CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

40-084

Generic Name: Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5/500 mg and 7.5/750 mg

Sponsor: King Pharmaceuticals, Inc.

Approval Date: June 1, 1995

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
40-084

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-084

APPROVAL LETTER

ANDA 40-084

JUN 1 1995

King Pharmaceuticals, Inc.
Attention: John M. Gregory
501 Fifth Street
Bristol, TN 37620

Dear Sir:

This is in reference to your abbreviated new drug application dated April 27, 1993, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for [redacted] (Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/500 mg and 7.5 mg/750 mg, respectively).

Reference is also made to your amendments dated August 31, 1993, March 31, and May 1, 1995 and correspondence dated April 28, 1995.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your [redacted] (Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/500 mg and 7.5 mg/750 mg, respectively) to be bioequivalent and, therefore, therapeutically equivalent to those of the listed drug (Vicodin® and Vicodin® ES, 5 mg/500 mg and 7.5 mg/750 mg, respectively, of Knoll Pharmaceutical Company). Your dissolution testing should be incorporated into the stability and quality control programs using the same method proposed in your application.

Under 21 CFR 314.70, 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. 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-240). 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, at the time of their initial use, to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253.

Sincerely yours,

/S/ 6/1/95

Douglas L. Sporn
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-084

Final Printed Labeling

FINAL PRINT LABELS
Hydrocodone Bitartrate and Acetaminophen Tablets, USP
5 mg./ 500 mg.

Usual Dosage: See package insert for complete dosage recommendations.

Caution: Federal law prohibits dispensing without prescription.

NDC 60793-023-01
HYDROCODONE BITARTRATE
and ACETAMINOPHEN
TABLETS, USP CIII
(Warning: May be habit forming.)
5 mg/500 mg

Each Tablet Contains:
Hydrocodone Bitartrate .... 5 mg
(Warning: May be habit forming.)
Acetaminophen .... 500 mg

100 Tablets

KING PHARMACEUTICALS

Manufactured By:
King Pharmaceuticals, Inc.
Bristol, TN 37620

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

932027

3/95

APPROVED JUN 1995

Usual Dosage: See package insert for complete dosage recommendations.
Caution: Federal law prohibits dispensing without prescription.
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TABLETS, USP CIII
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932027
3/95
APPROVED JUN 1995

FINAL PRINT LABELS
Hydrocodone Bitartrate and Acetaminophen Tablets, USP
7.5 mg./ 750 mg.

Usual Dosage: See package insert for complete dosage recommendations.

Caution: Federal law prohibits dispensing without prescription.

NDC 60793-024-01
HYDROCODONE BITARTRATE and ACETAMINOPHEN TABLETS, USP (CIII)
(Warning: May be habit forming.)
7.5 mg/750 mg

Each Tablet Contains:
Hydrocodone Bitartrate . . . 7.5 mg
(Warning: May be habit forming.)
Acetaminophen . . . . 750 mg

100 Tablets

KING PHARMACEUTICALS

Manufactured By:
King Pharmaceuticals, Inc.
Bristol, TN 37620

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

932033

3/95

Usual Dosage: See package insert for complete dosage recommendations.

Caution: Federal law prohibits dispensing without prescription.

NDC 60793-024-01
HYDROCODONE BITARTRATE and ACETAMINOPHEN TABLETS, USP (CIII)
(Warning: May be habit forming.)
7.5 mg/750 mg

Each Tablet Contains:
Hydrocodone Bitartrate . . . 7.5 mg
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Dispense in a tight, light-resistant container as defined in USP.

932033

3/95

HYDROCODONE BITARTRATE* AND ACETAMINOPHEN TABLETS, USP 5/500 and 7.5/750

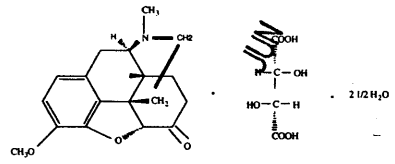
C III

*Warning: May be habit forming

DESCRIPTION

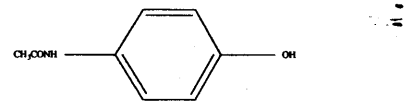
Hydrocodone bitartrate and Acetaminophen Tablets are supplied in tablet form for oral administration.

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



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

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



$C_8H_9NO_2$ MW = 151.16

Each HYDROCODONE BITARTRATE* AND ACETAMINOPHEN, USP 5/500 tablet contains:
Hydrocodone Bitartrate, USP.....5 mg
(*Warning: May be habit forming)
Acetaminophen, USP.....500 mg
In addition each HYDROCODONE BITARTRATE* AND ACETAMINOPHEN, USP 5/500 tablet contains the following inactive ingredients: Magnesium Stearate NF, Pregelatinized Starch NF, (Corn) Starch NF, Stearic Acid NF, D & C Yellow No. 10 Lake 17% and Purified Water USP.

Each HYDROCODONE BITARTRATE* AND ACETAMINOPHEN, USP 7.5/750 tablet contains:
Hydrocodone Bitartrate, USP.....7.5 mg
(*Warning: May be habit forming)
Acetaminophen, USP.....750 mg
In addition each HYDROCODONE BITARTRATE* AND ACETAMINOPHEN, USP 7.5/750 tablet contains the following inactive ingredients: Magnesium Stearate NF, Pregelatinized Starch NF, (Corn) Starch NF, Stearic Acid NF, FD&C Blue No. 1 Lake 12% and Purified Water USP.

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 pre-existing 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.

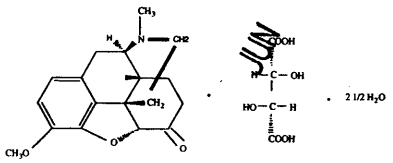
Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

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

administration.

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



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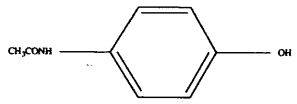

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Each HYDROCODONE BITARTRATE* AND ACETAMINOPHEN, USP 7.5/750 tablet contains:
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(*Warning: May be habit forming)
Acetaminophen, USP.....750 mg
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See 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.

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INDICATIONS AND USAGE

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CONTRAINDICATIONS

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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.

Revised 3/95

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 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 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.

HYDROCODONE BITARTRATE* AND ACETAMINOPHEN TABLETS, USP 5/500: The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets.

HYDROCODONE BITARTRATE* AND ACETAMINOPHEN TABLETS, USP 7.5/750: The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 5 tablets.

HOW SUPPLIED

Each HYDROCODONE BITARTRATE* AND ACETAMINOPHEN, USP 5/500 tablet contains Hydrocodone Bitartrate 5 mg (***Warning:** May be habit forming) and Acetaminophen 500 mg. It is available as a light yellow, round bisected tablet debossed with a KPI 12 identification number.

Bottles of 100..... NDC No. 60793-023-01

Each HYDROCODONE BITARTRATE* AND ACETAMINOPHEN, USP 7.5/750 tablet contains Hydrocodone Bitartrate 7.5 mg (***Warning:** May be habit forming) and Acetaminophen 750 mg. It is available as a light blue, round bisected tablet debossed with a KPI 2 identification number.

Bottles of 100..... NDC No.60793-024-01

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

A Schedule III Narcotic.

Federal (USA) law prohibits dispensing without prescription.

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 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 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.

HYDROCODONE BITARTRATE* AND ACETAMINOPHEN TABLETS, USP 5/500: The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets.

HYDROCODONE BITARTRATE* AND ACETAMINOPHEN TABLETS, USP 7.5/750: The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 5 tablets.

HOW SUPPLIED

Each HYDROCODONE BITARTRATE* AND ACETAMINOPHEN, USP 5/500 tablet contains Hydrocodone Bitartrate 5 mg (***Warning:** May be habit forming) and Acetaminophen 500 mg. It is available as a light yellow, round bisected tablet debossed with a KPI 12 identification number.

Bottles of 100..... NDC No. 60793-023-01

Each HYDROCODONE BITARTRATE* AND ACETAMINOPHEN, USP 7.5/750 tablet contains Hydrocodone Bitartrate 7.5 mg (***Warning:** May be habit forming) and Acetaminophen 750 mg. It is available as a light blue, round bisected tablet debossed with a KPI 2 identification number.

Bottles of 100..... NDC No.60793-024-01

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

A Schedule III Narcotic.

Federal (USA) law prohibits dispensing without prescription.

KING PHARMACEUTICALS

Manufactured by:
King Pharmaceuticals
Bristol, Tennessee 37620

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-084

CHEMISTRY REVIEW(S)

1. **CHEMIST'S REVIEW NO.**: 1

2. **ANDA #**: 40-084

3. **NAME AND ADDRESS OF APPLICANT**:

RSR Laboratories, Inc.
501 Fifth Street
Bristol, TN 37620

4. **LEGAL BASIS FOR ANDA SUBMISSION**:Innovator drugs - Anexsia® (5 mg/500 mg), Beecham; and Vicodin ES® (7.5 mg/750 mg), Knoll. No patents or exclusivity remaining. Therapeutic Equivalence Category AA.

5. **SUPPLEMENTS(s)**:N/A

6. **PROPRIETARY NAME**: [redacted]

7. **NONPROPRIETARY NAME**: Hydrocodone Bitartrate and Acetaminophen Tablet

8. **SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Firm: 4.27.93 - Original submission **Subject of this review.**

10. **PHARMACOLOGICAL CATEGORY**: Analgesic

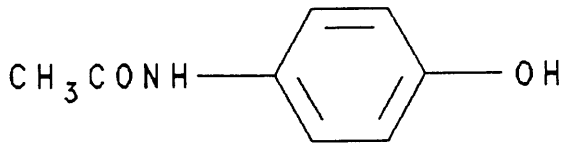
11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:See Review Element# 37, for LOA see text.

13. **DOSAGE FORM**: Tablets

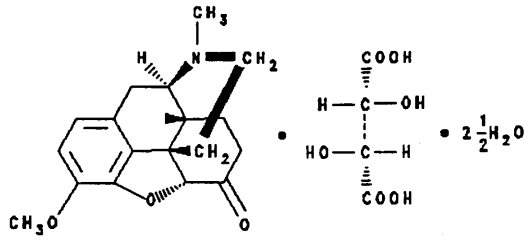
14. **POTENCY**: 5 mg /500 mg and 7.5 mg/750 mg

15. **CHEMICAL NAME AND STRUCTURE**:



Acetaminophen USP

$C_8H_9NO_3$; M.W. = 151.16
4'-Hydroxyacetanilide. CAS [103-90-2]



Hydrocodone Bitartrate USP

$C_{18}H_{21}NO_3 . C_4H_6O_6 . 2\frac{1}{2}H_2O$

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

16. **RECORDS AND REPORTS**:Labeling review, K. Roberts, 6.11.93, Not satisfactory

17. **COMMENTS**:

18. **CONCLUSIONS AND RECOMMENDATIONS**: The application has chemistry and labeling deficiencies and is NOT APPROVABLE.

19. **REVIEWER: U. V. Venkataram** **DATE COMPLETED:** 7.28.93

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1. **CHEMIST'S REVIEW NO.:** 2

2. **ANDA #:** 40-084

3. **NAME AND ADDRESS OF APPLICANT:**

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, TN 37620

4. **LEGAL BASIS FOR ANDA SUBMISSION:** Innovator drugs - Anexsia® (5 mg/500 mg), Beecham; and Vicodin ES® (7.5 mg/750 mg), Knoll. No patents or exclusivity remaining. Therapeutic Equivalence Category AA.

