutes. Note reference acetaminophen does not meet the "Q" specification.

# OFFICE OF GENERIC DRUGS
# DIVISION OF BIOEQUIVALENCE

ANDA/~~AADA~~ # 40248 SPONSOR: UCB pharma.
DRUG: Hydrocodone Bitartrate & Acetaminophen
DOSAGE FORM: Tablets
STRENGTH(s): 7.5 mg/325 mg & 10 mg/325 mg
TYPE OF STUDY: ~~Single~~/~~Multiple~~ ~~Fasting~~/~~Fed~~
STUDY SITE:

STUDY SUMMARY:

N/A

DISSOLUTION:
Acceptable

PRIMARY REVIEWER: A P Patel BRANCH: 3
INITIAL: /S/ DATE: 6/25/97

BRANCH CHIEF: Dr. R. M. Mhatre, Ph. D. BRANCH: 3
INITIAL: /S/ DATE: 6/30/97

DIRECTOR
DIVISION OF BIOEQUIVALENCE
INITIAL: /S/ DATE: 1/26/98

DIRECTOR
OFFICE OF GENERIC DRUGS
INITIAL: DATE:

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 40-248

# ADMINISTRATIVE DOCUMENTS

**ANDA APPROVAL SUMMARY**

ANDA: 40-248
DRUG PRODUCT: Hydrocodone Bitartrate and Acetaminophen USP
DOSAGE FORM: Tablet for Oral Administration
STRENGTH: 7.5 mg/325 mg; 10 mg/325 mg

FIRM: UCB Pharma, Inc.
Attention: Mary D. Alonso
1950 Lake Park Drive
Smyrna, GA 30080

CGMP STATEMENT/EIR UPDATE STATUS

Section 306(k) certification is submitted (pp. 1 003).
cGMP certification of compliance is provided (pp. 2 004).

Acceptable EIR is recommended by the Office of Compliance, 2/23/00.

Facilities included are:

1. The Hydrocodone Bitartrate drug substance is manufactured by:
   Mallinckrodt Chemical, Inc.
   3600 North 2nd Street
   St. Louis, MO 63147

   The Acetaminophen [redacted] drug substance is manufactured by:
   Mallinckrodt Chemical, Inc.
   100 Louis Latzer Drive
   Greenville, IL 62246

2. The manufacturing and processing, bulk packaging, and control operations (testing and stability testing) are to be performed at:

   Mallinckrodt Chemicals [redacted]
   58 Pearl Street
   Hobart, New York 13788

   Mallinckrodt Chemicals [redacted]
   13 Railroad Avenue
   P.O. Box P
   Hobart, New York 13788

3. The labeling and finished bottle packaging facility:

Mallinckrodt Chemicals
18 Cornell Avenue
Hobart, New York 13788

4.

5.

BIO STUDY

Requests for waiver of *in vivo* bioequivalence study requirements for both dosage strengths have been reviewed and granted by the Division of Bioequivalence. Dissolution testing requirements corresponding to those in the *USP* monograph are recommended for these products.

VALIDATION

Drug substances and products are subjects of compendial monographs. Despite this, William Rickman of the OGD had requested methods validation. Christine Cash of the Southeast Regional Laboratory (HFR-SE660) concluded in a Memorandum dated 7/23/97 that the method appears to be satisfactory.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? Yes

Stability Tests and Specifications

| Test | Specification | |
|---|---|---|
| | 7.5 mg/325 mg Tablet | 10 mg/325 mg Tablet |
| Description | 0.3125" x 0.500", pastel blue capsule-shaped, one side debossed "960"; the | 0.3125" x 0.500", pastel yellow capsule-shaped, one side debossed "940"; the |

| | | |
|---|---|---|
| | opposite side debossed "ucb". | opposite side debossed "ucb". |
| Organoleptic | No unusual odor, visible deterioration, or physical tactile change. | No unusual odor, visible deterioration, or physical tactile change. |
| Disintegration | NMT 30 min. | NMT 30 min. |
| Thickness (") | Target 0.275" ± 10%* | Target 0.275" ± 10%* |
| Hardness (Kg) | [illegible] | [illegible] |
| Dosage Wt. (mg) | 499 mg ± 5% | 502 mg ± 5% |
| Assay (mg)<br><br>Acetaminophen<br>Hydrocodone Bitartrate | <br><br>325 mg [illegible]<br>7.5 mg [illegible] | <br><br>325 mg [illegible]<br>10 mg [illegible] |
| Dissolution | NLT 80% (Q) in 30 min. | NLT 80% (Q) in 30 min. |
| Impurities:<br>[illegible] | <br>NMT [illegible] | <br>NMT [illegible] |
| [illegible] | NMT [illegible] | NMT [illegible] |
| [illegible] | NMT [illegible] | NMT [illegible] |
| [illegible] | NMT [illegible] | NMT [illegible] |
| Other Related Substances | NMT [illegible] | NMT [illegible] |
| Total Related Substances | NMT [illegible] | NMT [illegible] |

* Tentative

Stability data for the following are included:

7.5 mg/325 mg

| Lot # | Batch Size | Sample | Test Conditions |
|---|---|---|---|
| 9636 | [illegible] tablets | Unit Dose | 40±2°C/75±5% RH/6 months<br>30±2°C/60±5% RH/3 months |

| | | |
|---|---|---|
| | | 25±2°C/60±5% RH/36 months |
| | 100's | 40±2°C/75±5% RH/6 months |
| | | 25±2°C/60±5% RH/36 months |
| | Bulk | 25±2°C/60±5% RH/6 months |

10 mg/325 mg

| Lot # | Batch Size | Sample | Test Conditions |
|---|---|---|---|
| 9635 | ~~~ tablets | Unit Dose | 40±2°C/75±5% RH/6 months |
| | | | 30±2°C/60±5% RH/6 months |
| | | | 25±2°C/60±5% RH/36 months |
| | | 100's | 40±2°C/75±5% RH/6 months |
| | | | 25±2°C/60±5% RH/36 months |
| | | Bulk | 25±2°C/60±5% RH/6 months |

The 36 months room temperature testing results conform to the specifications. The firm requests a 24-month expiration dating period for both strengths packaged in either ~~~ bottles or unit dose blister packages.

Post-approval commitments are in accordance with FDA Stability Guidelines.

LABELING

Professional labeling - satisfactory, C. Park, 4/7/00.

STERILIZATION VALIDATION (IF APPLICABLE)

N/A

SIZE OF BIO/STABILITY BATCHES(FIRM'S SOURCE OF NDS OK?)

7.5 mg/325 mg EXP 9636 ~~~ tablets

10 mg/325 mg EXP 9635 ~~~ tablets

Drug substances are compendial.
The DMFs were found satisfactory.

