CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-307

APPROVAL LETTER

ANDA 40-307

JUL 26 2000

Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970-5019

Dear Madam:

This is in reference to your abbreviated new drug application dated April 13, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 2.5 mg/500 mg, 7.5 mg/500 mg, 7.5 mg/650 mg and 10 mg/650 mg.

Reference is also made to your amendments dated July 30, 1998, October 11, 1999, April 12, 2000, and July 11, 2000.

We have completed the review of this abbreviated application and have concluded that each of the four strengths of drug product is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Hydrocodone Bitartrate and Acetaminophen Tablets USP, 2.5 mg/500 mg, 7.5 mg/500 mg, 7.5 mg/650 mg and 10 mg/650 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Hydrocodone Bitartrate and Acetaminophen Tablets USP, 2.5 mg/500 mg, 7.5 mg/500 mg, 7.5 mg/650 mg and 10 mg/650 mg, respectively, of Mikart, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

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

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

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

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

Sincerely yours,

Gary Buehler 7/27/00
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-307

APPROVED DRAFT LABELING

Usual Dosage: See package brochure for complete dosage recommendations.

Dispense with a child-resistant closure in a tight, light-resistant container as defined in the USP/NF.

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

BARR LABORATORIES, INC.
Pomona, NY 10970

R8-99
1120895020102

BARR LABORATORIES, INC.

Hydrocodone* Bitartrate and Acetaminophen Tablets, USP

7.5 mg / 650 mg

Each tablet contains:
Hydrocodone* Bitartrate.....7.5 mg
*Warning: May be habit forming.
Acetaminophen.....650 mg

Rx only

100 Tablets

NDC 0555-0895-02

APPROVED

0555-0895-02

SAMPLE

Exp. Date:

Lot No.:

Tablets, USP

7.5 mg / 500 mg

Each tablet contains:
Hydrocodone* Bitartrate.....7.5 mg
*Warning: May be habit forming.
Acetaminophen.....500 mg

Rx only

100 Tablets

0555-08

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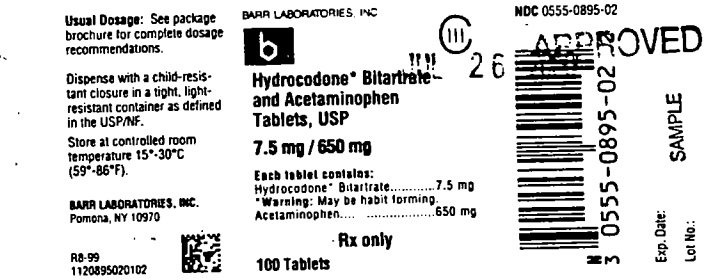
Exp. Date:

Lot No.:



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BARR LABORATORIES, INC.
Pomona, NY 10970

R8-99
1120895020102

BARR LABORATORIES, INC

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7.5 mg / 650 mg

Each tablet contains:
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*Warning: May be habit forming.
Acetaminophen.....650 mg

Rx only

100 Tablets

NDC 0555-0895-02

APPROVED

0555-0895-02

SAMPLE

Exp. Date:

Lot No.:

Barr's

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Usual Dosage: See package brochure for complete dosage recommendations.

Dispense with a child-resistant closure in a tight, light-resistant container as defined in the USP/NF.

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

BARR LABORATORIES, INC.

Hydrocodone* Bitartrate and Acetaminophen Tablets, USP 7.5 mg / 500 mg

Each tablet contains:
Hydrocodone* Bitartrate.....7.5 mg
***Warning:** May be habit forming.
Acetaminophen.....500 mg

Rx only

500 Tablets

BARR LABORATORIES, INC.
Pomona, NY 10970

R8-99
1120897040102

NDC 0555-0897-04

JUL 26 2000

APPROVED

0 0555-0897-04 3

SAMPLE

Exp. Date:

Lot No.:

tartrate and Acetaminophen

7.5 mg/500 mg,
nd 10 mg/650 mg

Strength in Package size of 500's

INC.