5. **SUPPLEMENTS(s):** N/A

6. **PROPRIETARY NAME:** [redacted]

7. **NONPROPRIETARY NAME:** Hydrocodone Bitartrate and Acetaminophen Tablet

8. **SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Firm: 4.27.93 - Original submission
2.22.94 - Amendment **Subject of this review.**

FDA: 8.17.93 - NA letter

10. **PHARMACOLOGICAL CATEGORY:** Analgesic

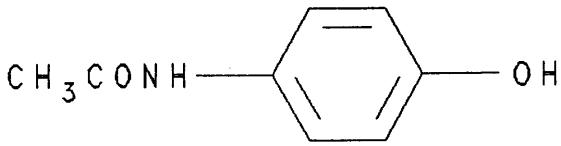
11. **Rx or OTC:** Rx

12. **RELATED IND/NDA/DMF(s):** See Review Element# 37, for LOA see text.

13. **DOSAGE FORM:** Tablets

14. **POTENCIES:** 5 mg /500 mg and 7.5 mg/750 mg

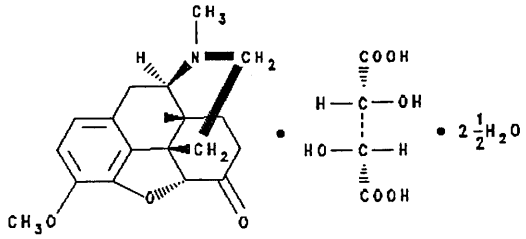
5. **CHEMICAL NAME AND STRUCTURE:**



Acetaminophen USP

$C_8H_9NO_3$; M.W. = 151.16

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



Hydrocodone Bitartrate USP

$C_{18}H_{21}NO_3 . C_4H_6O_6 . 2\frac{1}{2}H_2O$

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

16. **RECORDS AND REPORTS**:Labeling review, K. Roberts, 6.11.93, Not Satisfactory; Not Satisfactory, A. Vezza, 5.13.94

17. **COMMENTS**:

[redacted]

18. **CONCLUSIONS AND RECOMMENDATIONS**: The application has chemistry and labeling deficiencies and is NOT APPROVABLE.

19. **REVIEWER: U. V. Venkataram** **DATE COMPLETED:** 7.6.94

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OFFICE OF GENERIC DRUGS

DIVISION OF CHEMISTRY II

ANDA REVIEW

1. **CHEMIST'S REVIEW NO.**: 3

2. **ANDA #**: 40-084

3. **NAME AND ADDRESS OF APPLICANT**:

   King Pharmaceuticals, Inc.
   501 Fifth Street
   Bristol, TN 37620

4. **LEGAL BASIS FOR ANDA SUBMISSION**:Innovator drugs - Anexsia® (5 mg/500 mg), Beecham; and Vicodin ES® (7.5 mg/750 mg), Knoll. No patents or exclusivity remaining. Therapeutic Equivalence Category AA.

5. **SUPPLEMENTS(s)**:N/A

6. **PROPRIETARY NAME**: [redacted]

7. **NONPROPRIETARY NAME**: Hydrocodone Bitartrate and Acetaminophen Tablet

8. **SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

   Firm: 4.27.93 - Original submission
   2.22.94 - Amendment
   10.6.94 - Amendment **Subject of this review.**

   FDA: 8.17.93 - NA letter
   8.2.94 - NA letter

10. **PHARMACOLOGICAL CATEGORY**: Analgesic

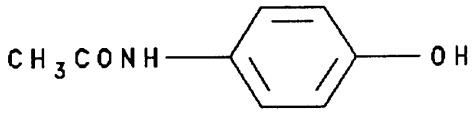
11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:See Review Element# 37, for LOA see text.

13. **DOSAGE FORM**: Tablets

14. **POTENCIES**: 5 mg /500 mg and 7.5 mg/750 mg

. **CHEMICAL NAME AND STRUCTURE:**

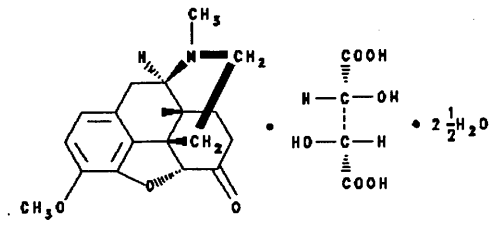


Acetaminophen $C_8H_9NO_2$

Acetaminophen USP

$C_8H_9NO_3$; M.W. = 151.16

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



Hydrocodone Bitartrate $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$

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

. **RECORDS AND REPORTS**:Labeling review, K. Roberts, 6.11.93, Not Satisfactory; Not Satisfactory, A. Vezza, 5.13.94; not satisfactory, A. Vezza, 1.18.95

17. **COMMENTS**:

18. **CONCLUSIONS AND RECOMMENDATIONS**: The application has chemistry and labeling deficiencies and is NOT APPROVABLE.

19. **REVIEWER: U. V. Venkataram** **DATE COMPLETED:** 2.2.95

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OFFICE OF GENERIC DRUGS

DIVISION OF CHEMISTRY II

ANDA REVIEW

1. **CHEMIST'S REVIEW NO.**: 4

2. **ANDA #**: 40-084

3. **NAME AND ADDRESS OF APPLICANT**:

   King Pharmaceuticals, Inc.
   501 Fifth Street
   Bristol, TN 37620

4. **LEGAL BASIS FOR ANDA SUBMISSION**:Innovator drugs - Anexsia® (5 mg/500 mg), Beecham; and Vicodin ES® (7.5 mg/750 mg), Knoll. No patents or exclusivity remaining. Therapeutic Equivalence Category AA.

5. **SUPPLEMENTS(s)**:N/A

6. **PROPRIETARY NAMES**: [redacted]

7. **NONPROPRIETARY NAME**: Hydrocodone Bitartrate and Acetaminophen Tablet

8. **SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

   Firm: 4.27.93 - Original submission
   2.22.94 - Amendment
   10.6.94 - Amendment
   3.31.95 - Amendment **Subject of this review.**
   4.28.95 & 5.1.95 - Telephone amendments **Subject of this review**

   FDA: 8.17.93 - NA letter
   8.2.94 - NA letter
   2.27.95 - NA letter
   4.27.95 & 5.1.95 - Telephone request (TAmes)

10. **PHARMACOLOGICAL CATEGORY**: Analgesic

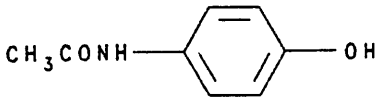
11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:See Review Element# 37, for LOAs see text.

13. **DOSAGE FORM**: Tablets

14. **POTENCIES**: 5 mg /500 mg and 7.5 mg/750 mg

15. **CHEMICAL NAME AND STRUCTURE:**

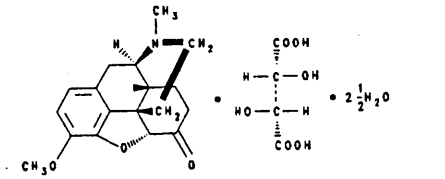


Acetaminophen $C_8H_9NO_2$

Acetaminophen USP

$C_8H_9NO_3$; M.W. = 151.16

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



Hydrocodone Bitartrate $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$

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

16. **RECORDS AND REPORTS**:Labeling review, K. Roberts, 6.11.93, Not Satisfactory; Not Satisfactory, A. Vezza, 5.13.94; not satisfactory, A. Vezza, 1.18.95; work sheet, A Vezza/A.Payne, 4.21.95 Acceptable.

17. **COMMENTS**:

18. **CONCLUSIONS AND RECOMMENDATIONS**: The application as amended is satisfactory with regard to CMC and labeling sections and can be APPROVED.

19. **REVIEWER: U. V. Venkataram** **DATE COMPLETED:** 5.22.95 ; 5.26.95

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-084

BIOEQUIVALENCE REVIEW

SEP 13 1993

Hydrocodone Bitartrate/Acetaminophen
5 mg/500 mg and 7.5 mg/750 mg Tablets
ANDA #40-084
Reviewer: YC Huang
40084W.493

RSR Laboratories, Inc.
Bristol, TN
Submission date:
April 27, 1993
August 31, 1993

Review of Waiver Request

The firm requested a waiver of the in vivo bioequivalence study requirements for its [redacted] (hydrocodone bitartrate/acetaminophen) Tablets, 5 mg/500 mg and [redacted] (hydrocodone bitartrate/acetaminophen) Tablets, 7.5 mg/750 mg. The firm cited Anexia (hydrocodone bitartrate/acetaminophen) Tablets, 5 mg/500 mg [Beecham] and Vicodin ES (hydrocodone bitartrate/acetaminophen) Tablets, 7.5 mg/750 mg [Knoll] as the reference drug products. After receiving the advice from the Division (on selection of the reference product for the 5 mg/500 mg strength and the need for multiple time points on the dissolution data), the firm submitted an amendment on August 31, 1993 citing Knoll's Vicodin as the reference product for the 5 mg/500 mg strength. The amendment contains the dissolution data (10, 20, and 30 minutes) comparing the test products with those of the marketed products, Vicodin and Vicodin ES (both are manufactured by Knoll).

Composition of the test products

Ingredient	5 mg/500mg tablet (amount per tablet)	7.5 mg/750 mg tablet (amount per tablet)
Hydrocodone Bitartrate USP	0.005 g	0.0075 g
Acetaminophen USP	0.500 g	0.750 g
Pregelatinized Starch NF	[redacted]	[redacted]
Starch NF	[redacted]	[redacted]
Stearic Acid NF	[redacted]	[redacted]
Magnesium Stearate NF	[redacted]	[redacted]
D & C Yellow No.10 Lake 17%	[redacted]	[redacted]
FD&C Blue #1 Aluminum Lake 12%	[redacted]	[redacted]
Purified Water USP	[redacted]	[redacted]
TOTAL	0.635000 g	0.925000 g

[redacted]

Comparative dissolution testing The results of the comparative dissolution testing are summarized in Table 1.

Comments

1. The test products meet the criteria for waiver of in vivo bioequivalence requirements set forth in CFR 320.22(c) as follows:

a. The drug product, hydrocodone bitartrate/acetaminophen, is listed as AA drug in the Orange Book. Products coded as AA contain active ingredients and dosage forms that are not regarded as presenting either actual or potential bioequivalence problems.

b. The in vitro dissolution data for the test products are acceptable.

Recommendation

1. The Division of Bioequivalence agrees that the information submitted by RSR Laboratories demonstrates that its hydrocodone bitartrate/acetaminophen, 5 mg/500 mg and 7.5 mg/750 mg tablets fall under 21 CFR 320.22 (c) of the bioavailability/bioequivalence regulations. The waiver of the in vivo bioequivalence study requirements for the test products is granted.

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 pH 5.8 phosphate buffer using USP XXII apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than — (Q) each of the labeled amounts of acetaminophen and hydrocodone bitartrate are dissolved in 30 minutes.