PROPOSED PRODUCTION BATCH

The proposed production batch sizes are:

7.5 mg/325 mg: ~~~ tablets, ~~~

10 mg/325 mg: ~~~ tablets, ~~~

COMPONENTS AND COMPOSITION (Vol. 2.1, 3/5/98 Amendment):

| | 7.5/325 mg/tablet | 10/325 mg/tablet |
|---|---|---|
| Hydrocodone Bitartrate *USP* | 7.500 | 10.00 |
| Acetaminophen *USP* ( | | |
| Croscarmellose Sodium *NF* | | |
| Colloidal Silicon Dioxide *NF* | | |
| Stearic Acid *NF* | | |
| Microcrystalline Cellulose *NF* ( | | |
| Starch *NF* -Corn Starch) | | |
| FD&C Blue # 1 Lake | | |
| D&C Yellow # 10 Lake | | |
| Total Tablet Weight | 499.41 | 501.91 |

[redacted]

LABORATORY CONTROLS (IN-PROCESS AND FINISHED DOSAGE FORM)

In-Process and Release Tests and Specifications:

[redacted]

of the label claim with a RSD of NMT [redacted]

Bulk Drug Product Release Testing:

| Test | Specification | |
|---|---|---|
| | 7.5 mg/325 mg Tablet | 10 mg/325 mg Tablet |

| | | |
|---|---|---|
| Description | 0.3125" x 0.500", pastel blue capsule-shaped, one side debossed "960"; the opposite side debossed "ucb". | 0.3125" x 0.500", pastel yellow capsule-shaped, one side debossed "940"; the opposite side debossed "ucb". |
| Disintegration | NMT 30 min. | NMT 30 min. |
| Thickness (") | Target 0.275" ± 10% (0.248"-0.302") | Target 0.275" ± 10% (0.248"-0.302") |
| Hardness (Kg) | [redacted] | [redacted] |
| Friability (%) | NMT [redacted] | NMT [redacted] |
| Average Wt. (mg) | 499 mg ± 5% (475 mg-523 mg) | 502 mg ± 5% (477 mg-527 mg) |
| Assay (mg)<br><br>Acetaminophen<br>Hydrocodone Bitartrate | <br><br>325 mg [redacted]<br>7.5 mg [redacted] | <br><br>325 mg [redacted]<br>10 mg [redacted] |
| Content Uniformity | *USP <905>* | *USP <905>* |
| Dissolution | NLT 80% (*Q*) in 30 min. | NLT 80% (*Q*) in 30 min. |
| ID:<br><br>Acetaminophen<br><br>HC Bitartrate | <br><br>*USP* p. 752 (blue-gray color.<br>$t_R$ compares to std. | <br><br>*USP* p. 752 (blue-gray color.<br>$t_R$ compares to std. |

| | | |
|---|---|---|
| Impurities: | | |
| [redacted] | NMT [redacted] | NMT [redacted] |
| [redacted] | NMT [redacted] | NMT [redacted] |
| [redacted] | NMT [redacted] | NMT [redacted] |
| [redacted] | NMT [redacted] | NMT [redacted] |
| Other Impurities | NMT [redacted] for each. | NMT [redacted] for each. |
| Total Impurities | NMT [redacted] | NMT [redacted] |

ANDA 74-699
F/T by:
40-248div.sum V:\firmsam\watson\ltrs&rev\40-248div.sum

APPEARS THIS WAY
ON ORIGINAL

# FDA CDER EES
# ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT



Application: **ANDA 40248/000**
Stamp: **24-FEB-1997** Regulatory Due:
Applicant: **UCB PHARMA**
**1950 LAKE PARK DR**
**SMYRNA, GA 30080**

Priority:
Org Code: **600**
Action Goal:
District Goal: **24-APR-1998**
Brand Name:
Established Name: **HYDROCODONE BITARTRATE;ACETAMINOPHEN**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **7.5MG/325MG&10 MG/325M**

FDA Contacts: **T. AMES** **(HFD-640)** **301-827-5849 , Project Manager**
**J. SIMMONS** **(HFD-810)** **301-594-2570 , Team Leader**

Overall Recommendation:

**ACCEPTABLE on 23-FEB-2000 by S. FERGUSON (HFD-324) 301-827-0062**
**ACCEPTABLE on 23-DEC-1998 by J. D AMBROGIO (HFD-324) 301-827-0062**
**ACCEPTABLE on 22-MAY-1997 by J. D AMBROGIO (HFD-324) 301-827-0062**

Establishment: **1317295**
**MALLINCKRODT CHEMICAL INC**
**58 PEARL ST**
**HOBART, NY 13788**

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **14-DEC-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment: **1319618**
**MALLINCKRODT CHEMICAL INC**
**13 RAILROAD AVE**
**HOBART, NY 13788**

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **20-DEC-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE OTHER TESTER**

Establishment: **1319687**
**MALLINCKRODT CHEMICAL INC**
**18 CORNELL AVE**
**HOBART, NY 13788**

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE PACKAGER**

# ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Milestone Date **13-DEC-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

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Establishment: **1419579**
**MALLINCKRODT CHEMICAL INC**
**LOUIS LATZER DRIVE**
**GREENVILLE, IL 62246**

DMF No: —
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **13-DEC-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

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Establishment: **1940521**
**MALLINCKRODT CHEMICAL INC**
**3600 NORTH 2ND ST**
**SAINT LOUIS, MO 63147**

DMF No: —
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **23-FEB-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

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Establishment: —

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **13-DEC-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: —

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Establishment: —

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**

Responsibilities: —

# ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Last Milestone: **OC RECOMMENDATION**
Milestone Date **05-JAN-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

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# FDA CDER EES
# ESTABLISHMENT EVALUATION REQUEST
# SUMMARY REPORT

Application: **ANDA 40284/004**
Stamp: **01-SEP-2000** Regulatory Due:
Applicant:

Priority:
Org Code: **600**
Action Goal:
District Goal: **01-FEB-2001**
Brand Name:
Established Name: **ORPHENADRINE CITRATE**
Generic Name:
Dosage Form: **EXT (EXTENDED-RELEASE TABLET**
Strength: **100 MG**

FDA Contacts: **R. YU** **, Project Manager**
**D. GILL** **(HFD-623)** **301-827-5848** **, Team Leader**

Overall Recommendation:

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **06-SEP-2000**

Responsibilities:

APPEARS THIS WAY
ON ORIGINAL

# Telephone Conversation Memorandum

**ANDA: 40-248** FIRM: UCB Pharma

DRUG: Hydrocodone Bitartrate & Acetaminophen

PERSONS INVOLVED:
FDA: Jeen Min, Glen Smith, and Tao-chin Wang

Firm: Mary Alonso PHONE NUMBER: 770-437-5621

DATE: April 5, 2000 Time: 2:00 PM

The firm will update the following:
1. In process control testing:

   a. [redacted]

2. Stability Data:

   a. Update the unit dose configuration to be 60 tablets 2X3.

   b. Update the [redacted]

   c. Change the stability protocol to agree with the July 7th, 1999 amendment for the expiration dating calculation.

   d. Update the [redacted] used for the bottles.

Jeen Min, R. Ph.
Project Manager, Div Chem II, Team 9, OGD

/S/ 4/10/2000

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION
**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
*(Title 21, Code of Federal Regulations, 314 & 601)*

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY
APPLICATION NUMBER

**APPLICANT INFORMATION**

NAME OF APPLICANT
UCB PHARMA, INC.