NDC 0555-0895-04

artrate
en

.....7.5 mg
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.....650 mg
ispensing without

JUL 26 2000

APPROVED

0555-0895-04 6

SAMPLE

Exp. Date:

Lot No.:

SAMPLE

HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP

C III

Revised NOVEMBER 1998
1007360101

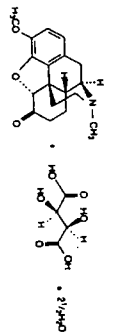
Rx only

APPROVED
JUL 26 2000

DESCRIPTION:

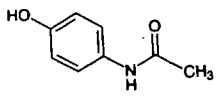
Hydrocodone bitartrate and acetaminophen is supplied in tablet form for oral administration.

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:



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



$C_8H_9NO_2$ Molecular Weight: 151.17

Each 2.5 mg/500 mg tablet contains:
Hydrocodone Bitartrate.....2.5 mg
Acetaminophen.....500 mg

Each 5 mg/500 mg tablet contains:
Hydrocodone Bitartrate.....5 mg
Acetaminophen.....500 mg

Each 7.5 mg/500 mg tablet contains:
Hydrocodone Bitartrate.....7.5 mg
Acetaminophen.....500 mg

Each 7.5 mg/650 mg tablet contains:
Hydrocodone Bitartrate.....7.5 mg
Acetaminophen.....650 mg

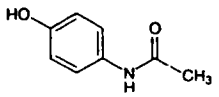
Each 7.5 mg/750 mg tablet contains:
Hydrocodone Bitartrate.....7.5 mg
Acetaminophen.....750 mg

Each 10 mg/500 mg tablet contains:
Hydrocodone Bitartrate.....10 mg
Acetaminophen.....500 mg

Each 10 mg/650 mg tablet contains:
Hydrocodone Bitartrate.....10 mg
Acetaminophen.....650 mg

In addition each tablet contains the following inactive ingredients: Crospovidone, magnesium stearate, pregelatinized starch, and povidone.

The 2.5 mg/500 mg also contains FD&C



$C_8H_9NO_2$ Molecular Weight: 151.17

Each 2.5 mg/500 mg tablet contains:
Hydrocodone Bitartrate.... 2.5 mg
Acetaminophen.....500 mg

Each 5 mg/500 mg tablet contains:
Hydrocodone Bitartrate..... .5 mg
Acetaminophen... ... ...500 mg

Each 7.5 mg/500 mg tablet contains:
Hydrocodone Bitartrate.....7.5 mg
Acetaminophen.....500 mg

Each 7.5 mg/650 mg tablet contains:
Hydrocodone Bitartrate.....7.5 mg
Acetaminophen.....650 mg

Each 7.5 mg/750 mg tablet contains:
Hydrocodone Bitartrate.....7.5 mg
Acetaminophen .....750 mg

Each 10 mg/500 mg tablet contains:
Hydrocodone Bitartrate.. ...10 mg
Acetaminophen.....500 mg

Each 10 mg/650 mg tablet contains:
Hydrocodone Bitartrate.....10 mg
Acetaminophen.....650 mg

In addition each tablet contains the following inactive ingredients: Crospovidone, magnesium stearate, pregelatinized starch, and povidone.

The 2.5 mg/500 mg also contains FD&C red no. 40 aluminum lake HT

The 5 mg/500 mg does not contain any dyes.

The 7.5 mg/500 mg also contains D&C yellow no. 10 aluminum lake and FD&C blue no. 1 aluminum lake.

The 7.5 mg/650 mg also contains FD&C yellow no. 6 aluminum lake.

The 7.5 mg/750 mg also contains D&C yellow no. 10 aluminum lake.

The 10 mg/500 mg also contains FD&C blue no. 1 aluminum lake, FD&C red no. 40 aluminum lake HT and D&C yellow no. 10 aluminum lake

The 10 mg/650 mg also contains FD&C blue no.1 aluminum lake.

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 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:
Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure:

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:

[illegible] sis, 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.

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.

(Over)

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 the 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:

The following 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 must be

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

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

2.5 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.

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/500 mg: The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dose should not exceed 6 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 dose should not exceed 6 tablets.

7.5 mg/750 mg: The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dose should not exceed 5 tablets.

10 mg/500 mg: The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dose should not exceed 6 tablets.