/S/

Yih-Chain Huang, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMhatre
FT INITIALED RMhatre

/S/ Date 9/10/93

cc: ANDA #40-084 (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-658 (Mhatre, Huang), Drug File, Division File

YCHuang/09-08-93/40084W.493

Table 1. In Vitro Dissolution Testing

Drug (Generic Name): Hydrocodone Bitartrate/Acetaminophen
Dose Strength: 5 mg/500 mg and 7.5 mg/750 mg
ANDA No.: 40-084
Firm:RSR Laboratories
Submission Date: April 27, 1993 and August 31, 1993
File Name:40084W.493

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: pH 5.8 Phosphate buffer, Volume: 900 mL
Specifications: NLT — in 30 minutes
Reference Drug: Knoll's Vicodin and Vicodin ES Tablets
Assay Methodology: [redacted]

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product (Lot #PLT-55) 5 mg/500 mg Hydrocodone Bitartrate/acetaminophen ** Acetaminophen data **			Reference Product (Knoll) Lot # 10760363 (Vicodin) 5 mg/500 mg ** Acetaminophen data**		
	Mean %	Range	%CV	Mean %	Range	%CV
10	82.2	[redacted]	3.7	73.6	[redacted]	9.6
20	93.8	[redacted]	3.6	79.2	[redacted]	5.9
30	94.6	[redacted]	3.7	81.8	[redacted]	4.8

** Hydrocodone bitartrate data **

Sampling Times (Minutes)	Test Product Lot # (see above) Strength(mg)			Reference Product Lot # (see above) Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
10	91.0	[redacted]	1.1	89.6	[redacted]	6.7
20	93.4	[redacted]	1.2	95.4	[redacted]	2.6
30	93.2	[redacted]	1.2	98.4	[redacted]	3.2

Sampling Times (Minutes)	Test Product (Lot #PLT-58) 7.5 mg/750 mg Hydrocodone bitartrate/Acetaminophen ** Acetaminophen data **			Reference Product (Knoll) Lot #10770771 (Vicodin ES) Hydrocodone bitartrate/ Acetaminophen, 7.5 mg/750mg ** Acetaminophen data **		
	Mean %	Range	%CV	Mean %	Range	%CV
10	82.6		2.5	93.4		3.3
20	92.2		3.2	99.7		2.0
30	97.0		1.4	99.0		2.1

** Hydrocodone bitartrate data **

Sampling Times (Minutes)	Test Product Lot # (see above) Strength(mg)			Reference Product Lot # (see above) Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
10	94.9		1.3	94.6		1.6
20	96.9		1.3	96.4		1.5
30	97.4		1.5	96.4		1.5

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OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 40-084/Supplement SPONSOR: KING
DRUG: HYDROCODONE BITARTRATE/ACETAMINOPHEN
DOSAGE FORM: TABLET
STRENGTHS/(s): 10 mg/660 mg
TYPE OF STUDY: N/A

WAIVER/DISSOLUTION:

ANDA #40-084 approved on 6/1/95 for two strengths of APAP/HCB tablets: 500 mg/5 mg and 750 mg/7.5 mg; both rated AA.
Supplement to ANDA #40-084 for new strength 660 mg/10 mg
Based on approved Suitability Petition (10/27/92); RLD designated in Petition was Vicodin® ES (APAP/HCB 750 mg/7.5 mg, Knoll) which is rated AA
Sponsor requested waiver of in vivo BE requirements based on dissolution testing results
Results of dissolution testing: Sponsor used USP method, but reported results for 18 tablets. Since the minimum amount dissolved for either component from any tablet was ——, at 10 minutes, the results were accepted (specifications are NLT —%/30 min for both AI).
Conclusion: Application is acceptable under 21 CFR 320.22(c).

PRIMARY REVIEWER: James D. Henderson, Ph.D. BRANCH: II
INITIAL: /S/ DATE 12-11-95

BRANCH CHIEF: Rabindra N. Patnaik, Ph.D BRANCH: II
INITIAL: /S/ DATE 12/11/95

DIRECTOR, DIVISION OF BIOEQUIVALENCE:
Keith K. Chan,
INITIAL: /S/ DATE 12/12/95

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-084

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 31, 1995

FROM: Yana Mille
Yana Mille, Acting Director Division of Labeling and Program Support

SUBJECT: ANDA 40-084, Hydrocodone Bitartrate and Acetaminophen Tablets, Reference Listed Drug

TO: The File

On April 27, 1993, RSR Laboratories submitted an application for Hydrocodone Bitartrate and Acetaminophen Tablets citing two reference listed drugs:

5 mg/500 mg - Anexsia (Beecham)
7.5 mg/500 mg - Vicodin ES (Knoll)

At the time they submitted the application, the Orange Book did not designate a reference listed drug for the product so the application was filed without comment.

At some time between May 19, 1993, and September 13, 1993, the Office of Generic Drugs became aware the firm had cited the incorrect reference listed drugs. According to the September 13, 1993, Bio review of waiver request, the firm was advised that the reference listed drug for the 5 mg/500 mg product was Vicodin (Knoll). Indeed, on August 31, 1993, RSR submitted correspondence to the application comparing dissolution data of the 5 mg/500 mg product to the appropriate reference listed drug, Vicodin.

However, the 356h's submitted by the RSR and subsequently King Pharmaceuticals Inc. (ownership of the application was transferred on February 17, 1994) continued to reflect Anexsia as the reference listed drug for the 5 mg/500 mg product. This was noticed while the application was undergoing office level review. It was determined that the firm needed to submit new 505(j) information prior to approval. In addition, the firm also submitted a revised 356(h) which should ensure that future submissions cite the correct reference listed drug.

In summary, the firm now has cited the correct reference listed drug, has submitted the necessary 505(j) information, the dissolution data for this AA drug is based on the correct reference listed drug (RLD) according to the bio review and the labeling will not be affected by the change in RLD.

KING PHARMACEUTICALS
501 Fifth Street
Bristol, Tennessee 37620

Fax Cover Sheet

DATE:	May 31, 1995	TIME:	9:14 AM
TO:	Mr. Peter Rickman FDA / OGD	PHONE: FAX:	301-594-0315 301-594-1174
FROM:	Tom Rogers	PHONE: FAX:	615-989-6237 615-989-6113
RE:	ANDA 40-084 Requested Information		

Number of pages including cover sheet: 3

Message

Following this cover is a revised Form 356h listing Vicodin as the reference listed drug for the 5/500 strength tablet. This revised form is dated 3/31/95, and the contents section is marked similarly to the 356h submitted in our 3/31/95 amendment to the application. This form was dated in this fashion so that you could replace the most recently submitted Form 356h if you so desire. Please call if any further information is required. Thank you for your assitance.

APPEARS THIS WAY
ON ORIGINAL

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

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: December 31, 1992
See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314).*

NAME OF APPLICANT
King Pharmaceuticals, Inc.

DATE OF SUBMISSION
March 31, 1995

ADDRESS *(Number, Street, City, State and Zip Code)*
501 Fifth Street
Bristol, Tennessee 37620

TELEPHONE NO. *(Include Area Code)*
(615) 989-6200

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)*
ANDA #40-084

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*
Hydrocodone Bitartrate and Acetaminophen, USP

PROPRIETARY NAME *(If any)*
Hydrocodone Bitartrate and Acetaminophen Tablets, USP

CODE NAME *(If any)*

CHEMICAL NAME
4,5a-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5); 4, hydroxyacetanilide

DOSAGE FORM
Tablets

ROUTE OF ADMINISTRATION
Oral

STRENGTH(S)
5.0 mg/500 mg
7.5 mg/750 mg

PROPOSED INDICATIONS FOR USE
For relief of moderate to moderately severe pain.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314.420)* REFERRED TO IN THIS APPLICATION:

SEE ATTACHED LIST.

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☒ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION
Vicodin® Tablets	Knoll
Vicodin® ES Tablets	Knoll

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☒ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OR APPLICATION *(e.g., Part 314.70(b)(2)(iv))* _____

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

CONTENTS OF APPLICATION

This application contains the following items: *(Check all that apply)*

X	1. Index
	2. Summary (21 CFR 314.50 (c))
X	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
	i. draft labeling *(4 copies)*
X	ii. final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case reports forms (21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. Applicant certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. OTHER *(Specify)*

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. 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.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
John M. Gregory	John M Gregory	03/31/95

ADDRESS *(Street, City, State, Zip Code)*	TELEPHONE NO. *(Include Area Code)*
501 Fifth Street, Bristol, TN 37620	(615) 989-6200

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

KING PHARMACEUTICALS
501 Fifth Street
Bristol, Tennessee 37620

Fax Cover Sheet

DATE:	May 30, 1995	TIME:	4:49 PM
TO:	Mr. Peter Rickman FDA / OGD	PHONE: FAX:	301-594-0315 301-594-1174
FROM:	Tom Rogers	PHONE: FAX:	615-989-6237 615-989-6113
RE:	ANDA 40-084 Requested Information		

Number of pages including cover sheet: 3

Message

I believe that the following pages will provide the information needed in association with your review of the ANDA referenced above. Please call if I can be of further assistance.

APPEARS THIS WAY
ON ORIGINAL

N/C ... 5/31/95

Certification Required by Generic Drug Enforcement Act of 1992

Pursuant to Section 306(k) of the Generic Drug Enforcement Act of 1992 (amending the Federal Food, Drug, and Cosmetic Act), King Pharmaceuticals hereby certifies that it is not debarred and that it did not and will not use in any capacity the services of any person debarred under subsections 306(a) or 306(b) in connection with this application. King Pharmaceuticals forther states that it has no relevant conviction information to list as no employees of the firm or its affiliates have been convicted of any relevant crime described in section 306(a) or 306(b) of the Generic Drug Enforcement Act of 1992.

N T Miller

Norman T. Miller
Senior Director, Regulatory Affairs

5/30/95
Date

APPEARS THIS WAY
ON ORIGINAL

OK JSP 5/31/95

Side-by-Side Comparison Between Reference Listed Drug and Generic Drug

	LISTED DRUG	PROPOSED DRUG
	Vicodin (hydrocodone bitartrate / acetaminophen tablets, USP 5mg/ 500mg)	Hydrocodone bitartrate / acetaminophen tablets, USP 5mg/ 500 mg
Conditions of Use	For the relief of moderate to moderately severe pain	For the relief of moderate to moderately severe pain
Active Ingredients	Hydrocodone bitartrate, USP / Acetaminophen, USP	Hydrocodone bitartrate, USP / Acetaminophen, USP
Dosage Form	Tablet	Tablet
Route of Administration	Oral	Oral
Strength	5 mg / 500 mg	5 mg / 500 mg

APPEARS THIS WAY
ON ORIGINAL

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 30, 1995

TO: 40-084

FROM: Peter Rickman, CSO, Reg. Support Branch

SUBJECT: Request for Additional Infomation

I called King Pharmaceuticals and talked to Tom Rogers to request 505(j)(2)(a) infomation or comparative data for generic and reference listed drug, and a revised dabarment/list of convictions statement that includes all affiliated people. Tom said he would fax me a copy then follow with hard copies.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE *(Check One)* ☐ Original ☒ FollowUp ☐ FUR	DATE 4.28.95	PHONE NO. (301)594-0305	EER ID # 19401
REQUESTORS NAME: Ubrani V. Venkataram	DIVISION: Office of Generic Drugs		MAIL CODE: HFD-647
APPLICATION AND SUPPLEMENT NUMBER: ANDA 40-084			
BRAND NAME: None	ESTABLISHED NAME: Hydrocodone Bitartrate and Acetaminophen		
DOSAGE STRENGTH: 5 mg/500 mg & 7.5 mg/750 mg		STERILE ☐Yes ☒ No	
PROFILE CLASS: TCM	PRIORITY CLASSIFICATION *(See SMG CDER-4820.3)*		
APPLICANT'S NAME: King Pharmaceuticals, Inc. (Formerly RSR Laboratories)			
APPLICANT'S ADDRESS: 501-551 Fifth Street, Bristol, TN 37620			
COMMENTS :Pre-approval inspection			