DATE OF SUBMISSION
13 APRIL 2000

TELEPHONE NO. *(Include Area Code)*
770-437-5555

FACSIMILE (FAX) Number *(Include Area Code)*
770-437-5507

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
1950 LAKE PARK DRIVE
SMYRNA, GA 30080

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

**PRODUCT DESCRIPTION**

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*
HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP 7.5 MG/325 MG AND 10 MG/325 MG

PROPRIETARY NAME *(trade name)* IF ANY

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM:
TABLETS

STRENGTHS:
7.5 MG/325 MG AND 10 MG/325 MG

ROUTE OF ADMINISTRATION:
ORAL

(PROPOSED) INDICATION(S) FOR USE:
MODERATE TO MODERATELY SEVERE PAIN

**APPLICATION INFORMATION**

APPLICATION TYPE
(check one) ☐ NEW DRUG APPLICATION (21 CFR 314.50) ☒ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
FDA DEFICIENCIES OUTLINED IN 05 APRIL 2000 TELEPHONE CONTACT

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

**ESTABLISHMENT INFORMATION**

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

**Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)**

| This application contains the following items: *(Check all that apply)* | |
|---|---|
| X | 1. Index |
| | 2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling |
| | 3. Summary (21 CFR 314.50 (c)) |
| | 4. Chemistry section |
| X | A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2) |
| | B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request) |
| | C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2) |
| | 5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2) |
| | 6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2) |
| | 7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4)) |
| | 8. Clinical data section (e.g. 314.50 (d) (5), 21 CFR 601.2) |
| | 9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2) |
| | 10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2) |
| | 11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2) |
| | 12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2) |
| | 13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c)) |
| | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A)) |
| | 15. Establishment description (21 CFR Part 600, if applicable) |
| | 16. Debarment certification (FD&C Act 306 (k)(1)) |
| X | 17. Field copy certification (21 CFR 314.5 (k) (3)) |
| | 18. User Fee Cover Sheet (Form FDA 3397) |
| | 19. OTHER (Specify) |

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

**Warning:** a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | TYPED NAME AND TITLE | DATE |
|---|---|---|
| Mary Alonso | MARY ALONSO<br>MANAGER, REGULATORY AFFAIRS | 13 APRIL 2000 |

| ADDRESS (*Street, City, State, and ZIP Code*) | Telephone Number |
|---|---|
| 1950 LAKE PARK DRIVE<br>SMYRNA, GA 30080 | ( 770 ) 437-5621 |

**Public reporting burden for this collection of information** is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

ucb Pharma
UCB Pharma, Inc. - 1950 Lake Park Drive - Smyrna, Georgia 30080

## CERTIFICATION OF THE FIELD OFFICE COPY [§314.96]

UCB Pharma, Inc., the applicant of Abbreviated New Drug Application #40-248 Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/325 mg and 10 mg/325 mg, herewith certifies that a "true" copy of the Amendment #5 – "Telephone Amendment", dated 13 April 2000, has been sent to the appropriate field office listed below:

FOOD AND DRUG ADMINISTRATION
Atlanta District Office
60 Eighth Street, SE
Atlanta, GA 30309

Additionally, UCB Pharma, Inc. herewith certifies that a "true" copy of all amendments to this application will be provided to the field office.

Mary D. Alonso
Mary D. Alonso
Manager, Regulatory Affairs

13 April 2000
Date

UCB Pharma, Inc. - 1950 Lake Park Drive - Smyrna, Georgia 30080

## STATEMENT OF CONFIDENTIALITY

All of the data and information contained in the attached materials are privileged and confidential as trade secrets and commercial information of UCB PHARMA, INC.

Under no condition is the disclosure of any portion of the attached materials to any person or entity other than the Food and Drug Administration authorized without prior consent of the applicant.

ANDA #40-248
Hydrocodone Bitartrate and Acetaminophen Tablets, USP
7.5 mg/325 mg and 10 mg/325 mg

Amendment #5: Telephone Amendment
13 April 2000

**SPONSOR: UCB PHARMA, INC.**
**1950 LAKE PARK DRIVE**
**SMYRNA, GA 30080**

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ANDA #40-248
Hydrocodone Bitartrate and Acetaminophen Tablets, USP
7.5 mg/325 mg and 10 mg/325 mg

Amendment #5: Telephone Amendment
13 April 2000

# 1. SUMMARY OF 05 APRIL 2000 TELECONFERENCE

# AGENCY TELEPHONE CONTACT

| | |
|---|---|
| **Date of Contact:** | 05-Apr-2000 |
| **Application #/Product:** | ☒ ANDA #40-248: HcB and Acet. Tabs USP, 7.5/325 mg<br>☐ Other: |
| **Subject:** | Comments On 6 March 2000 Amendment |
| **Participants:** | **Agency** *(Name/ Title/ Division/ Agency)*<br>1. Jeen Min, Project Manager, DLPS, OPS, CDER, FDA<br>2. Tao Wang, Review Chemist, DCII, OPS, CDER, FDA<br>3. Glen Smith, Chemistry Group Leader, DCII, OPS, CDER, FDA<br>**UCB** *(Name/Title/Department)*<br>1. Mary Alonso, Manager Regulatory Affairs |

SUMMARY:

Information requested by the agency for submission in a telephone amendment:

2. Revise the in-process methods for the [redacted] and test tablets to add a paragraph at the beginning to identify which tests given in the procedure are applicable for [redacted], and which are applicable for test tablets.

3. Revise the stability protocols to update the description of the unit dose configurations to reflect cards of 6's.

4. Revise the stability protocols to modify the statement under Expiration Dating section to reflect that the expiry of the product will be based on the date of commingling of the API with the excipients in the process.

5. Provide a brief written summary of the chronology regarding the change in company name from [redacted] for the [redacted] as listed in the stability protocols.

6. The response to Question #5 c identifies the [redacted] used to manufacture the [redacted] bottles used to package the exhibit batches of the 7.5/325 tablets as [redacted] and [redacted]. The 10/325 tablets were packaged in [redacted] bottles made from [redacted] only. However, the stability summary reports submitted show that both [redacted] were used in the [redacted] bottles used to package the 10/325 tablets. Please clarify.

ANDA #40-248
Hydrocodone Bitartrate and Acetaminophen Tablets, USP
7.5 mg/325 mg and 10 mg/325 mg

Amendment #5: Telephone Amendment
13 April 2000

## 2. UCB PHARMA, INC. RESPONSE

APPEARS THIS WAY
ON ORIGINAL

Amend #5

# Redacted 3

# Page(s) of trade secret and /or confidential commercial information

This APPROVAL SUMMARY supersedes the one prepared on July 28, 1999.

(APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

---

ANDA Number: 40-248 Date of Submission: April 4, 2000

Applicant's Name: UCB Pharma, Inc.

Established Name: Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/325 mg and 10 mg/325 mg

---

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? yes

Container Labels: 100S

*Satisfactory in FPL as of August 17, 1998 submission.*

Unit Dose Blister Label:

*Satisfactory in FPL as of August 17, 1998 submission.*

Unit Dose Carton Labeling: 60s

*Satisfactory in FPL as of April 4, 2000 submission.*

Professional Package Insert Labeling (Two separate inserts for 7.5 mg/325 mg & 10 mg/325 mg strengths):

*Satisfactory as of April 4, 2000 submission.*

Revisions needed post-approval: Insert

1. Relocate "Rx only" to immediately beneath the title of the insert.
2. May delete the " ——— :... "statement under the DESCRIPTION section.

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes - The firm submitted this application based on a petition that was approved June 8, 1987 for Mikart Inc. This petition allowed for the strengths this firm has proposed. See section II in Vol. 1.1.

What is the RLD on the 356(h) form: Vicodin® 5/500

NDA Number: ANDA 88-058

NDA Drug Name: Vicodin® 5/500

NDA Firm: Knoll Laboratories

Date of Approval of NDA Insert and supplement #: Based on the labeling guidance for Hydrocodone Bitartrate and Acetaminophen Tablets, USP, Revised 4/94.

Was this approval based upon an OGD labeling guidance? Yes

Basis of Approval for the Container Labels:
Vicodin labels submitted for the side-by-side review.

Basis of Approval for the Carton Labeling:
Vicodin container labels submitted for the side-by-side review.

Other Comments:
There is no NDA for this drug product. Vicodin and Lortab are both listed as RLDs in the Orange Book.

---

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling guidance for Hydrocodone Bitartrate and Acetaminophen Tablets USP, Revised 4/94. The generic firm has proposed separate inserts for each strength. After discussion with John Grace this was found to be acceptable.