10 mg/650 mg: The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dose should not exceed 6 tablets.

HOW SUPPLIED:

Hydrocodone Bitartrate and Acetaminophen Tablets, USP are available as:

2.5 mg/500 mg: Light pink mottled, capsule-shaped, scored tablet. Debossed with b/896 on one side and plain on the other side. Available in bottles of:

100 NDC 0555-0896-02

500 NDC 0555-0896-04

5 mg/500 mg: White, capsule-shaped, scored tablet. Debossed with b/915 on one side and plain on the other side. Available in bottles of:

100 NDC 0555-0915-02

SAMPLE

HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP

C III

Revised NOVEMBER 1998
1007360101

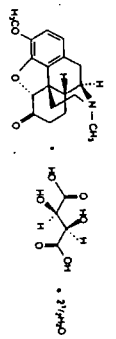
Rx only

APPROVED
JUL 26 2000

DESCRIPTION:

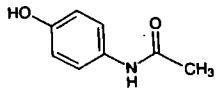
Hydrocodone bitartrate and acetaminophen is supplied in tablet form for oral administration.

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:



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



$C_8H_9NO_2$ Molecular Weight: 151.17

Each 2.5 mg/500 mg tablet contains:
Hydrocodone Bitartrate.....2.5 mg
Acetaminophen.....500 mg

Each 5 mg/500 mg tablet contains:
Hydrocodone Bitartrate.....5 mg
Acetaminophen.....500 mg

Each 7.5 mg/500 mg tablet contains:
Hydrocodone Bitartrate.....7.5 mg
Acetaminophen.....500 mg

Each 7.5 mg/650 mg tablet contains:
Hydrocodone Bitartrate.....7.5 mg
Acetaminophen.....650 mg

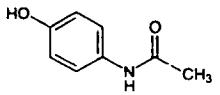
Each 7.5 mg/750 mg tablet contains:
Hydrocodone Bitartrate.....7.5 mg
Acetaminophen.....750 mg

Each 10 mg/500 mg tablet contains:
Hydrocodone Bitartrate.....10 mg
Acetaminophen.....500 mg

Each 10 mg/650 mg tablet contains:
Hydrocodone Bitartrate.....10 mg
Acetaminophen.....650 mg

In addition each tablet contains the following inactive ingredients: Crospovidone, magnesium stearate, pregelatinized starch, and povidone.

The 2.5 mg/500 mg also contains FD&C



$C_8H_9NO_2$ Molecular Weight: 151.17

Each 2.5 mg/500 mg tablet contains:
Hydrocodone Bitartrate.....2.5 mg
Acetaminophen.....500 mg

Each 5 mg/500 mg tablet contains:
Hydrocodone Bitartrate.....5 mg
Acetaminophen .....500 mg

Each 7.5 mg/500 mg tablet contains:
Hydrocodone Bitartrate.....7.5 mg
Acetaminophen.....500 mg

Each 7.5 mg/650 mg tablet contains:
Hydrocodone Bitartrate.....7.5 mg
Acetaminophen.....650 mg

Each 7.5 mg/750 mg tablet contains:
Hydrocodone Bitartrate.....7.5 mg
Acetaminophen.....750 mg

Each 10 mg/500 mg tablet contains:
Hydrocodone Bitartrate.....10 mg
Acetaminophen.....500 mg

Each 10 mg/650 mg tablet contains:
Hydrocodone Bitartrate.....10 mg
Acetaminophen.....650 mg

In addition each tablet contains the following inactive ingredients: Crospovidone, magnesium stearate, pregelatinized starch, and povidone.

The 2.5 mg/500 mg also contains FD&C red no. 40 aluminum lake HT.

The 5 mg/500 mg does not contain any dyes.

The 7.5 mg/500 mg also contains D&C yellow no. 10 aluminum lake and FD&C blue no. 1 aluminum lake.

The 7.5 mg/650 mg also contains FD&C yellow no. 6 aluminum lake.

The 7.5 mg/750 mg also contains D&C yellow no. 10 aluminum lake.

The 10 mg/500 mg also contains FD&C blue no. 1 aluminum lake, FD&C red no. 40 aluminum lake HT and D&C yellow no. 10 aluminum lake.