FACILITIES TO BE EVALUATED

(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	FKEY CIRTS ID	HFD-324 USE ONLY	
1. applicant at above address	Manufacturing, QC, packaging and stability	TCM	KING 19430	AC	8/31/93
2. [redacted]	[redacted]	CCS	MALS 19432	AC	12/13/94
3. [redacted]	[redacted]	CCS	MALS 19432	AC	12/13/94
4. [redacted]	[redacted]	NEC	LEAR 19432	AC	8/24/93
5. [redacted]	[redacted]	NEC	LINSH 19432	AC	10/25/94

FOR HFD-324 USE ONLY:	CSO Annette Dequeant	DATE RECEIVED	5/12/95
	CGMP COMPLIANCE STATUS Acceptable	DATE	5/12/95

FORM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324.
cc: ANDA 40-084 HFD-647/Div File, HFD-615/MBennett, HFD-647/CSO, HFD-647/UVVenkataram
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ANDA APPROVAL SUMMARY

ANDA:40-084 **DRUG PRODUCT:**Hydrocodone Bitartrate and Acetaminophen

FIRM: King Pharmaceuticals **DOSAGE FORM:**Tablets

STRENGTHS:5 mg/500 mg and 7.5 mg/750 mg

CGMP STATEMENT/EIR UPDATE STATUS: Update requested, 2.2.95 ok 5.12.95

BIO STUDY: Drug products are rated AA in orange book. No bio-equivalence study required. Satisfactory in-vitro data, waiver request granted, Y. C. Huang, 9.10.93. Recommended dissolution test and specifications are as follows: 900 mL pH 5.8 phosphate buffer, USP XXII apparatus II, 50 rpm, NLT [redacted] (Q) in 30 mins.

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
The drug substances and drug products are articles in USP 23 (USP XXII, Supplement 8). The firm also proposes to use the compendial methods for [redacted] The methods were validated by the Philadelhia DO, 12.14.93. Description of dosage form has been revised since then to reflect change in name of the applicant.

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

Stability protocol is satisfactory.

The following containers/closures are used:

Product	Size	Container	Closure	Others*
5 mg/500 mg	100's	100cc oblong white, [redacted]	[redacted]	cotton
7.5 mg/750 mg	100's	160cc oblong white, [redacted]	[redacted]	cotton

*no desiccant included.

Lot#/Batch Size	Accelerated Stability (40°C/ 75% RH)	CRT Stability (28°C)	Comments
PLT-55/ [redacted]	100's/3 months	100's/24 months	satisfactory
PLT-58/ [redacted]	100's/3 months	100's/24 months	satisfactory
PLT-55/ [redacted]	100's/3 months	100's/6 months	satisfactory

[redacted] bottles - [redacted]
[redacted] bottles - [redacted]

LABELING: Worksheet, A. Vezza/4.24.95

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): N/A; DMFs [redacted] and [redacted] are satisfactory.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

see above

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

Batch Size	Exhibit Batches	Production Batches
5 mg/500 mg	[redacted]	[redacted]
7.5 mg/750 mg	[redacted]	[redacted]

The manufacturing process including process instructions, process parameters and in-process controls are the same for the exhibit and production batches. The equipment are of similar design and function. The production batch sizes meet OGD PPG # 22-90.

CHEMIST: /S/ **DATE:** 5.26.95.

SUPERVISOR: /S/ **DATE:** 5.26.95

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File in Div File 40-084

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE: 4/27/95

NDA NUMBER: 40-084

IND NUMBER:

TELECON/MEETING

INITIATED BY: ☐ APPLICANT/SPONSOR ☒ FDA

MADE: ☐ BY TELEPHONE ☐ IN PERSON

PRODUCT NAME: Hydrocodone Bitartrate and Acetaminophen

FIRM NAME: King Pharmaceuticals, Inc.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Tom Rogers

TELEPHONE NO.: 615-989-6237

Called firm to clarify the discrepancy between the product description found on the final printed insert and the manufacturing Batch record (of the 10/6/94 submission, pg. 007.)

Tom Rogers informed me that the package insert was the correct description and that the manufacturing batch record contained the error.

I requested he send in a corrected copy of the manufacturing batch record in its entirety, first by fax with hardcopy to follow. He said he would comply with this request.

SIGNATURE: /S/

DIVISION: OGD/Chem II/Br. 7

FORM FD 2587 (11/77)

ORIGINAL IND/NDA

U. S. GOVERNMENT PRINTING OFFICE-1984-432-976/7126

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

3.1 M

ESTABLISHMENT EVALUATION REQUEST

PRIORITY

REQUEST TYPE *(Check One)* ☒ Original ☐ FollowUp ☒ FUR	DATE 2.2.95	PHONE NO. (301)594-0305	EER ID # 7107
REQUESTORS NAME: Ubrani V. Venkataram	DIVISION:Office of Generic Drugs		MAIL CODE: HFD-647
APPLICATION AND SUPPLEMENT NUMBER: ANDA 40-084			
BRAND NAME: None	ESTABLISHED NAME:Hydrocodone Bitartrate and Acetaminophen		
DOSAGE STRENGTH: 5 mg/500 mg & 7.5 mg/750 mg		STERILE ☐Yes ☒ No	
PROFILE CLASS: TCM	PRIORITY CLASSIFICATION *(See SMG CDER-4820.3)*		
APPLICANT'S NAME: King Pharmaceuticals, Inc. (Formerly RSR Laboratories)			
APPLICANT'S ADDRESS: 501-551 Fifth Street, Bristol, TN 37620			
COMMENTS :Pre-approval inspection			

EXPEDITE

FACILITIES TO BE EVALUATED

(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	FKEY CIRTS ID	HFD-324 USE ONLY	
1. applicant at above address	Manufacturing, QC, packaging and stability	TCM	KIPB 18925	AC	8/31/93
2 [redacted]	[redacted]	CCS	MALS 18926	AC	12/23/94
3 [redacted]	[redacted]	CCS	MALS 18926	AC	12/23/94
4 [redacted]	[redacted]	NEC	LELR 18929	AC	5/21/93
5 [redacted]	[redacted]	NEC	VNSH 18929	AC	10/25/91

FOR HFD-324 USE ONLY:	CSO Administrative Requirements	DATE RECEIVED FEB 15 1995
	CGMP COMPLIANCE STATUS Acceptable	DATE 2/23/95

FORM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324.
cc: NDA 40-084 HFD-647/Div File, HFD-615/MBennett, HFD-647/CSO, HFD-647/UVVenkataram
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REVIEW OF PROFESSIONAL LABELING #2

Original Amendment

DRAFT - Container Labels and Insert Labeling

DATE OF REVIEW: January 18, 1995

ANDA #: 40-084

NAME OF FIRM: King Pharmaceuticals, Inc.

NAME OF DRUG: Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/500 mg and 7.5 mg/750 mg

DATE OF SUBMISSION: October 6, 1994

COMMENTS:

CONTAINER: (100's and 500's) Satisfactory

INSERT:

1. GENERAL COMMENT

   We note that you have submitted two package inserts for this product. Please note that we would accept one insert incorporating both strengths. Please comment.

2. PRECAUTIONS, Pediatric Use.

   ... in pediatric patients have not ...

3. ADVERSE REACTIONS, Penultimate paragraph.

   ... reactions, rash, thrombocytopenia ... (add comma).

4. DRUG ABUSE AND DEPENDENCE, Abuse and Dependence - Second paragraph, fourth line.

   ... several weeks of ... (delete ——

5. OVERDOSAGE, Acetaminophen, third paragraph.

   In adults, hepatic ... (add comma).

6. DOSAGE AND ADMINISTRATION (for 7.5 mg/750 mg tablet)
   The total daily dosage should not exceed 5 tablets

6. HOW SUPPLIED, Last paragraph.

... without prescription. (delete [redacted]

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their insert labeling, then prepare and submit final print labels and labeling. Should further information become available relating to the safety and efficacy of this product, you may be asked to further revise your labeling prior to approval.

3. FOR THE RECORD

   a. This review was based on the Labeling Guidance (Revised 4/94) for Hydrocodone Bitartrate and Acetaminophen Tablets USP.

   b. Storage/dispensing recommendations:

      ANDA: 15°-30°C; tight, light resistant container

      NDA: There is none.

      USP: tight, light resistant container

Adolph Vezza

cc: ANDA 40084OCT.94
HFD-613/AVezza/CZimmermann/JPhillips (no cc
njg/1/27/95/40084OCT.94
Review
final

/S/ 1/27/95 /S/ 1/27/95 /S/ 4/30/95

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE: 8/17/94

NDA NUMBER: 40-084

IND NUMBER:

TELECON/MEETING

INITIATED BY: [x] APPLICANT/SPONSOR [ ] FDA

MADE: [ ] BY TELEPHONE [ ] IN PERSON

PRODUCT NAME: Hydrocodone Bitartrate and Acetaminophen Tablets USP

FIRM NAME: King Pharmaceuticals

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Thomas Rodgers

TELEPHONE NO.: 1-615-989-6232

Firm contacted to relate clarifications to FAX dated August 10, 1994. (attached) The attached responses prepared by U Venkataram were related. Also, explained the major/minor classification and referred Mr. Rogers to PTP6 #38-93.

APPEARS THIS WAY ON ORIGINAL

SIGNATURE: /S/

DIVISION: OGD

FORM FD 2587 (11/71)

ORIGINAL IND/NDA

U. S. GOVERNMENT PRINTING OFFICE: 1984-432-976/7126

ANDA 40084
King Pharmaceutical, Inc.
1-615-989-6200

Response to Fax dated 8/10/94

1. The proposed approach is satisfactory. In addition, it may be appropriate to determine the detection and quantitation limits for the actives in the ——— assay. These limits then serve as the detectable limits for the degradants. Then from the ~~~ assay of the actives the area of each peak other than that of actives and known degradants is determined and their percentage with respect to total area (excluding solvent) is calculated. This will give percent individual degradant. A sum total of all the degradants can be similarly calculated.

2. Yes. This is because the applicant may not be submitting protocols in the future (e.g., in Annual reports). The identification of source in stability report will assist in developing product stability as a function of the NDS source.

   Yes. Listing excipients in the report will also allow for comparison of stability of different lots in AR.

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING

Original Amendment

DRAFT - Container Labels and Insert Labeling

DATE OF REVIEW: May 4, 1994

ANDA #: 40-084

NAME OF FIRM: King Pharmaceuticals, Inc.