2. Other information pertaining labeling review of this product

   a. Acetaminophen information in the labeling guidance was obtained from the labeling of FIORICET WITH CODINE (NDA: 20-232), approved 7/30/92. The labeling for NDA 20-232 was last approved 5/20/98. There is no new information regarding acetaminophen in this last approved labeling as compared to the one approved 7/30/92.

   b. The RLD for this product is Vicodin® tablets (ANDA 88-058, Knoll Pharm), 5 mg/500 mg. The labeling of Viodin® was last appproved 9/10/92.

   c. According to the Orange Book, Norco® tablets, (ANDA 40-148, Watson), is a RLD for 10 mg/325 mg. The labeling for this product was last approved 2/14/97.

   d. Refer to the file folder for information on the background for the labeling guidance, scoring & dosage information.

3. Patent/ Exclusivities:

   There are no patents or exclusivities that pertain to this drug product.

4. Storage/Dispensing Conditions:

   NDA: Store at controlled room temperature 15□ - 30□ C (59□ - 86□ F). Dispense in a tight, light-resistant container as defined in the USP.

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

   USP: Preserve in tight, light-resistant containers.

5. Scoring:

   NDA: Vicodin Tablet is Scored.

   ANDA: Not Scored.

There is no NDA for this product. All of these products have mixed scoring configurations. The 5/325 Lortab tablet was not scored but the Vicodin tablet is. After discussion with John Grace the differences in the scoring configurations were found to be acceptable.

6. Product Line:

The innovator markets their product in bottles of 100s, 500s and unit dose packages of 100 (4 x 25).

The applicant proposes to market their product in bottles of 100s and unit dose packages of 60 (6 x 10)

7. The tablet imprintings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). See pages 9-019 and 9-012, Vol. 1.9.

8. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on pages 1-171 and 1-172, Vol. 1.1.

9. All manufacturing will be performed by [redacted] The labeling and finished bottle packaging will be performed by [redacted] which is a subsidiary of [redacted] The unit dose will be packaged by [redacted] All other outside firms are utilized for testing. See pages 2-010 and 011, Vol. 1.2.

10. Container/Closure:

This product will be packaged as follows:

The bottles of 100 will be packaged in [redacted] bottles with a CRC cap.

The unit dose tablets will be packaged in clear [redacted] film type blisters with foil backing. See page 4-012, Vol. 1.4.

11. The unit dose carton labeling bears "Dispense in..." statement same as the one found on the container labels.

12. The following statements in the OVERDOSAGE section will very likely be revised at a future date because of a consult response received on 5/16/97 for ANDA 88-584 (Dihydrocodeine/APAP/Caffeine) from Dr. Christina Fang (HFD-550 - DAAODP). Dr. Christina Fang suggested that these statements are unsubstantiated and thus should be deleted. However, since these statements appear in the labeling for a number of APAP containing products in the market places, OGD asked HFD-550 to reconsider Dr. Fang's recommendation. Dr. Morderchai Averbuch at HFD-550 responded that an overdose warning on acetaminophen should be included in the labeling and proposed a revised overdose section for APAP (See the copy of the e-mail from Dr. Morderchai Averbuch in the file holder for Dihydrocodeine/APAP/Caffeine for detail). This revised overdose section still does not appear in the last approved insert labeling of Fioricet with codeine Capsules (NDA 22-232/S-008, approved 5/20/98).

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

b. The toxic dose for adults for acetaminophen is 10 g.

13. The firm has changed the packaging of unit-dose from 100 (4 x25) to 60 (6 x 10). This amendment submitted 4/4/00 reflects this change of the carton and insert labeling.

Date of Review: 4/6/00 Date of Submission: 4/4/00

Primary Reviewer: Chan Park Date: /S/ 4/7/00

Team Leader: Charlie Hoppes Date:

/S/ 4/10/00

cc:

ANDA 40-248
DUP/DIVISION FILE
HFD-613/Cpark/CHoppes (no cc)
V:\FIRMSNZ\UCBPHARM\LTRS&REV\40248.APL2
Review

APPEARS THIS WAY
ON ORIGINAL

(APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

---

ANDA Number: 40-248 Date of Submission: July 7, 1999

Applicant's Name: UCB Pharma, Inc.

Established Name: Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/325 mg and 10 mg/325 mg

---

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? NO (11)- Acceptable

Container Labels: 100S

*Satisfactory in FPL as of August 17, 1998 submission.*

Unit Dose Blister Label:

*Satisfactory in FPL as of August 17, 1998 submission.*

Unit Dose Carton Labeling: 100s

*Satisfactory in FPL as of July 7, 1999 submission.*

Professional Package Insert Labeling (Two separate inserts for 7.5 mg/325 mg & 10 mg/325 mg strengths):

*Satisfactory as of August 17, 1998 submission.*

Revisions needed post-approval: Insert

1. Relocate "Rx only" to immediately beneath the title of the insert.

2. May delete the [redacted] "statement under the DESCRIPTION section.

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes - The firm submitted this application based on a petition that was approved June 8, 1987 for Mikart Inc. This petition allowed for the strengths this firm has proposed. See section II in Vol. 1.1.

What is the RLD on the 356(h) form: Vicodin® 5/500

NDA Number: ANDA 88-058

NDA Drug Name: Vicodin® 5/500

NDA Firm: Knoll Laboratories

Date of Approval of NDA Insert and supplement #: Based on the labeling guidance for Hydrocodone Bitartrate and Acetaminophen Tablets, USP, Revised 4/94.

Was this approval based upon an OGD labeling guidance? Yes

Basis of Approval for the Container Labels:
Vicodin labels submitted for the side-by-side review.

Basis of Approval for the Carton Labeling:
Vicodin container labels submitted for the side-by-side review.

Other Comments:
There is no NDA for this drug product. Vicodin and Lortab are both listed as RLD's in the Orange Book.

---

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling guidance for Hydrocodone Bitartrate and Acetaminophen Tablets USP, Revised 4/94. The generic firm has proposed separate inserts for each strength. After discussion with John Grace this was found to be acceptable.

2. Other information pertaining labeling review of this product

   a. Acetaminophen information in the labeling guidance was obtained from the labeling of FIORICET WITH CODINE (NDA: 20-232), approved 7/30/92. The labeling for NDA 20-232 was last approved 5/20/98. There is no new information regarding acetaminophen in this last approved labeling as compared to the one approved 7/30/92.

b. The RLD for this product is Vicodin® tablets (ANDA 88-058, Knoll Pharm), 5 mg/500 mg. The labeling of Viodin® was last appproved 9/10/92.

c. According to the Orange Book, Norco® tablets, (ANDA 40-148, Watson), is a RLD for 10 mg/325 mg. The labeling for this product was last approved 2/14/97.

d. Refer to the file folder for information on the background for the labeling guidance, scoring & dosage information.

3. Patent/ Exclusivities:

There are no patents or exclusivities that pertain to this drug product.

4. Storage/Dispensing Conditions:

NDA: Store at controlled room temperature 15° - 30° C (59° - 86° F). Dispense in a tight, light-resistant container as defined in the USP.

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

USP: Preserve in tight, light-resistant containers.

5. Scoring:

NDA: Vicodin Tablet is Scored.

ANDA: Not Scored.

There is no NDA for this product. All of these products have mixed scoring configurations. The 5/325 Lortab tablet was not scored but the Vicodin tablet is. After discussion with John Grace the differences in the scoring configurations were found to be acceptable.

6. Product Line:

The innovator markets their product in bottles of 100s, 500s and unit dose packages of 100 (4 x 25).

The applicant proposes to market their product in bottles of 100s and unit dose packages of 100 (4 x 25).

7. The tablet imprintings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human

Use; Final Rule, effective 9/13/95). See pages 9-019 and 9-012, Vol. 1.9.

8. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on pages 1-171 and 1-172, Vol. 1.1.

9. All manufacturing will be performed by D.M. Graham, Hobart NY. The labeling and finished bottle packaging will be performed by Pharm Tech Packaging which is a subsidiary of D.M. Graham. The unit dose will be _____. See pages 2-010 and 011, Vol. 1.2.

10. Container/Closure:

This product will be packaged as follows:

The bottles of 100 will be packaged in ___ bottles with a CRC cap.

The unit dose tablets will be packaged in clear ___ film type blisters with foil backing. See page 4-012, Vol. 1.4.

11. The unit dose carton labeling bears "Dispense in..." statement same as the one found on the container labels.

12. The following statements in the OVERDOSAGE section will very likely be revised at a future date because of a consult response received on 5/16/97 for ANDA 88-584 (Dihydrocodeine/APAP/Caffeine) from Dr. Christina Fang (HFD-550 - DAAODP). Dr. Christina Fang suggested that these statements are unsubstantiated and thus should be deleted. However, since these statements appear in the labeling for a number of APAP containing products in the market places, OGD asked HFD-550 to reconsider Dr. Fang's recommendation. Dr. Morderchai Averbuch at HFD-550 responded that an overdose warning on acetaminophen should be included in the labeling and proposed a revised overdose section for APAP (See the copy of the e-mail from Dr. Morderchai Averbuch in the file holder for Dihydrocodeine/APAP/Caffeine for detail). This revised overdose section still does not appear in the last approved insert labeling of Fioricet with codeine Capsules (NDA 22-232/S-008, approved 5/20/98).

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

b. The toxic dose for adults for acetaminophen is 10 g.

---

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Date of Review: 7/28/99 Date of Submission: 7/7/99

Primary Reviewer: Chan Park Date: /S/ 8/6/99

Team Leader: Charlie Hoppes Date: /S/ 8/6/99

cc:

ANDA 40-248
DUP/DIVISION FILE
HFD-613/Cpark/CHoppes (no cc)
V:\FIRMSNZ\UCBPHARM\LTRS&REV\40248.apl
Review

/S/ 8/6/99

APPEARS THIS WAY
ON ORIGINAL

Telephone Conversation Memorandum

ANDA: 40-248

DRUG: Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/325 mg and 10 mg/325 mg

FIRM: UCB Pharma, Inc.

PERSONS INVOLVED: Mary Alonso, UCB Pharma
Tim Ames, FDA

PHONE NUMBER: 770-437-5621
770-437-5507

DATE: March 23 1999

Background:

Firm faxed in request for clarification dated 3/16/99 (see attached). Chemistry Reviewer, Bob Permisohn provided responses (see attached).

The attached clarifications were conveyed and faxed to the firm. They accepted these clarifications and thanked the agency for this assistance.

Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem II, Branch 6, OGD

/S/

cc: ANDA 40-248
Division file (1)
HFD-617/TAmes/PHONE.189
File: V:\firmsnz\ucbpharm\telecons\phone.189

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**Page(s) of trade secret and /or confidential commercial information**

**REVIEW OF PROFESSIONAL LABELING**
**DIVISION OF LABELING AND PROGRAM SUPPORT**
**LABELING REVIEW BRANCH**

---

ANDA Number: **40-248** Date of Submission: **August 17, 1998**

Applicant's Name: **UCB Pharma, Inc.**

Established Name: **Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/325 mg and 10 mg/325 mg**

---

Labeling Deficiencies:

Unit Dose Carton Label

Please include the "Each Tablet Contains" information on the main panel as seen on the container label.

Please revise your unit dose container labels, as instructed above, and submit in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

/S/ for

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

**APPROVAL SUMMARY** (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? NO (11)

Container Labels: 100S
*Satisfactory as of August 17, 1998 submission.*
Unit Dose Blister Label:
*Satisfactory as of August 17, 1998 submission.*
Unit Dose Carton Label:

Professional Package Insert Labeling:
*Satisfactory as of August 17, 1998 submission.*
Revisions needed post-approval: Insert - Relocate **"Rx only"** to immediately beneath the title of the insert

**BASIS OF APPROVAL:**

Was this approval based upon a petition? Yes - The firm submitted this application based on a petition that was approved June 8, 1987 for Mikart Inc. This petition allowed for the strengths this firm has proposed. See section II in Vol. 1.1.

What is the RLD on the 356(h) form: Vicodin® 5/500

NDA Number: ANDA 88-058

NDA Drug Name: Vicodin® 5/500

NDA Firm: Knoll Laboratories

Date of Approval of NDA Insert and supplement #: Based on the labeling guidance for Hydrocodone Bitartrate and Acetaminophen Tablets, USP, Revised 4/94.

Was this approval based upon an OGD labeling guidance? Yes

Basis of Approval for the Container Labels:
Vicodin labels submitted for the side-by-side review.

Basis of Approval for the Carton Labeling:
Vicodin container labels submitted for the side-by-side review.

Other Comments:
There is no NDA for this drug product. Vicodin and Lortab are both listed as RLD's in the Orange Book.

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# REVIEW OF PROFESSIONAL LABELING CHECK LIST

| Established Name | Yes | No | N.A. |
|---|---|---|---|
| Different name than on acceptance to file letter? | | X | |
| Is this product a USP item? If so, USP supplement in which verification was assured. USP 23 | X | | |
| Is this name different than that used in the Orange Book? Orange Book lists Acetaminophen first. | X | | |
| **Error Prevention Analysis** | | | |
| Has the firm proposed a proprietary name? NO. | | X | |
| **Packaging** | | | |
| Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. | | X | |
| Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. | | X | |
| Does the package proposed have any safety and/or regulatory concerns? | | X | |
| Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration? | | X | |
| Is the strength and/or concentration of the product unsupported by the insert labeling? | | X | |
| Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect? | | | X |
| Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? | | X | |
| Are there any other safety concerns? | | X | |
| **Labeling** | | | |
| Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label). | | X | |
| Has applicant failed to clearly differentiate multiple product strengths? | | X | |
| Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines) | | X | |
| Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA) | | X | |
| Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed? | | X | |
| Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED? | | X | |
| Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported. | | X | |
| **Scoring:** Describe scoring configuration of RLD and applicant (page #) in the FTR | | | |
| Is the scoring configuration different than the RLD? | X | | |
| Has the firm failed to describe the scoring in the HOW SUPPLIED section? | | X | |
| **Inactive Ingredients:** (FTR: List page # in application where inactives are listed) | | | |

| | Yes | No | N.A. |
|---|---|---|---|
| Does the product contain alcohol? If so, has the accuracy of the statement been confirmed? | | X | |
| Do any of the inactives differ in concentration for this route of administration? | | X | |
| Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)? | | X | |
| Is there a discrepancy in inactives between DESCRIPTION and the composition statement? | | X | |
| Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported? | | X | |
| Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray? | | X | |
| Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) | | X | |
| **USP Issues:** (FTR: List USP/NDA/ANDA dispensing/storage recommendations) | | | |
| Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable? | | X | |
| Does USP have labeling recommendations? If any, does ANDA meet them? | | X | |
| Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? | | X | |
| Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. | | X | |
| **Bioequivalence Issues:** (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) | | | |
| Insert labeling references a food effect or a no-effect? If so, was a food study done? | | X | |
| Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why. | | X | |
| **Patent/Exclusivity Issues?:** FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. | | X | |

**FOR THE RECORD: (portions taken from previous review)**

1. Review based on the labeling guidance for Hydrocodone Bitartrate and Acetaminophen Tablets USP, Revised 4/94. The generic firm has proposed separate inserts for each strength. After discussion with John Grace this was found to be acceptable.