The 10 mg/650 mg also contains FD&C blue no.1 aluminum lake.

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 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:
Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure:

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:

sis, 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.

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.

(Over)

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 the 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:

The following 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 must

6

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

2.5 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.

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/500 mg: The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dose should not exceed 6 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 dose should not exceed 6 tablets.

7.5 mg/750 mg: The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dose should not exceed 5 tablets.

10 mg/500 mg: The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dose should not exceed 6 tablets.

10 mg/650 mg: The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dose should not exceed 6 tablets.

HOW SUPPLIED:

Hydrocodone Bitartrate and Acetaminophen Tablets, USP are available as:

2.5 mg/500 mg: Light pink mottled, capsule-shaped, scored tablet. Debossed with b/896 on one side and plain on the other side. Available in bottles of:

100 NDC 0555-0896-02

500 NDC 0555-0896-04

5 mg/500 mg: White, capsule-shaped, scored tablet. Debossed with b/915 on one side and plain on the other side. Available in bottles of:

100 NDC 0555-0915-02

as needed for pain. The total daily dose should not exceed 6 tablets.

10 mg/650 mg: The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dose should not exceed 6 tablets.

HOW SUPPLIED:

Hydrocodone Bitartrate and Acetaminophen Tablets, USP are available as:

2.5 mg/500 mg: Light pink mottled, capsule-shaped, scored tablet. Debossed with b/896 on one side and plain on the other side. Available in bottles of:

100 NDC 0555-0896-02

500 NDC 0555-0896-04

5 mg/500 mg: White, capsule-shaped, scored tablet. Debossed with b/915 on one side and plain on the other side. Available in bottles of:

100 NDC 0555-0915-02

500 NDC 0555-0915-04

7.5 mg/500 mg: Light green, capsule-shaped, scored tablet. Debossed with b/897 on one side and plain on the other side. Available in bottles of:

100 NDC 0555-0897-02

500 NDC 0555-0897-04

7.5 mg/650 mg: Peach, capsule-shaped, scored tablet. Debossed with b/895 on one side and plain on the other side. Available in bottles of:

100 NDC 0555-0895-02

500 NDC 0555-0895-04

7.5 mg/750 mg: Light yellow, capsule-shaped, scored tablet. Debossed with b/736 on one side and plain on the other side. Available in bottles of:

100 NDC 0555-0736-02

500 NDC 0555-0736-04

10 mg/500 mg: Light beige mottled, capsule-shaped, scored tablet. Debossed with b/919 on one side and plain on the other side. Available in bottles of:

100 NDC 0555-0919-02

500 NDC 0555-0919-04

10 mg/650 mg: Blue mottled, capsule-shaped, scored tablet. Debossed with b/898 on one side and plain on the other side. Available in bottles of:

100 NDC 0555-0898-02

500 NDC 0555-0898-04

Dispense with a child-resistant closure in a tight, light-resistant container as defined in the USP/NF.

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

A schedule CIII narcotic.

MANUFACTURED BY
BARR LABORATORIES, INC.
POMONA, NY 10970

BR- 896, 915, 897, 895, 736, 919, 898
Revised NOVEMBER 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-307

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 40-307

3. NAME AND ADDRESS OF APPLICANT
Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970-5019

4. LEGAL BASIS FOR SUBMISSION
The RLDs are Mikart's

2.5 mg/500 mg (89-698)
7.5 mg/500 mg (89-699)
7.5 mg/650 mg (89-689)
10 mg/650 mg (81-223)

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Hydrocodone Bitartrate and Acetaminophen Tablets USP

9. AMENDMENTS AND OTHER DATES:
Firm :
4-13-98: Original application
7-13-99: Amendment
4-12-00: Amendment
7-11-00: Tele-amendment

FDA:
5-21-98: acknowledgement

10. PHARMACOLOGICAL CATEGORY
Analgesic and Antitussive

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

and 20 for LOAs.