NAME OF DRUG: Trade: [redacted]
Generic: Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/500 mg and 7.5 mg/750 mg

DATE OF SUBMISSION: February 22, 1994

COMMENTS:

CONTAINER:

1. Insert a space between all numbers and "mg"

2. We encourage you to differentiate your two product strengths by using contrasting colors, boxing, etc.

3. We have forwarded your proposed proprietary names [redacted] to the CDER Labeling and Nomenclature Committee for review and comment. We will defer final comment on your proposal until the comments are received.

INSERT:

The labeling for this drug has recently been revised. Therefore, please revise your insert labeling to be in accord with the enclosed Labeling Guidance (revised April 1994) for Hydrocodone Bitartrate and Acetaminophen Tablets USP.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their insert labeling, then prepare and submit draft labels and labeling for our review and comment.

3. Please enclose Labeling Guidance with letter out.

Adolph Vezza

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE *(Check One)* ☑ Original ☐ Follow-Up ☐ FUR	DATE 9-28-15	PHONE NO. [illegible]	EER ID #
REQUESTOR'S NAME [illegible]		DIVISION [illegible]	MAIL CODE HFD- (00)
APPLICATION AND SUPPLEMENT NUMBER 40-[illegible]			
BRAND NAME [illegible]		ESTABLISHED NAME	
DOSAGE AND STRENGTH Tablets 5mg/325mg + 7.5 mg/75 mg			STERILE ☐ YES ☑ NO
PROFILE CLASS TCH		PRIORITY CLASSIFICATION *(See SMG CDER-4820.3)*	
APPLICANT'S NAME [illegible] Inc.			
ADDRESS [illegible] Bristol, TN 37620			
COMMENTS			

APPEARS THIS WAY
ON ORIGINAL

FACILITIES TO BE EVALUATED

(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	F KEY/ CIRTS ID	HFD-324 USE ONLY	
1. [illegible] Bristol, TN 37620	manufacturer of [illegible]	TCH			
2. [illegible]	[illegible]				
3. [illegible]	[illegible]				
[illegible]	[illegible]				
[illegible]	[illegible]				

FOR HFD-324 USE ONLY:	CSO	DATE RECEIVED
	CGMP COMPLIANCE STATUS	DATE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE (Check One)	DATE	PHONE NO.	EER ID #
☐ Original ☐ Follow-Up ☐ FUR	8.10.93	(301) 295-8315	

REQUESTOR'S NAME	DIVISION	MAIL CODE
Laura M. Thurmond / UV Verification	Office of Generic Drugs	HFD- 632

APPLICATION AND SUPPLEMENT NUMBER
40 624

BRAND NAME	ESTABLISHED NAME
Hydrocodone Bitartrate/Acetaminophen	

DOSAGE AND STRENGTH	STERILE
Tablets 5mg/500mg + 7.5mg/750mg	☐ YES ☒ NO

PROFILE CLASS	PRIORITY CLASSIFICATION (See SMG CDER-4820.3)
TCM	

APPLICANT'S NAME
RSR Laboratories Inc.

ADDRESS RSR Laboratories, Inc.
511 Fifth Street
Bristol, TN 37620

COMMENTS

APPEARS THIS WAY
ON ORIGINAL

FACILITIES TO BE EVALUATED
(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	F KEY/ CIRTS ID	HFD-324 USE ONLY
1. RSR Laboratories, Inc. 511 Fifth Street (501-551 Fifth Street) Bristol, TN 37620	Manufacturer of final dosage form (Encapsulation)	TCM		
2.				
3.				

FOR HFD-324 USE ONLY:	CSO	DATE RECEIVED
	CGMP COMPLIANCE STATUS	DATE

FORM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324. Remaining Copies: Requesting Office

REVIEW OF PROFESSIONAL LABELING

ANDA

DRAFT - Container Labels and Insert Labeling

DATE OF REVIEW: 6-3-93

ANDA #: 40-084

NAME OF FIRM: RSR Laboratories, Inc.

NAME OF DRUG: Trade: [redacted]
Generic: Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/500 mg and 7.5 mg/750 mg

DATE OF SUBMISSION: 4-27-93

COMMENTS:

Container: (100's)

1. Include the established name directly below the proprietary name:

   Hydrocodone* Bitartrate and Acetaminophen Tablets USP

   *Warning: May be habit forming.

   [Note: We encourage the inclusion of "USP"]

2. We would encourage a prominent expression of strength immediately beneath the established name.

   "5 mg/500 mg" or "7.5 mg/750 mg"

3. 7.5 mg/750 mg - "Usual Dosage" rather than " [redacted]

4. Delete [redacted] before your storage recommendations.

5. Your controlled substance symbol for your 5 mg/500 mg product obliterates the print on your label. In addition, your symbol on your 7.5 mg/750 mg labels is barely discernable.

Insert:

1. General Comments

   a. We note the quality of submission is very poor and difficult to read. Please improve upon the quality. We defer final review and comment until such time.

   b. The established name should be used at least once in the running text in association with the proprietary name [refer to 21 CFR 201.10(g)(1) for guidance].

2. 5 mg/500 mg

   a. Replace ' [redacted] with "hydrocodone bitartrate and acetaminophen tablets" throughout the text of the insert.

   b. Title - Revise the established name to read:

      Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/500 mg

      [Note: We encourage the inclusion of the strength]

   c. DESCRIPTION

      i) Paragraph 1 - Revise to read:

         Each tablet for oral administration contains: .... In addition, each tablet contains the following inactive ingredients ...

         (Note: Please include the botanical source of the starch)

      ii) Paragraph 2, line 4 -

         "α" rather than '—

      iii) Paragraph 3, line 3 -

         ... odorless, crystalline ...

         (include the comma)

iv) "Its structural formula is..."

d. PRECAUTIONS - "Pregnancy" rather than '

e. DRUG ABUSE AND DEPENDENCE

i) "Controlled Substances Act" (plural)

ii) Paragraph 1 should be split into two paragraphs. The new paragraph begins with, "Psychic dependence, physical ..."

f. HOW SUPPLIED

i) Revise to read - (Hydrocodone* Bitartrate and Acetaminophen Tablets USP)(*Warning: May be habit forming), 5 mg/500 mg is available as ...

ii) We encourage you to include the dispensing recommendations.

3. 7.5 mg/750 mg

a. Title - Include the established name and expression of strength:

Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/750 mg

b. DESCRIPTION

i) Refer to comments 2c.(ii), and 2c.(iii) and 2c.(iv) above.

ii) Paragraph 1, sentence 1 - Revise to read:

Each Tablet (Hydrocodone Bitartrate and Acetaminophen Tablets USP), for oral administration, contains.... In addition, each tablet contains the following inactive ingredients ...

(Note: Please include the botanical source of the starch and "1" after "FD&C Blue No.")

c. WARNINGS - Delete the first paragraph. This information does not pertain to your product.

d. PRECAUTIONS, Pregnancy

i) "Pregnancy" rather than '

ii) Paragraph 2, line 9 - "There" (capital "T")

e. ADVERSE REACTIONS, paragraph 1, line 5 -

...these adverse reactions ...

f. DRUG ABUSE AND DEPENDENCE - "Controlled Substances Act" (plural)

g. OVERDOSAGE

i) Paragraph 4, line 2 - "syrup of ipecac"

ii) Paragraph 5, line 3 - "overdose" (spelling)

iii) Paragraph 6, line 1 - "overdose" (spelling)

h. HOW SUPPLIED

i) Include the established name and proprietary names as follows:

(Hydrocodone* Bitartrate and Acetaminophen Tablets USP)(*Warning: May be habit forming), 7.5 mg/750 mg is available as...

ii) We would encourage the inclusion of the "CAUTION: Federal law..." statement.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their labels and labeling, then prepare and submit twelve final printed labels and labeling (or draft, if you prefer). Should further information become available relating to the safety and efficacy of this product, you may be asked to further revise your labeling prior to approval.

3. FOR THE RECORD

a. This review is based on the Labeling Guidance revised 8/87, with minor modification.

b. Storage/dispensing recommendations - 15°-30°C; tight, light-resistant

c. Scoring - Both strengths are scored. (There is no innovator product)

d. [redacted]

Khyati Roberts

/S/ 4/13

cc: HFD-638/KRoberts/JPhillips (no cc)
mpd/6/10/93/40084apr.93
REVIEW
Final

/S/ 4/14/93

APPEARS THIS WAY
ON ORIGINAL

File in Jan Ref

[DESI 7289]

CODEINE WITH ACETAMINOPHEN, ASPIRIN, AND CAFFEINE FOR ORAL USE

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated a report received from the National Academy of Sciences—National Research Council, Drug Efficacy Study Group, on trigesic with codeine tablets (NDA 7-289) containing codeine, acetaminophen, aspirin, and caffeine; E. R. Squibb & Sons, Division Olin Mathieson Chemical Corp., 745 Fifth Avenue, New York, N.Y. 10022.

Such drugs are regarded as new drugs (21 U.S.C. 321(p)). Supplemental new drug applications are required to revise the labeling in and to update previously approved applications providing for such drugs. A new drug application is required from any person marketing such drug without approval.

A. *Effectiveness classification.* 1. The Food and Drug Administration has considered the Academy's report, as well as other available evidence, and concludes that combination drugs containing codeine with acetaminophen, aspirin, and caffeine are effective for the relief of mild to moderate pain.

B. *Conditions for approval and marketing:* The Food and Drug Administration is prepared to approve abbreviated new drug applications and abbreviated supplements to previously approved new drug applications under conditions described herein.

1. *Form of drug.* Preparations containing codeine, acetaminophen, aspirin, and caffeine are in tablet form suitable for oral administration.

2. *Labeling conditions.* a. The label bears the statement, "Caution: Federal law prohibits dispensing without prescription."

b. The drug is labeled to comply with all requirements of the Act and regulations, and the labeling bears adequate information for safe and effective use of the drug(s). The indication for use is: For the relief of mild to moderate pain.

3. *Marketing status.* Marketing of such drugs may be continued under the conditions described in the notice entitled Conditions for Marketing New Drugs Evaluated in Drug Efficacy Study, published in the FEDERAL REGISTER July 14, 1970 (35 FR 11273), as follows:

a. For holders of "deemed approved" new drug applications (i.e., an application which became effective on the basis of safety prior to October 10, 1962), the submission of a supplement for revised labeling and an abbreviated supplement for updating information as described in paragraph (a)(1) (i) and (iii) of the notice of July 14, 1970.

b. For any person who does not hold an approved or effective new drug application, the submission of an abbreviated new drug application as described in paragraph (a)(3)(i) of that notice.

c. For any distributor of the drug, the use of labeling in accord with this announcement for any such drug shipped within the jurisdiction of the Act as described in paragraph (b) of that notice.

A copy of the Academy's report has been furnished to the firm referred to above. Communications forwarded in response to this announcement should be identified with the reference number DESI 7289, directed to the attention of the appropriate office listed below, and addressed to the Food and Drug Administration, 5500 Fishers Lane, Rockville, MD 20852.

Supplements (identify with NDA number): Office of Scientific Evaluation (BD-100), Bureau of Drugs.

Requests for the Academy's report: Drug Efficacy Study Information Control (BD-66), Bureau of Drugs.

All other communications regarding this announcement: Drug Efficacy Study Implementation Project Office (BD-60), Bureau of Drugs.