2. Patent/ Exclusivities:

   There are no patents or exclusivities that pertain to this drug product.

3. Storage/Dispensing Conditions:

   NDA: Store at controlled room temperature 15° - 30° C (59° - 86° F). Dispense in a tight, light-resistant container as defined in the USP.

10. Review done with red jackets - There are 11 FPL of each labeling piece in the blue jacket.

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Date of Review: 11-6-98 Date of Submission: 8-17-98

Primary Reviewer: Adolph Vezza /S/ Date: 11/16/98

Team Leader: Charlie Hoppes /S/ Date: 11/16/98

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cc:

ANDA 40-248
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/11/6/98/X:\NEW\FIRMSNZ\UCBPHARM\LTRS&REV\40248NA2.L
Review

# REVIEW OF PROFESSIONAL LABELING
# DIVISION OF LABELING AND PROGRAM SUPPORT
# LABELING REVIEW BRANCH

---

ANDA Number: **40-248** Date of Submission: **February 21, 1997**

Applicant's Name: **UCB Pharma, Inc.**

Established Name: **Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/325 mg and 10 mg/325 mg**

Labeling Deficiencies:

1. CONTAINER (100s)

   a. We encourage you to differentiate your product strengths by the use of boxing, contrasting colors or some other means.

   b. Delete the comma that follows "temperature" in the storage temperature recommendations.

   c. Please ensure that the controlled substance symbol does not obscure any text.

   d. Replace the ~ with a colon in the "Warning: May be habit forming." statement.

2. UNIT DOSE BLISTER

   a. Revise to read ~ rather than "Tablets" in the established name.

   b. Revise to read "Manufactured for UCB Pharma, Inc." (or Mfg. for...).

3. UNIT DOSE CARTON (100s - 4 x 25)

   See comments under CONTAINER.

4. INSERT

   a. PRECAUTIONS

      Pediatric Use - Revise to read as follows:

      ...in pediatric patients have not...

b. OVERDOSAGE

Signs and Symptoms, Acetaminophen - Revise to read "overdoses" rather than ——— in the last sentence of the last paragraph.

c. DOSAGE AND ADMINISTRATION

The last sentence should read "...not exceed 6 tablets." (For **both** inserts)

d. HOW SUPPLIED

i. Revise to read ——— rather than "contain" and "capsule-shaped" (add hyphen) in the first sentence.

ii. Revise the 7.5 mg/325 mg insert to read "...debossed ucb on one side and 960 on the other..." rather than "...ucb/960...". In addition revise the 10 mg/325 mg insert to read "...debossed ucb on one side and 940 on the other side...".

iii. See comment b under CONTAINER.

Please revise your unit dose blister and container labels, carton and insert labeling, as instructed above, and submit final printed container and unit dose labels, carton and insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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 of your proposed labeling with your last submission with all differences annotated and explained.

/S/

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

**APPROVAL SUMMARY** (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels:

Unit Dose Blister Label:

Unit Dose Carton Label:

Professional Package Insert Labeling:

Revisions needed post-approval:

**BASIS OF APPROVAL:**

Was this approval based upon a petition? Yes - The firm submitted this application based on a petition that was approved June 8, 1987 for Mikart Inc. This petition allowed for the strengths this firm has proposed. See section II in Vol. 1.1.

What is the RLD on the 356(h) form: Vicodin® 5/500

NDA Number: ANDA 88-058

NDA Drug Name: Vicodin® 5/500

NDA Firm: Knoll Laboratories

Date of Approval of NDA Insert and supplement #: Based on the labeling guidance for Hydrocodone Bitartrate and Acetaminophen Tablets, USP, Revised 4/94.

Was this approval based upon an OGD labeling guidance? Yes

Basis of Approval for the Container Labels:
Vicodin labels submitted for the side-by-side review.

Basis of Approval for the Carton Labeling:
Vicodin container labels submitted for the side-by-side review.

Other Comments:
There is no NDA for this drug product. Vicodin and Lortab are both listed as RLD's in the Orange Book.

| | | | |
|---|---|---|---|
| **Patent/Exclusivity Issues?:** FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. | | X | |

*******NOTES TO THE PROJECT MANAGER*******

**Please assure the NOTE TO THE CHEMIST is answered prior to faxing the labeling comments. Thanks.**

*******NOTES/QUESTIONS TO THE CHEMIST:*******

**See comment d ii. under INSERT. Do you concur?**

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**FOR THE RECORD:**

1. Review based on the labeling guidance for Hydrocodone Bitartrate and Acetaminophen Tablets USP, Revised 4/94. The generic firm has proposed separate inserts for each strength. After discussion with John Grace this was found to be acceptable.

2. Patent/ Exclusivities:

   There are no patents or exclusivities that pertain to this drug product.

3. Storage/Dispensing Conditions:

   NDA: Store at controlled room temperature 15° - 30° C (59° - 86° F). Dispense in a tight, light-resistant container as defined in the USP.

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

   USP: Preserve in tight, light-resistant containers.

4. Scoring:

   NDA: Vicodin Tablet is Scored.
   ANDA: Not Scored.

   There is no NDA for this product. All of these products have mixed scoring configurations. The 5/325 Lortab tablet was not scored but the Vicodin tablet is. After discussion with John Grace the differences in the scoring configurations were found to be acceptable.

5. Product Line:

   The innovator markets their product in bottles of 100s, 500s and unit dose packages of 100 (4 x 25).

   The applicant proposes to market their product in bottles of 100s and unit dose packages of 100 (4 x 25).

11/

E L E C T R O N I C  M A I L  M E S S A G E

Date: 01-May-1997 04:46pm EDT
From: William Rickman
RICKMAN
Dept: HFD-615 MPN2 113
Tel No: 301-594-0315 FAX 301-594-0174

TO: STANLEY E ROBERTS (ORA) ( SROBERTS@ORA.FDA.GOV @INTERNET )

Subject: RE: Methods Verification

The Office of Generic Drugs has accepted for filing the following ANDAs:

75-088 cromolyn sodium ophthalmic solution USP, 4%
King Pharm., Inc.
Att: Thomas Rogers
501 Fifth street
Bristol, TN 37620
(423)989-8001

40-248 ✓ hydrocodone bitartrate and acetaminophen tablets USP, 7.5 mg/325 mg and
] g/325 mg
[ Pharma, Inc.
Att: Patricia Fritz
1950 Lake Park Drive
Smryna, GA 30080
(770)437-5500

Establishment: [redacted]

Responsibilities: [redacted]

DMF No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **DRAFT** **15-APR-1997**
Last Comp. St.: **NONE**

---

Establishment: [redacted]

Responsibilities: [redacted]

DMF No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **DRAFT** **15-APR-1997**
Last Comp. St.: **NONE**

---

Establishment: [redacted]

Responsibilities: [redacted]

DMF No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **DRAFT** **15-APR-1997**
Last Comp. St.: **NONE**

---

Overall Recommendation:

APPEARS THIS WAY
ON ORIGINAL

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 40-248

# CORRESPONDENCE

UCB Pharma

UCB Pharma, Inc. - 1950 Lake Park Drive - Smyrna, Georgia 30080

13 April 2000

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

NEW CORRESP
NC to FA

**ANDA #40-248**
**Hydrocodone Bitartrate and Acetaminophen Tablets, USP**
**7.5 mg/325 mg and 10 mg/325 mg**

**Amendment #5**

**"Telephone Amendment"**

Dear Sir or Madam:

Reference is made to UCB Pharma's Abbreviated New Drug Application (ANDA) #40-248 for Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/325 mg and 10 mg/325 mg submitted for filing on 21 February 1997, accepted for filing on 01 May 1997, Amendment #1 filed 05 March 1998, Amendment #2 filed 17 August 1998, Amendment #3 filed 07 July 1999 and Amendment #4 filed 06 March 2000. Reference is also made to a telephone conversation with Jeen Min, Tao Wang and Glen Smith of the Food and Drug Administration on 05 April 2000 that outlined specific deficiencies within the pending application.