13. DOSAGE FORM
Tablet

14. POTENCY
2.5 mg/500 mg, 7.5 mg/500 mg,
7.5 mg/650 mg and 10 mg/650 mg

15. CHEMICAL NAME AND STRUCTURE

Acetaminophen:
C8H9NO2 M.W. 151.16
Chemical name: Acetamide, N-(4hydroxyphenyl)-4'-Hydroxyacetanilide

Hydrocodone Bitartrate:

C18H21NO3.C4H6O6.22H2O M.W. 494.5
Morphinan-6-one, 4,5-epoxy-3-methoxy-17-methyl,(5a)-,[R-(R*,*)]-2,3-dihydroxybutanedioate(1:1), hydrate(2:5).
4,5a-Epoxy-3methoxy-17-methylmorphinan-6-one tartrate(1:1) hydrate (2:5).
Anhydrous 449.46

17. COMMENTS

a. EER: **Acceptable**

Requested for Barr Laboratories Inc. (Forest, VA, Northvale, NJ and Pomona, NY),

Note: A summary of the findings from the initial inspection were submitted in a memo from Compliance dated November 17, 1998. The investigator included a note to the chemist expressing concern over the lack of validation for determination of impurities in the APIs. The review chemist has determined that the applicant conducts testing for the the major known impurities in both the APIs and final drug product. Method descriptions and validation data have been provided.

b. MV (method validation; N/A): **Acceptable**

Active drug substance and drug dosage form are both compendial items per USP 23.

c. Bio-Review: **Acceptable** per H. Nguyen reviewed on 8-4-98.

d. Labeling review: **Acceptable** per review dated 11/10/99.

e. DMFs: satisfactory

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable.

19. REVIEWER: Andrew J. Langowski

DATE COMPLETED: 05/26/00; 07/11/00

Page(s) 17

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

chem Rev 3

5/26/00

NOV 30 1998

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-307 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Hydrocodone Bitartrate and Acetaminophen Tablets USP, 2.5 mg/500 mg, 7.5 mg/500 mg, 7.5 mg/650 mg and 10 mg/650 mg

The deficiencies presented below represent Major deficiencies.

Chemistry Deficiencies:

1. Regarding the components and composition:

   Your component/composition statement indicates that the finished product does not retain any water. However, you have provided a limit of NMT for water in the finished product at release and stability. Please comment. Please revise and resubmit your composition statement as appropriate.

2. Regarding drug substance:

   Please submit TLC chromatograms and the Rf values used for identification testing of Acetaminophen, USP.

3. The submission fails to provide a complete formula card and satisfactory batch records. In this regard:

   a. Please include the sources of the active ingredient in the master formula card. Revise and resubmit.

   b. Please submit your in-process controls to include testing of the bulk granulations for uniformity as well as applicable specifications prior to tableting in the blank batch record. Please note that we do not review the process validation protocols.

   c. Pages 12-00175 - 12-00196 for test batch lots #7T89707 & # 7T89505 in volume 1.3 are missing. Please submit the missing pages.

4. Regarding finished product:

   a It is recommended that batch size, the sources of active ingredients, batch type (e.g., pilot or production), manufacturing site be included in the release certificate for the finished product.

Please submit a revised blank release certificate.

b. Regarding the stability-indicating nature of your assay method:

i. Please provide a list of known degradation products that may be expected under acid and basic hydrolysis, oxidation, heat and UV light.

ii. Please submit, in percentages, the assay values for the active ingredients and degradation products in tabular form.

c. Please include limits for individual and total impurities/degradation products in your finished product release certificates and stability reports. Please revise and resubmit.

d. The specification for is high and is not supported by data. Please tighten and resubmit the blank release and stability test specifications.

5. Your application fails to contain a satisfactory stability protocol and supporting stability data. In this regard:

a. Please include the description of drug product for each combination strength in the stability data report.

b. The stability summary report does not include all the tests and specifications that are included in your description of stability program and protocol (See Section XVII of your original submission). In this regard:

i. The report does not include test specifications for appearance. Appearance in the stability summary report should include more specific information such as hardness, color, odor, cracks and chips.

ii. The stability report has not been presented in the format proposed in your description of stability program and protocol. Please include the stability testing specifications in the stability data report. Please submit, separately, stability data for the accelerated, room temperature studies and container/closure system.

c. Please include formulation (composition) as part of the stability data report.