All identical, related, or similar products, not the subject of an approved new drug application, are covered by the new drug application reviewed and are subject to this notice. See 21 CFR 130.40 (37 FR 23185, October 31, 1972). Any person who wishes to determine whether a specific product is covered by this notice should write to the Food and Drug Administration, Bureau of Drugs, Office of Compliance (BD-300), 5600 Fishers Lane, Rockville, MD 20352.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-53, as amended; 21 U.S.C. 352, 355) and the Administrative Procedure Act (5 U.S.C. 554) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: January 26, 1973.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.73-2017 Filed 2-1-73;8:45 am]

*Tralgon Elixir; Trigesic - OTC
Tragesic with Codeine - Rx

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-084

CORRESPONDENCE

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

1-800-336-7783
1-615-989-6200
Fax 1-615-989-6113

Thomas K. Rogers, III
Manager
Regulatory Affairs

May 1, 1995

Mr. Tim Ames, CSO
Division of Chemistry, II
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NDA ORIG AMENDMENT

Re: Minor Amendment - ANDA #40-084; Hydrocodone Bitartrate and Acetaminophen Tablets, USP,
5 mg./500 mg. and 7.5 mg./750 mg.

Dear Mr. Ames:

The enclosed scale-up batch records for both of the above referenced tablet strengths have been revised in response to our telephone conversations of 4/27/95 and 5/1/95. The revisions consist of changing the tablet monograms from —— designations to KPI 12 for the 5/500 tablet strength and to KPI 2 for the 7.5/750 tablet strength. These tablet monograms are consistent with the final labeling that was submitted with the 3/31/95 Minor Amendment to the Application.

Additionally, the product numbers on the batch records have also been revised. The product number is merely an in-house identification numbering system. Should you have any further questions, please contact me directly at 615-989-6237 or by FAX at 615-989-6113. Thank you for your assistance in this matter.

Yours truly,

Thomas K. Rogers, III

enclosure
cc: Mr. Jeff Gregory
Mr. John Gregory
Mr. Norm Miller

TR/40-084-8.doc

RECEIVED
MAY 02 1995
GENERIC DRUGS

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

1-800-336-7783
1-615-989-6200
Fax 1-615-989-6113

Thomas K. Rogers, III
Manager
Regulatory Affairs

April 28, 1995

NEW CORRESP

Mr. Tim Ames, CSO
Division of Chemistry, II
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: ANDA #40-084; Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 5 mg./500 mg. and 7.5 mg./750 mg.

Dear Mr. Ames:

The enclosed batch record for the 5/500 tablet strength is revised to correct the table monogram from [redacted] to KPI 12. This change was made in response to our telephone discussion on 4/27/95. Additionally, the product number on the batch record has also been revised. This number is merely an in-house product identification numbering system. A copy of this revised batch record has already been forwarded to you via FAX on 4/28/95, in accordance with your directions.

Should you have any further questions, please contact me directly at 615-989-6237 or by FAX at 615-989-6113. Thank you for your assistance in this matter.

Yours truly,

Thomas K. Rogers, III

enclosure
cc: Mr. Jeff Gregory
Mr. John Gregory
Mr. Norm Miller

TR/40-084-7.doc

RECEIVED

MAY 0 1 1995

GENERIC DRUGS

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

1-800-336-7783
1-615-989-6200
Fax 1-615-989-6113

Thomas K. Rogers, III
Manager
Regulatory Affairs

NM Noted to labeling for review then Chemistry for review /S/ 4/6/95

March 31, 1995

Frank O. Holcombe, Jr., Ph.D.
Acting Director
Division of Chemistry, II
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

labeling review worksheet done /S/ 4/6/95

AMENDMENT
N - AMFPL

Re: **Minor Amendment** - ANDA #40-084; Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 5 mg./500 mg. and 7.5 mg./750 mg.

Dear Dr. Holcombe:

An Abbreviated New Drug Application (ANDA) for Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 5 mg./500 mg. and 7.5 mg./750 mg. was submitted to the Agency on April 27, 1993, pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act. Major Amendments to the application were subsequently filed on February 22, 1994, and October 6, 1994. In its letter of February 27, 1995, the Agency advised that the submission was not approvable for the reasons stated. We are confident that this minor amendment appropriately and satisfactorily addresses the remaining outstanding deficiencies of the submission.

Additional tests were conducted for the purpose of generating data in response to the questions raised by the two remaining chemistry deficiencies. The data from these studies are presented within the identified subsections. The previously submitted draft inserts for each product strength have been combined into a single product insert as suggested in the general comment. Requested revisions to the text of the product insert have been made; these revisions are highlighted in the annotated copy of the final draft insert. Twelve (12) copies of the final print labels for 100 count bottles of each product strength and twelve (12) copies of final print product inserts are provided as requested. Please note that although the draft container labels for 500 count bottles were found to be acceptable, no stability data in larger size containers have been filed within this application. Consequently, no final print labels for larger containers have been included. To facilitate the review process, each deficiency noted in the letter has been addressed in point-by-point fashion within this response.

This amendment is herewith submitted in duplicate with the archival copy contained within a blue binder and the review copy in a red binder. We further certify that a true third copy of this amendment has been submitted concurrently via certified mail to the Nashville District Office of FDA. Inquiries concerning this application may be directed to my attention at the above address. Alternatively, I may be reached by phone directly at 615-989-6237 or by FAX at 615-989-6113.

Yours truly,

Thomas K. Rogers, III

cc: Mr. John M. Gregory
Mr. Jefferson J. Gregory
Mr. Norman T. Miller

TR/40-084-5.doc

RECEIVED
APR 0 5 1995
GENERIC DRUGS

NDA

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

DATE: 2/28/95

TO: King Pharmaceuticals, Inc. FROM: OGD
Attn: John M. Gregory Tim Ames
PHONE: 1-800-336-7783 PHONE: (301) 594-0309
FAX: 1-615-989-6232 FAX: (301) 594-0180

NUMBER OF PAGES: 12
(Excluding Cover Sheet)

With this facsimile, the Office of Generic Drugs is providing you with a copy of a not approvable letter requesting your response in the form of a **MINOR AMENDMENT** for the following abbreviated new drug/antibiotic application:

ANDA/AADA NUMBER: 40-084 DATE OF LETTER: 2/27/95
NAME OF DRUG PRODUCT: Actagesic & Actagesic ES

SPECIAL INSTRUCTIONS:

Attn: Tom Rogers

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 40-084

King Pharmaceuticals, Inc.
Attention: John M. Gregory
501 Fifth Street
Bristol, TN 37620

FEB 27 1995

Dear Sir:

This is in reference to your abbreviated new drug application dated April 27, 1993, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for (Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/500 mg and 7.5 mg/750 mg, respectively).

Reference is also made to your amendment dated October 6, 1994.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

1. [redacted]

2. [redacted]

B. Labeling Deficiencies

CONTAINER: (100's and 500's) Satisfactory

INSERT:

1. GENERAL COMMENT

We note that you have submitted two package inserts for this product. Please note that we would accept one insert incorporating both strengths. Please comment.

2. PRECAUTIONS, Pediatric Use.

... in pediatric patients have not ...

3. ADVERSE REACTIONS, Penultimate paragraph.

... reactions, rash, thrombocytopenia ... (add comma).

4. DRUG ABUSE AND DEPENDENCE, Abuse and Dependence - Second paragraph, fourth line.

... several weeks of ... (delete ——

5. OVERDOSAGE, Acetaminophen, third paragraph.

In adults, hepatic ... (add ——

6. HOW SUPPLIED, Last paragraph.

... without prescription. (delete —

7. DOSAGE AND ADMINISTRATION (for 7.5 mg/750 mg tablet). The total daily dosage should not exceed 5 tablets.

We request you revise your insert labeling, then prepare and submit final print labels and labeling. Should further information become available relating to the safety and efficacy of this product, you may be asked to further revise your labeling prior to approval.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this

APPEARS THIS WAY
ON ORIGINAL

letter will be considered a MINOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/

Frank O. Holcombe, Jr., Ph.D.
Acting Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: Enclosure

Labeling Guidance
Revised 4/94

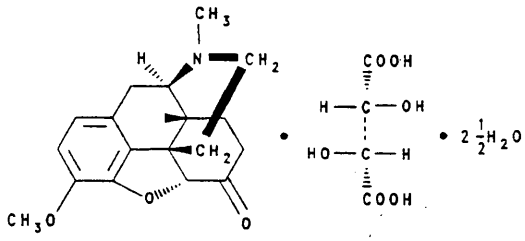
CIII

HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS USP

DESCRIPTION

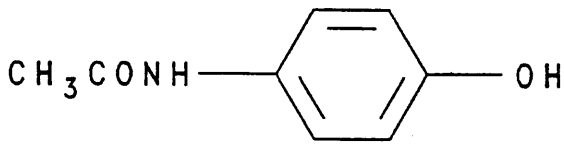
Hydrocodone bitartrate and acetaminophen is supplied in tablet form for oral administration.

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



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

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



$C_8H_9NO_2$ MW = 151.16

Each tablet contains:
Hydrocodone Bitartrate ___mg
(Warning: May be habit forming
Acetaminophen ___mg

In addition each tablet contains the following inactive ingredients:

We note that in accordance with good pharmaceutical practice, all dosage forms should be labeled to cite all the inactive ingredients (refer to USP General Chapter <1091> for guidance). We believe this is an important public health measure.

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-ß-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 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 pre-existing 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 children have not been established.

ADVERSE REACTIONS

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

Other adverse reactions include:

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

Gastrointestinal System: Prolonged administration of 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 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.

[*Choose the appropriate statement(s) based upon the strength of your product.*]

5 mg/500 mg: The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets.

7.5 mg/650 mg: 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

- Established name and strength
- Packaging
- Shape, color, coating, scoring, etc...
- Special handling and storage conditions

Manufacturer/Distributor's name and place of business.
Date of latest revision.

GUIDELINES FOR CONTAINER LABELS

1. Applicants have proposed a variety of formats in expressing the name of this product. The established name for this product is:

HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS USP

[Note: We would encourage the inclusion of "USP"]

To meet both the requirements for use of the established name and the need to easily identify the intended product without undue repetition, we suggest the following:

Hydrocodone* Bitartrate ___ **mg**
and
Acetaminophen ___ **mg**
Tablets USP

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

Please note that the milligram amounts of hydrocodone bitartrate and acetaminophen would appear in a separate print type or colored boxes so as not to be a part of the established name, yet be positioned such that the drug component is easily identifiable to the appropriate strength.

If the above format is not possible we suggest the following:

Hydrocodone* Bitartrate and Acetaminophen Tablets USP
___ mg/__ mg

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

2. We recommend the Usual Dosage statement read:

Usual Dosage: See package insert for complete dosage recommendations.

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

1-800-336-7783
1-615-989-6200
Fax 1-615-989-6232

October 6, 1994

N/AC
AMENDMENT
draft
labeling

Mr. Doug Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

review completed
12/1/18/95

Re: Major Amendment - ANDA #40-084; Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 5 mg./500 mg. and 7.5 mg./750 mg.

Dear Mr. Sporn:

An Abbreviated New Drug Application (ANDA) for Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 5 mg./500 mg. and 7.5 mg./750 mg. was submitted to the Agency on April 27, 1993, pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act. A Major Amendment to this application was subsequently filed on February 22, 1994. In its letter of August 2, 1994, the Agency advised that the submission was not approvable for the reasons stated. A letter requesting clarification on two of the deficiencies cited was sent to the Agency on August 10, 1994, and Mr. Tim Ames responded to our inquiries by telephone on August 17, 1994. A copy of that letter and an internal memorandum which summarizes the conversation with Mr. Ames are provided with this letter. We are confident that this amendment appropriately and satisfactorily addresses the remaining outstanding deficiencies of the submission.