Herewith submitted in duplicate, is a telephone amendment to address the FDA's deficiencies outlined in the above referenced telephone conversation.

Should you have any additional questions, please feel free to contact the undersigned at (770)-437-5621 by telephone or (770)-437-5507 by facsimile.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 14 2000
OGD

Sincerely,

Mary D. Alonso

Mary D. Alonso
Manager, Regulatory Affairs

UCB Pharma

UCB Pharma, Inc. - 1950 Lake Park Drive - Smyrna, Georgia 30080

04 April, 2000

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

FDA ORIG AMENDMENT
N/FA

**ANDA #40-248**
**Hydrocodone Bitartrate and Acetaminophen Tablets, USP**
**7.5 mg/325 mg and 10 mg/325 mg**

**Amendment 5**
**Telephone Amendment**

Dear Sir or Madam,

Reference is made to UCB Pharma's Abbreviated New Drug Application (ANDA) # 40-248 for Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 7.5 mg/325 mg and 10 mg/325 mg submitted on 21 February 1997, accepted for filing on 01 May 1997. Also, reference is made to Amendments filed to the application on 05 March 1998, 17 August 1998, 07 July 1999 and 06 March 2000. Reference is also made to a FDA deficiency letter received via facsimile dated 07 of February 2000 that outlined specific deficiencies within the pending application and a subsequent teleconference on 21 March 2000 with Mr. Chan Park.

Mr. Park requested new final printed labeling (FPL) for the hospital unit dose cartons and the package inserts for the changes in blister cards from ——— and in cartons from 100 (4x25) to ———. Mr. Chan indicated that true color printer proofs of the carton would be acceptable.

Herewith submitted in duplicate, is a telephone amendment providing a side-by-side comparison of the previously submitted FPL with the revised labeling, and 12 copies of new final printed labeling for each strength.

Should you have any additional questions, please contact the undersigned at (770) 437-5559 by telephone or (770) 437-5507 by facsimile.

Sincerely,

Diane F. Vandeputte, Ph.D.
Senior Manager, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 05 2000
OGD

UCB Pharma

UCB Pharma, Inc. - 1950 Lake Park Drive - Smyrna, Georgia 30080

06 March 2000

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

NDA ORIG AMENDMENT
FA

**ANDA #40-248**
**Hydrocodone Bitartrate and Acetaminophen Tablets, USP**
**7.5 mg/325 mg and 10 mg/325 mg**

**Amendment #4**

**"Facsimile Amendment"**

Dear Sir or Madam:

Reference is made to UCB Pharma's Abbreviated New Drug Application (ANDA) #40-248 for Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/325 mg and 10 mg/325 mg submitted for filing on 21 February 1997, accepted for filing on 01 May 1997, Amendment #1 filed 05 March 1998, Amendment #2 filed 17 August 1998, and Amendment #3 filed 07 July 1999. Reference is also made to a deficiency letter received via facsimile from the Food and Drug Administration dated 07 of February 2000 that outlined specific deficiencies within the pending application.

Herewith submitted in duplicate, is a facsimile amendment to address the FDA's deficiencies outlined in the above referenced letter.

Should you have any additional questions, please feel free to contact the undersigned at (770)-437-5621 by telephone or (770)-437-5507 by facsimile.

Sincerely,

Mary D. Alonso

Mary D. Alonso
Manager, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 0 7 2000
OGD

Tel. (770) 437-5500

UCB Pharma

UCB Pharma, Inc. - 1950 Lake Park Drive - Smyrna, Georgia 30080

July 7, 1999

FPL

ORIG AMENDMENT

Ac

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

**ANDA #40-248**
**Hydrocodone Bitartrate and Acetaminophen Tablets, USP**
**7.5 mg/325 mg and 10 mg/325 mg**

**Amendment #3**

**"Major Amendment"**

Dear Sir or Madam:

Reference is made to UCB Pharma's Abbreviated New Drug Application (ANDA) #40-248 for Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/325 mg and 10 mg/325 mg submitted for filing on February 21, 1997, accepted for filing on May 1, 1997 and Amendment #1 filed March 5, 1998. Reference is also made to a deficiency letter received via facsimile from the Food and Drug Administration dated March 4, 1999 which outlined specific "major" deficiencies within the pending application.

Herewith submitted in duplicate, is a major amendment to address the FDA's deficiencies outlined in the above referenced letter.

Should you have any additional questions, please feel free to contact the undersigned at (770)-437-5621 by telephone or (770)-437-5507 by facsimile.

Sincerely,

Mary D. Alonso

Mary D. Alonso
Senior Regulatory Affairs Associate

ucb Pharma

1950 Lake Park Drive
Smyrna, Georgia 30080
Telephone: 770-437-5550
Fax: 770-437-5507

→ BoP 4/14/99 Related comments to (UV's) firm 5/14/99. No comment from reviewer (S)

# FAX

**Date** 04/9/99

Number of pages including cover sheet 5

| | | | |
|---|---|---|---|
| **To:** | **Tim Ames** | **From:** | **Mary D. Alonso** |
| Phone: | **(301)-827-5798** | Phone: | **(770)-437-5621** |
| Fax: | **(301)-443-3839** | Fax: | **(770)-437-5507** |
| CC: | **ANDA 40-248 General Correspondence** | | |

2

REMARKS:

☐ Urgent ☒ For your review ☐ Reply ASAP ☐ Please comment

Dr. Ames,

Please contact me at (770)-437-5621 if any of the pages of the transmission are illegible or if I may be of further assistance.

Sincerely,

Mary D Alonso

Mary Alonso

**If you did not receive all the pages, please contact the sender.**

ucb Pharma
UCB Pharma, Inc. - 1950 Lake Park Drive - Smyrna, Georgia 30080

April 9, 1999

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

**ANDA #40-248**
**Hydrocodone Bitartrate and Acetaminophen Tablets, USP**
**7.5 mg/325 mg and 10 mg/325 mg**

**General Correspondence**

Dear Sir or Madam:

Reference is made to UCB Pharma's Abbreviated New Drug Application (ANDA) #40-248 for Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/325 mg and 10 mg/325 mg submitted for filing on February 21, 1997; accepted on May 1, 1997 with additional amendments submitted on March 5, 1998 and August 17, 1998. Reference is also made to a second deficiency letter received on March 4, 1999 that outlined specific "major" deficiencies within the pending application and a clarification facsimile received on March 22, 1999.

We would like to thank the Office of Generic Drugs for providing the additional information on the general issues identified in the UCB letter of March 16, 1999. We recognize the considerable time and effort that went into preparing the clarification facsimile document and appreciate the timely assistance.

In addition, we acknowledge that the issues identified in the original March 16, 1999 clarification letter were not appropriately defined or properly communicated to the OGD by UCB. Therefore, in an effort to provide an accurate and comprehensive response we respectfully request additional clarification to the most recent deficiency letter. The specific issues in need of clarification are described following this cover.

Again, we appreciate this opportunity for clarification. Should you have any additional questions, please feel free to contact the undersigned at (770)-437-5621 by telephone or (770)-437-5507 by facsimile.