Sincerely yours,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-307

Bioequivalence Review(s)

Hydrocodone Bitartrate & Acetaminophen Tablets USP
ANDA # 40-307: 2.5/500 mg, 7.5/500 mg,
7.5/650 mg & 10/650 mg
Reviewer: Hoainhon Nguyen
WP # 40307dw.498

Barr Laboratories
Pomona, NY
Submission Date:
April 13, 1998
July 30, 1998

Review of Dissolution Data and Waiver Request

The firm has submitted comparative dissolution data for the test and reference products, at the above strengths, in support of a request for waiver of in-vivo bioequivalence requirements for the test product in accordance with 21CFR 320.22(b).

Amendment submitted on July 30, 1998 provides additional explanation for the composition statement concerning the quantities of Hydrocodone Bitartrate and Crospovidone listed.

Dissolution Results:

See the results at the end of the review.

Comments:

1. The dissolution data for the test and reference products are acceptable.

2. Hydrocodone Bitartrate/Acetaminophen Tablets USP, 2.5/500 mg, 7.5/500 mg, 7.5/650 mg, and 10/650 mg, are classified as an AA product in the agency's Approved Drug Products with Therapeutic Equivalence Evaluations Book.

3. The additional explanation for the compositions of all strengths of the test product is acknowledged. There is no further question concerning the compositions at this time.

Recommendations:

1. The dissolution testing conducted by Barr Laboratories on its Hydrocodone Bitartrate/Acetaminophen Tablets USP, 2.5/500 mg, 7.5/500 mg, 7.5/650 mg, and 10/650 mg, lots # 7T89601, 7T89702, 7T89501, and 7T89801, respectively, LK483, is acceptable.

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 at 37°C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

> Not less than , of the labeled amounts of Acetaminophen and Hydrocodone Bitartrate in the dosage form are dissolved in 30 minutes.

2. The Division of Bioequivalence agrees that the information submitted by Barr demontrates that its Hydrocodone Bitartrate/Acetaminophen Tablets, 2.5/500 mg, 7.5/500 mg, 7.5/650 mg, and 10/650 mg, fall under 21 CFR 320.22 (b) of the Bioavailability /Bioequivalence Regulations. The waiver of an *in vivo* bioequivalence study for the test product is granted. Barr's Hydrocodone Bitartrate/Acetaminophen Tablets, 2.5/500 mg, 7.5/500 mg, 7.5/650 mg, and 10/650 mg, are deemed bioequivalent to Mikart's Hydrocodone Bitartrate/Acetaminophen Tablets, 2.5/500 mg, 7.5/500 mg, 7.5/650 mg, and 10/650 mg, respectively.

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 8/4/98

Concur: Date: 8/6/98
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

USP Dissolution Testing Procedure and Specifications

Drug (Generic Name): Hydrocodone Bitartrate/Acetaminophen Tablets Firm: Barr Laboratories
Dose Strength: 2.5/500 mg, 7.5/500 mg, 7.5/650 mg & 10/650 mg ANDA # 40-307
Submission Date: April 13, 1998

Table - In-Vitro Dissolution Testing

Conditions for Dissolution Testing:

USP XXIII Basket __ Paddle X RPM 50 No. Units Tested: 12
Medium: pH 5.8 phosphate buffer Volume: 900 ml
Reference Drug: (Manuf.) Hydrocodone Bitartrate/Acetaminophen; Mikart
Assay Methodology: _____
USP Specifications: NLT issolved in 30 minutes

Results of In-Vitro Dissolution Testing:

Test Product
Lot # 7T89601
Strength (mg) 2.5 mg Hydrocodone Bitar. 500 mg Acetaminophen

Reference Product*
Lot # 950588E
Strength (mg) 2.5 mg Hydrocodone Bitar. 500 mg Acetaminophen

Acetaminophen:

Sampling Time (Min.)	Mean % Dissol.	Range	(CV%)	Mean % Dissol.	Range	(CV%)
10	99		(1.5)	100		(1.6)
20	100		(0.7)	101		(1.3)
30	100		(0.6)	101		(1.4)
45	100		(0.6)	100		(1.2)