As requested, additional analytical test methods for monitoring potential degradants in the drug product have been added to both the release and stability test procedures. The sampling plan for in-process monitoring of tablet weights has been revised to comply with _____. Appropriate revisions to the proposed batch records and the stability data record sheets have been made as requested, and additional stability data for the new container / closure system are provided for review. To facilitate the review process, each deficiency noted in the letter has been addressed in point-by-point fashion.

OCT 11

Nadine
10-20-94

Inquiries concerning this application may be directed to my attention at the above address or by calling (615) 989-6200.

Yours truly,

KING PHARMACEUTICALS, INC.

John M. Gregory
Chief Executive Officer

APPEARS THIS WAY
ON ORIGINAL

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

1-800-336-7783
1-615-989-6200
Fax 1-615-989-6232

October 6, 1994

Roger Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: Amendment - ANDA #40-084;
Hydrocodone Bitartrate and Acetaminophen Tablets, USP

Dear Dr. Williams:

In accordance with 21 CFR 314.60, the purpose of this letter is to certify that a true copy of the above referenced Amendment, submitted to the Office of Generic Drugs, on October 6, 1994 was sent on the same date to the Nashville District of the Food and Drug Administration.

Yours sincerely,

KING PHARMACEUTICALS, INC.

Norman T. Miller

Norman T. Miller
Director, Regulatory Affairs

Attachment
(Federal Express
Tracking # 2880494385)

ORIGINAL

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

1-800-336-7783
1-615-989-6200
Fax 1-615-989-6113

Norman T. Miller
Director
Regulatory Affairs

August 8, 1994

C. Greg Guyer, Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ORIG NEW CORRES
NAI 8/8/94
YSI

Re: MAJOR AMENDMENT - ANDA #40-084; Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/500 mg [redacted] and 7.5 mg/750 mg [redacted]

Dear Dr. Guyer:

Reference is made to the Not Approvable letter of August 2, 1994, issued by your office in response to the Major Amendment submitted by King Pharmaceuticals, Inc. dated February 22, 1994, pertaining to our pending application (ANDA #40-084).

In accordance with 21 CFR 314.120(1), this letter is to inform you of our intention to file an amendment in response to the Not Approvable letter thereby extending the review period under 314.60. This will be considered a Major Amendment as the letter of response will so indicate.

If you should have any questions please contact me directly at (615) 989-6253.

Sincerely,

KING PHARMACEUTICALS, INC.

Norman T. Miller

Norman T. Miller
Director, Regulatory Affairs

NTM:ms

CERTIFIED MAIL - RETURN RECEIPT REQUESTED - P 376 510 78[illegible]

RECEIVED
AUG 16 1994
GENERIC DRUGS

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

1-800-336-7783
1-615-989-6200
Fax 1-615-989-6282

John Gregory
Chief Executive Officer

NEW CORRESPONDENCE

April 4, 1994

NEW CORRESP

Roger Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: The MAJOR AMENDMENT - ANDA #40-084; Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5mg/500mg [redacted], and 7.5mg/750mg [redacted], Submitted on February 22, 1994.

Dear Dr. Williams:

In accordance with 21 CFR 314.60, the purpose of this letter is to certify that a true copy of the above referenced Major Amendment, submitted to the Office of Generic Drugs, Division of Chemistry II, on February 22, 1994 was sent on that same date to the Nashville District of the Food and Drug Administration.

Yours sincerely,

KING PHARMACEUTICALS, INC.

John M Gregory

John M. Gregory
Chief Executive Officer

JMG:bhh

RECEIVED
APR 6 1994
GENERIC DRUGS

ANDA# 40-084

AUG 2 1994

King Pharmaceuticals
Attention: John M. Gregory
501 Fifth Street
Bristol, TN 37620

Dear Sir:

This is in reference to your abbreviated new drug application dated April 27, 1993, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for and ES™ (Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/500 mg and 7.5 mg/750 mg, respectively).

Reference is also made to your amendment dated February 22, 1994.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

1. Regarding manufacturing and processing:

[redacted]

[redacted]

2. Regarding containers and closures:

The USP test data that you have provided in support of Wheaton bottles is satisfactory. However, please note that you have not provided stability data of the product packaged in the proposed new container/closure system (i.e., using [redacted]. We require that the product stability data be determined in the exact marketed container/closure system. We acknowledge that the bottles from [redacted] are both bottles. You are hereby advised that you have two options to address the problem: 1) to determine stability data in the proposed new container/closure system, or 2) to provide USP test data for the previous container/closure system with the option of supplementing the application for the new container/closure system after approval.

3. Regarding laboratory controls:

[redacted]

4. Regarding the stability studies:

As requested in our previous Not Approvable letter please include drug substance sources and current product formulation in the stability report. Please revise and resubmit.

B. Labeling Deficiencies

CONTAINER:

1. Insert a space between all numbers and "mg"

2. We encourage you to differentiate your two product strengths by using contrasting colors, boxing, etc.

3. We have forwarded your proposed proprietary names [redacted], to the CDER Labeling and Nomenclature Committee for review and comment. We will defer final comment on your proposal until the comments are received.

INSERT:

The labeling for this drug has recently been revised. Therefore, please revise your insert labeling to be in accord with the enclosed Labeling Guidance (revised April 1994) for Hydrocodone Bitartrate and Acetaminophen Tablets USP.

We request you revise your insert labeling, then prepare and submit draft labels and labeling for our review and comment.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this

letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 8/1/94

C. Greg Guyer, Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure: Labeling Guidance

ANDA 40-084

MAR 2 1994

King Pharmaceuticals, Inc.
Attention: Norman T. Miller
501 Fifth Street
Bristol, TN 37620

Dear Sir:

We acknowledge receipt of your communication dated February 17, 1994, submitted as required by the provisions of Regulation 21 CFR 314.72(a) and Section 505(k) of the Federal Food, Drug and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/500 mg and 7.5 mg/750 mg.

Your letter details the transfer of ownership of the ANDA from RSR Laboratories, Inc. to King Pharmaceuticals, Inc.

Pursuant to 21 CFR 314.72(b), the new owner shall advise FDA about any change in the conditions of the approved application.

The material submitted is being retained as part of your application.

Sincerely yours,

/S/ for/

Robert W. Pollock 3-1-94
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-084
Division File
HFD-600/Reading File
Field Copy
Endorsements: HFD-615/Gordon Johnston, Chief date/__/__/__
HFD-615/PRickman, CSO/date2/28/94
HFD-615/WRussell, CSO /S/
WP File\russell\40-084
F/T by bcw/2-28-94
transfer of ownership

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

KING PHARMACEUTICALS

1-800-336-7783
1-615-989-6200
Fax 1-615-989-4232

Labeling review 5/14/94 ABS

February 22, 1994

RECEIVED
FEB 23 1994
GENERIC DRUGS

NDA ORIG AMENDMENT
N-AC
DRAFT
LABELING

VIA FEDERAL EXPRESS

C. Greg Guyer, Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

Re: MAJOR AMENDMENT - ANDA #40-084; Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5mg/500mg ——— and 7.5mg/750mg ———

Dear Dr. Guyer:

On April 27, 1993, the original applicant, RSR Laboratories, Inc., Bristol, Tennessee 37620, submitted the above referenced abbreviated new drug application. By your letter dated August 17, 1993, this applicant was notified that the application was deficient and, therefore, not approvable under Section 505 of the Act. Thereafter on December 31, 1993, RSR Laboratories, Inc. sold all of its assets related to its pharmaceutical business including the facility and equipment in which the referenced products are to be manufactured, and the subject application (ANDA #40-084), to a company which is now doing business as King Pharmaceuticals, Inc. ("KPI") in the same facility as the original applicant. A separate notification of the "change in ownership" of ANDA #40-084 has been filed in accordance with 21 CFR 314.72.

ORIGINAL

Turning to the matters addressed in your letter, please be advised that pursuant to 21 CFR 314.60, the new owner, King Pharmaceuticals, Inc., is submitting herewith in duplicate, a Major Amendment intended to remove all deficiencies cited in your aforementioned letter. The first two volumes of this amendment (labeled by the applicant as "Volume 1 - Chemistry" and "Volume 2 - Labeling"), includes information which responds in point-by-point fashion to the matters you have raised. In other words, each deficiency is addressed in the same order it appears in your August 17, 1993 letter, and is identified using your numbering sequence.

The remaining nine (9) volumes (labeled by the applicant as "Volume 3" through "Volume 11") contain data which validate the analytical method used for the release of the finished products, and for the stability program related to the products covered by this application. In this regard, it is important to note that the method described in this portion of the amendment is, in fact, a modification of the method appearing in Supplement 7 of USP XXII and, is not the method referred to in Item A.5.d. of your letter, which method was later published in Supplement 8 of USP XXII.

As explained at page 0137 of this submission, Dr. V. Scrinavasan of the USP has informed laboratory personnel in the employ of the applicant that numerous firms have had no success with the method presented in the 8th Supplement. Having been advised of the excellent results obtained with the applicant's modified method, Dr. Scrinavasan suggested a submission of this method to the USP for consideration as the official method, and also recommended a concurrent filing of the information with CDER. The USP submission was made on November 17, 1993.

Since that time, the applicant has been informed by Dr. Scrinavasan that another company has filed a modification of the Supplement 8 method for consideration as the official method. Upon being so advised, the applicant conducted a comparative

evaluation of the two modified methods. As shown in the report appended to this letter (Attachment 1), applicant's modified Supplement 7 method, which has been fully validated for both the 5mg/500mg and 7.5mg/750mg tablet potencies, is less time consuming and yields more accurate results than the other modified method.

Finally, it should be noted that following the receipt of your letter, applicant's facility was inspected by the Nashville District of the FDA in connection with this application. As evidenced by the letter provided as Attachment 2, the Nashville District has recommended approval of the subject application. Since, in the applicant's view, the information herewith submitted is sufficient to remove all deficiencies in ANDA #40-084, the applicant respectfully requests your timely concurrence with this recommendation. Please note also that once this application is approved, [redacted] Tablets will be distributed by KPI's sister company, Lotus Biochemical Corporation, Radford, Virginia 24143.

Should you have any questions regarding this amendment, please contact the undersigned at the above listed address or by calling (615) 989-6284.

Yours sincerely,
KING PHARMACEUTICALS, INC.

John M. Gregory
Chief Executive Officer

JMG:bhh
Attachments

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

KING PHARMACEUTICALS

1-800-336-7783
1-615-989-6200
Fax 1-615-989-4232

February 17, 1994

NEW CORRES

Roger Williams, M.D., Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: Change of Ownership - ANDA No. 40-084

Dear Dr. Williams:

This letter is to notify your office of a change in ownership of the referenced ANDA drug product which cover two (2) dosage strengths of tablets. The drug product and the two strengths are listed below.