Sincerely,

Mary D Alonso

Mary D. Alonso
Senior Regulatory Affairs Associate

4/9/99 attachments

# Redacted 3

# Page(s) of trade secret and /or confidential commercial information

ucb Pharma
UCB Pharma, Inc. - 1950 Lake Park Drive - Smyrna, Georgia 30080

March 16, 1999

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

**ANDA #40-248**
**Hydrocodone Bitartrate and Acetaminophen Tablets, USP**
**7.5 mg/325 mg and 10 mg/325 mg**

**General Correspondence**

Dear Sir or Madam:

Reference is made to UCB Pharma's Abbreviated New Drug Application (ANDA) #40-248 for Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/325 mg and 10 mg/325 mg submitted for filing on February 21, 1997; accepted on May 1, 1997 with additional amendments submitted on March 5, 1998 and August 17, 1998. Reference is also made to a second deficiency letter received on March 4, 1999 that outlined specific "major" deficiencies within the pending application.

UCB Pharma, Inc. would like to request a meeting with the project manager and reviewing chemist to clarify the issues defined in the March 4, 1999 major deficiency letter. Specifically, the issues to be discussed include:

- [redacted] issues raised in questions 2a, 2c, and 2d.
- Total impurities calculations and assay procedures addressed in questions 2f and [redacted]
- Bulk Stability Protocol issues as presented in question 3a.

Once these issues are clarified, the response to the March 4, 1999 deficiency letter will be submitted promptly to the agency.

In addition, UCB would like to discuss the one year review time taken to evaluate the March 5, 1998 amendment to this application. As early as September 23, 1998, UCB was informed in a telephone conversation with Tim Ames that the review of the application was closing and that a letter could be expected within 10 to 15 working days. Again, on December 16, 1998 UCB was informed in a telephone conversation with Tim Ames that the review on the application was completed and a letter would be issued within 10 to 15 working days. Yet, the actual letter was not received until March 4, 1999, exactly one year

from the date submitted. UCB is concerned the one year review of the amendment was excessive. Based on this situation, UCB would like to request that the amendment in response to the March 4, 1999 deficiency letter receive an expedited review.

Should you have any additional questions, please feel free to contact the undersigned at (770)-437-5621 by telephone or (770)-437-5507 by facsimile.

Sincerely,

Mary D. Alonso

Mary D. Alonso
Senior Regulatory Affairs Associate

ucb Pharma
UCB Pharma, Inc. - 1950 Lake Park Drive - Smyrna, Georgia 30080

August 17, 1998

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

NDA ORIG AMENDMENT

**ANDA # 40-248**
**Hydrocodone Bitartrate and Acetaminophen Tablets, USP**
**7.5 mg/325 mg and 10 mg/325 mg**

**Amendment # 2**

Dear Sir or Madam,

Reference is made to UCB Pharma's Abbreviated New Drug Application (ANDA) # 40-248 for Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 7.5 mg/325 mg and 10 mg/325 mg submitted on February 21, 1997 and accepted for filing on May 1, 1997. Reference is also made to a deficiency letter received via facsimile from the Food and Drug Administration dated September 29, 1997, which outlined specific "major" deficiencies within the pending application. In addition, reference is made to Amendment # 1, submitted March 5, 1998, explaining that Final Printed Labeling would be submitted at a later date due to additional changes required by the newly released Guidance on the Implementation of the FDA Modernization Act of 1997.

Herewith submitted in duplicate, is an amendment providing the following:

- UCB Pharma, Inc's response to the labeling deficiencies
- a side-by-side comparison of the FPL with the draft labeling
- 12 copies of Final Printed Labeling for each strength

Should you have any additional questions concerning the Final Printed Labeling, please contact the undersigned at (770) 437-5559 by telephone or (770) 437-5507 by facsimile.

Sincerely,

Diane F. Vandeputte, Ph.D.
Manager, Regulatory Affairs

RECEIVED
AUG 18 1998
GENERIC DRUGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Southeast Regional Laboratory

60 8th Street, N.E.
Atlanta, Georgia 30309

May 15, 1997

Ms. Patricia Fritz
UCB Pharmaceuticals, Inc.
1950 Lake Park Drive
Smyrna, GA 30080

Dear Ms. Fritz:

The US Food & Drug Administration (FDA) will be performing method verification studies on ANDA [redacted] hydrocodone bitartrate and acetaminophen tablets USP (7.5mg/325mg and 10mg/325mg). With your cooperation, we can promptly complete this portion of our evaluation of your application.

In order to perform the necessary testing, please provide us with a sample from the reserve portion of the lot used to establish the bioequivalence or bioavailability of your product. Ideally, this sample should be within the proposed expiration date. If it is beyond this date and there is another pre-approval batch within the expiration, send that instead. If no other batch is available, then the out-of-expiration batch is acceptable. If, however, a batch not in the ANDA is used, the batch record and Certificate of Analysis must be submitted as an unsolicited amendment to the application.

The sample should consist of the following: 1) three hundred (300) dosage units for each, 2) a copy of your worksheet for the analysis of the same lot with calculations, results and associated spectra and chromatograms.

Please forward these materials within ten (10) days of receipt of this letter via express or overnight mail to:

Stanley E. Roberts
US Food & Drug Administration
60 Eight Street, NE
Atlanta, GA 30309

APPEARS THIS WAY
ON ORIGINAL

In addition, in connection with other work that needs to be completed regarding your application, please include in your sample package a letter indicating whether an in-vivo or in-vitro bioequivalence study was performed. If so, please provide the facility name and address. If no study was done, include a letter so stating nevertheless.

Thank you in advance for you cooperation. Please do not hesitate to call or fax if you have questions. You may contact me directly by telephone at (404) 347-2131 ext. 5217, or by fax at (404) 347-4225.

Sincerely,

Jose H. Lebron
NDA/ANDA Team Leader

cc: William Rickman
Review Chemist (HFD-615)

ANDA 40-248

UCB Pharma, Inc.
Attention: Patricia A. Fritz
1950 Lake Park Drive
Smyma, GA 30080

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.

NAME OF DRUG: Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/325 mg and 10 mg/325 mg

DATE OF APPLICATION: February 21, 1997

DATE OF RECEIPT: February 24, 1997

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:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,

/S/

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

ucb Pharma
UCB Pharma, Inc. - 1950 Lake Park Drive - Smyrna, Georgia 30080

February 21, 1997

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

**Abbreviated New Drug Application**
**for**
**Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5/325**
**Hydrocodone Bitartrate and Acetaminophen Tablets, USP 10/325**

Dear Sir or Madam:

As provided under 21 CFR 314.54, UCB Pharma, Inc. is filing this ANDA for approval to market Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5/325 and Hydrocodone Bitartrate and Acetaminophen Tablets, USP 10/325.

This ANDA is being submitted based on an approved ANDA suitability petition under 21 CFR 314.93. The petition was filed under Section 505 (j) (2) (c) of the Act where the Agency has determined that the referenced product is suitable for submission as an ANDA. This petition filed as a new strength was approved on June 8, 1987 under Docket number 87 P-0129/CP. The petition states these products as being similar and related to the currently marketed Vicodin® brand tablet, containing 5 mg of hydrocodone bitartrate and 500 mg of acetaminophen.

The therapeutic equivalence rating of AA on various strengths of Acetaminophen and Hydrocodone Bitartrate Oral Tablets can be referenced in the 16th Edition of the 1996 Approved Drug Products with Therapeutic Equivalence Evaluations, pages 3 and 4. The dissolution assays of Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5/325 and Hydrocodone Bitartrate and Acetaminophen Tablets, USP 10/325 (USP 23, Apparatus 2 [paddles], 50 rpm, 900 mL, pH 5.8 phosphate buffer) demonstrate that the dissolution requirements are met according to the dissolution specifications listed in the USP 23 monograph for Hydrocodone Bitartrate and Acetaminophen Tablets.



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