Hydrocodone Bitartrate

Sampling Time (Min.)	Mean % Dissol.	Range	(CV%)	Mean % Dissol.	Range	(CV%)
10	100		(1.2)	104		3.7)
20	100		(1.1)	105		3.6)
30	101		(1.2)	106		(3.7)
45	100		(1.3)	105		(3.0)

Test Product
Lot # 7T89702
Strength (mg) 7.5 mg Hydrocodone Bitar.
500 mg Acetaminophen

Reference Product*
Lot # 950522D
Strength (mg) 7.5 mg Hydrocodone Bitar.
500 mg Acetaminophen

Acetaminophen:

Sampling Time (Min.)	Mean % Dissol.	Range	(CV%)	Mean % Dissol.	Range	(CV%)
10	95		(1.9)	96		(4.3)
20	97		(1.2)	98		(2.1)
30	97		(1.0)	98		(1.7)
45	96		(0.7)	98		(1.8)

Hydrocodone Bitartrate

Sampling Time (Min.)	Mean % Dissol.	Range	(CV%)	Mean % Dissol.	Range	(CV%)
10	98		(1.1)	98		(3.3)
20	98		(1.2)	100		(1.8)
30	98		(1.1)	100		(1.7)
45	98		(1.1)	100		(1.8)

Test Product
Lot # 7T89501
Strength (mg) 7.5 mg Hydrocodone Bitar.
650 mg Acetaminophen

Reference Product*
Lot # 950428C
Strength (mg) 7.5 mg Hydrocodone Bitar.
650 mg Acetaminophen

Acetaminophen:

Sampling Time (Min.)	Mean % Dissol.	Range	(CV%)	Mean % Dissol.	Range	(CV%)
10	100		(1.8)	99		(1.9)
20	102		(1.7)	101		(0.8)
30	102		(1.7)	101		(1.0)
45	101		(0.6)	101		(1.6)

Hydrocodone Bitartrate

Sampling Time (Min.)	Mean % Dissol.	Range	(CV%)	Mean % Dissol.	Range	(CV%)
10	102		(1.2)	100		(2.9)
20	104		(1.9)	102		(1.2)
30	103		(1.9)	102		(0.8)
45	102		(0.9)	102		(1.7)

Test Product
Lot # 7T89801
Strength (mg) 10 mg Hydrocodone Bitar.
650 mg Acetaminophen

Reference Product*
Lot # 951091j
Strength (mg) 10 mg Hydrocodone Bitar.
650 mg Acetaminophen

Acetaminophen:

Sampling Time (Min.)	Mean % Dissol.	Range	(CV%)	Mean % Dissol.	Range	(CV%)
10	100		(2.0)	101		(0.9)
20	102		(1.6)	102		(0.8)
30	101		(1.2)	102		(0.8)
45	101		(1.2)	102		(0.9)

Hydrocodone Bitartrate

Sampling Time (Min.)	Mean % Dissol.	Range	(CV%)	Mean % Dissol.	Range	(CV%)
10	102		(1.7)	102		(1.5)
20	103		(1.5)	103		(1.4)
30	103		(1.3)	103		(1.3)
45	103		(1.3)	103		(1.4)

*NOTE: All reference product lots used for dissolution testing were manufactured by Mikart although they were marketed under different trade names and by different firms.

BIOEQUIVALENCE COMMENTS

ANDA: 40-307 APPLICANT: Barr Laboratories

DRUG PRODUCT: Hydrocodone Bitartrate/Acetaminophen USP, 2.5/500 mg, 7.5/500 mg, 7.5/650 mg & 10/650 mg

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

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

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

Sincerely yours,

Dale P. Conner

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

Hydrocodone Bitartrate & Acetaminophen Tablets USP
ANDA # 40-307: 2.5/500 mg, 7.5/500 mg,
7.5/650 mg & 10/650 mg
Reviewer: Hoainhon Nguyen
WP # 40307dw.498

Barr Laboratories
Pomona, NY
Submission Date:
April 13, 1998
July 30, 1998

Review of Dissolution Data and Waiver Request

The firm has submitted comparative dissolution data for the test and reference products, at the above strengths, in support of a request for waiver of in-vivo bioequivalence requirements for the test product in accordance with 21CFR 320.22(b).