Hydrocodone Bitartrate and Acetaminophen, USP, 5 mg/500mg

Hydrocodone Bitartrate and Acetaminophen, USP, 7.5mg/750mg

The ownership change involves the transfer of the referenced ANDA product from the former owner, RSR Laboratories, Inc. 501 Fifth Street, Bristol, Tennessee 37620, to the new owner King Pharmaceuticals, Inc., 501 Fifth Street, Bristol, Tennessee 37620.

This transfer is a result of a buyout of RSR Laboratories, Inc., by King Pharmaceuticals, Inc., effective December 31, 1993.

Please find enclosed with this letter, FDA form 356h (Application to Market A New Drug For Human Use), signed by Mr. John M. Gregory, CEO of King Pharmaceuticals, Inc.

Also enclosed is a Transfer Agreement signed by Mr. Gregory and Mr. Jack Sitgreaves, President of RSR Laboratories, Inc., which outlines the terms of the transfer of two (2) ANDA products, one of which is the Hydrocodone Bitartrate and Acetaminophen product. This agreement also describes the commitments promised by King Pharmaceuticals, Inc., as described in Section 314.72.

If there are any questions or if clarification is needed, please contact me directly at (615) 989-6253.

Sincerely,

Norman T. Miller

Norman T. Miller
Director, Regulatory Affairs

RECEIVED
FEB 18 1994
GENERIC DRUGS

NTM:ms
Enclosures

RSR
LABORATORIES
ROBINSON • SITGREAVES • ROBINSON

Forward to Bio (J. Gross) for review
/s/ 9/8/93

August 31, 1993

BIOAVAILABILITY

VIA AIRBORNE EXPRESS

Dr. Jason Gross
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 128
Rockville, Maryland 20855

NEW CORRESP

RE: Minor Amendment to ANDA 40-084 for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5mg/500mg (———) and 7.5mg/750mg (———).

Dear Dr. Gross:

As instructed and pursuant to 21 CFR 314.60, we are submitting herewith, duplicate copies of information previously sent to you by fax machine. This information is in the form of graphs and tables and reflects the results of studies in which the dissolution rates of the above-referenced products, Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5mg/500mg (———) and 7.5mg/750mg (———) were compared with those of the marketed products, Vicodin™ and Vicodin ES™ (Small).

Should you have any questions regarding the enclosed documents, please contact me at your earliest convenience.

Yours sincerely,

RSR LABORATORIES, INC.

Lawrence P. Olon
Senior Vice President

LPO/kl
Enclosures

RECEIVED
SEP 0 2 1993
GENERIC DRUGS

/s/ 9.1.93

501 Fifth Street, P.O. Box 8700, [illegible], Tenn. 37621-8700 • (615) 989-4200 or 800-336-7783
A Quality Pharmaceutical Manufacturer

RSR LABORATORIES
ROBINSON • SITGREAVES • ROBINSON

NAI CSO 8/30/93

August 23, 1993

VIA AIRBORNE EXPRESS

NEW CORRESP

C. Greg Guyer, Ph.D., Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 128
Rockville, Maryland 20855

RE: ANDA 40-084
Hydrocodone Bitartrate and Acetaminophen Tablets USP,
5mg/500mg and 7.5mg/750mg

Dear Dr. Guyer:

In reference to your "Not Approvable" letter dated August 17, 1993, and pursuant to 21 CFR 314.120, please be advised that RSR Laboratories, Inc. intends to amend the above-referenced application to remove all deficiencies cited.

Yours sincerely,

RSR LABORATORIES, INC.

Lawrence P. Olon
Senior Vice President

LPO/kl

RECEIVED
AUG 24 1993
GENERIC DRUGS

/s/ 8/30/93

501 Fifth Street, P.O. Box 8700, Bristol, Tenn. 37621-8700 • (615) 989-4200 or 800-336-7783
A Quality Pharmaceutical Manufacturer

ANDA# 40-084

RSR Laboratories, Inc.
Attention: Lawrence P. Olon
501 Fifth Street
Bristol, TN 37620

Dear Sir:

This is in reference to your abbreviated new drug application dated April 27, 1993, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/500 mg [redacted] and 7.5 mg/750 mg [redacted]

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

1. Regarding the composition statement: Please revise and resubmit the [redacted]

2. Regarding the controls for the [redacted]

Redacted 2

pages of trade secret and /or confidential commercial information

analytical method that was used for product release and stability testing. Also submit data to show that the method is stability indicating.

d. Please submit system suitability data for the USP method. It should be noted that the USP assay method has been revised in Supplement 8. Since this is the official method, you should evaluate the official method and submit validation data for the same. Also COAs using compendial methods should be submitted. If you wish to use the compendial method for stability testing, then the USP method should also be shown to be stability indicating.

6. Regarding the stability studies:

a. Please include in the stability protocol tests for degradation products and also specifications for all test parameters. Test methods should be specified.

b. Please demonstrate that the assay method is stability indicating.

c. Please include the following in the stability report: product description, formulation, drug substance sources and resin used in bottle manufacture. Actual test dates should be recorded. Tests for degradation products should be included and available data should be submitted. Test methods should be specified. Please revise and resubmit.

7. Regarding control numbers: The procedure given in DMF ——. does not explain how the test batch number was derived. Please explain.

B. Labeling Deficiencies (DRAFT)

Container: (100's)

1. Include the established name directly below the proprietary name:

Hydrocodone* Bitartrate and Acetaminophen Tablets USP

*Warning: May be habit forming.

[Note: We encourage the inclusion of "USP"]

2. We would encourage a prominent expression of strength immediately beneath the established name.

   "5 mg/500 mg" or "7.5 mg/750 mg"

3. 7.5 mg/750 mg - "Usual Dosage" rather than [redacted]

4. Delete [redacted] ' before your storage recommendations.

5. Your controlled substance symbol for your 5 mg/500 mg product obliterates the print on your label. In addition, your symbol on your 7.5 mg/750 mg labels is barely discernable. Please revise accordingly.

Insert:

1. General Comments

   a. We note the quality of submission is very poor and difficult to read. Please improve upon the quality. We defer final review and comment until such time.

   b. The established name should be used at least once in the running text in association with the proprietary name [refer to 21 CFR 201.10(g)(1) for guidance].

2. 5 mg/500 mg

   a. Replace [redacted] with "hydrocodone bitartrate and acetaminophen tablets" throughout the text of the insert.

   b. Title - Revise the established name to read:

      Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/500 mg

      [Note: We encourage the inclusion of the strength]

   c. DESCRIPTION

      i) Paragraph 1 - Revise to read:

         Each tablet for oral administration contains: .... In addition, each tablet

contains the following inactive ingredients ...

(Note: Please include the botanical source of the starch)

ii) Paragraph 2, line 4 -

"α" rather than '—

iii) Paragraph 3, line 3 -

... odorless, crystalline ... (include the comma)

iv) "Its structural formula is..."

d. PRECAUTIONS - "Pregnancy" rather than ——

e. DRUG ABUSE AND DEPENDENCE

i) "Controlled Substances Act" (plural)

ii) Paragraph 1 should be split into two paragraphs. The new paragraph begins with, "Psychic dependence, physical ..."

f. HOW SUPPLIED

i) Revise to read - ——— (Hydrocodone* Bitartrate and Acetaminophen Tablets USP)(*Warning: May be habit forming), 5 mg/500 mg is available as ...

ii) We encourage you to include the dispensing recommendations.

3. 7.5 mg/750 mg

a. Title - Include the established name and expression of strength:

Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/750 mg

b. DESCRIPTION

i) Refer to comments 2c.(ii), and 2c.(iii) and 2c.(iv) above.

ii) Paragraph 1, sentence 1 - Revise to read:

Each [redacted] Tablet (Hydrocodone Bitartrate and Acetaminophen Tablets USP), for oral administration, contains.... In addition, each tablet contains the following inactive ingredients ...

(Note: Please include the botanical source of the starch and "1" after "FD&C Blue No.")

c. WARNINGS - Delete the first paragraph. This information does not pertain to your product.

d. PRECAUTIONS, Pregnancy

i) "Pregnancy" rather than [redacted]

ii) Paragraph 2, line 9 - "There" (capital "T")

e. ADVERSE REACTIONS, paragraph 1, line 5 -

...these adverse reactions ...

f. DRUG ABUSE AND DEPENDENCE - "Controlled Substances Act" (plural)

g. OVERDOSAGE

i) Paragraph 4, line 2 - "syrup of ipecac"

ii) Paragraph 5, line 3 - "overdose" (spelling)

iii) Paragraph 6, line 1 - "overdose" (spelling)

h. HOW SUPPLIED

i) Include the established name and proprietary names as follows:

[redacted] (Hydrocodone* Bitartrate and Acetaminophen Tablets USP)(*Warning: May be habit forming), 7.5 mg/750 mg is available as...

ii) We would encourage the inclusion of the "CAUTION: Federal law..." statement.

We request you revise your labels and labeling, then prepare and submit twelve final printed labels and labeling (or draft, if you prefer). Should further information become available relating to the safety and efficacy of this product, you may be asked to further revise your labeling prior to approval.

In addition to these deficiencies, please note and acknowledge the following in your response:

Your request for waiver is being evaluated by our Division of Bioequivalence and the deficiencies will be notified in a separate letter.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 8/16/93

C. Greg Guyer, Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-084

RSR Laboratories, Inc.
Attention: Lawrence P. Olon
501 Fifth Street
Bristol, TN 37620

MAY 19 1993

Dear Sir:

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

NAME OF DRUG: Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/750 mg, 5 mg/500 mg

DATE OF APPLICATION: April 27, 1993

DATE OF RECEIPT: April 28, 1993

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.

Sincerely yours,

/S/ for 5-19-93

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #40-084
DUP/Division File
HFC-130/JAllen
HFD-637/JSimmons
HFD-632/MBennett
HFD-600/Reading File
R/D initialed by
F/T by B:/40084ack.ltr hrw 5-5-93
Acknowledgement Letter!

505(j)(2)(A) information is acceptable for filing. 4-30-93 Edward M. Sherwood

RSR LABORATORIES

ROBINSON • SITGREAVES • ROBINSON

April 27, 1993

Roger Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: Abbreviated New Drug Application for [redacted] Tablets (Hydrocodone Bitartrate, USP, 5mg and Acetaminophen, USP, 500mg) and [redacted] Tablets (Hydrocodone Bitartrate, USP, 7.5mg and Acetaminophen, USP, 750mg)

Dear Dr. Williams:

RSR Laboratories, Inc., 501 Fifth Street, Bristol, Tennessee 37620, is submitting herewith an Abbreviated New Drug Application for the above referenced prescription drug products. This application, which consists of archival and review copies of five (5) volumes each, as well as three (3) separate copies of the Methods Validation data, is submitted in accordance with 21 U.S.C. §355(j) and the corresponding regulations of 21 CFR 314; and is based on the approved drugs, Anexsia® 5/500 Tablets [Beecham] and Vicodin ES® Tablets [Knoll], listed in the 1993 Approved Drug Products With Therapeutic Equivalence Evaluations [the "Orange Book"], 13th Edition, page 3-4.

Inquiries concerning this application may be directed to my attention at the above listed address or by calling (615) 989-4250.

We respectfully request your timely review of this submission.

Yours sincerely,

RSR LABORATORIES, INC.

Lawrence P. Olon
Senior Vice President

LPO:r

RECEIVED
APR 2 8 1993
GENERIC DRUGS