Amendment submitted on July 30, 1998 provides additional explanation for the composition statement concerning the quantities of Hydrocodone Bitartrate and Crospovidone listed.

Dissolution Results:

See the results at the end of the review.

Comments:

1. The dissolution data for the test and reference products are acceptable.

2. Hydrocodone Bitartrate/Acetaminophen Tablets USP, 2.5/500 mg, 7.5/500 mg, 7.5/650 mg, and 10/650 mg, are classified as an AA product in the agency's Approved Drug Products with Therapeutic Equivalence Evaluations Book.

3. The additional explanation for the compositions of all strengths of the test product is acknowledged. There is no further question concerning the compositions at this time.

Recommendations:

1. The dissolution testing conducted by Barr Laboratories on its Hydrocodone Bitartrate/Acetaminophen Tablets USP, 2.5/500 mg, 7.5/500 mg, 7.5/650 mg, and 10/650 mg, lots # 7T89601, 7T89702, 7T89501, and 7T89801, respectively, LK483, is acceptable.

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 at 37^{0}C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

> Not less than of the labeled amounts of Acetaminophen and Hydrocodone Bitartrate in the dosage form are dissolved in 30 minutes.

2. The Division of Bioequivalence agrees that the information submitted by Barr demontrates that its Hydrocodone Bitartrate/Acetaminophen Tablets, 2.5/500 mg, 7.5/500 mg, 7.5/650 mg, and 10/650 mg, fall under 21 CFR 320.22 (b) of the Bioavailability /Bioequivalence Regulations. The waiver of an *in vivo* bioequivalence study for the test product is granted. Barr's Hydrocodone Bitartrate/Acetaminophen Tablets, 2.5/500 mg, 7.5/500 mg, 7.5/650 mg, and 10/650 mg, are deemed bioequivalent to Mikart's Hydrocodone Bitartrate/Acetaminophen Tablets, 2.5/500 mg, 7.5/500 mg, 7.5/650 mg, and 10/650 mg, respectively.

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 5/4/98

Concur: Date: 5/6/98
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

BIOEQUIVALENCE COMMENTS

ANDA: 40-307 APPLICANT: Barr Laboratories

DRUG PRODUCT: Hydrocodone Bitartrate/Acetaminophen USP, 2.5/500 mg, 7.5/500 mg, 7.5/650 mg & 10/650 mg

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

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

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

Sincerely yours,

Dale P. Conner

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-307

ADMINISTRATIVE DOCUMENTS

DIVISION REVIEW SUMMARY

ANDA: 40-307

FIRM: Barr Laboratories, Inc.
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970-5019

DOSAGE FORM: Tablet STRENGTH: 2.5 mg/500 mg (89-698)
7.5 mg/500 mg (89-699)
7.5 mg/650 mg (89-689)
10 mg/650 mg (81-223)

DRUG: Hydrocodone Bitartrate and Acetaminophen

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable 11/16/98

BIO STUDY INFORMATION: Bio waiver granted. In-vitro dissolution data found acceptable per H. Nguyen on 8-4-98.

METHODS VALIDATION:

Active drug substance and drug dosage forms are both compendial items per USP 24.

STABILITY:

The containers used in the stability study are of the same size and material as those described in the container section. The firm submitted accelerated stability data for the product packaged in all container sizes.

The firm requests an expiration date of 24 months based on the data submitted.

The stability tests and specifications are as follows:

Product description and physical characteristics:

2.5 mg/500 mg:

Description: Light pink mottled, capsule-shaped, scored tablets. Debossed with b/896 on one side and plain on the other side (need in stability data report).

7.5 mg/500 mg:

Description: Light green, capsule-shaped, scored tablets. Debossed with b/897 on one side and plain on the other side (need in stability data report).

7.5 mg/650 mg:

Description: Peach, capsule-shaped, scored tablets. Debossed with b/895 on one side and plain on the other side (need in stability data report).

10 mg/650 mg:

Description: Blue mottled, capsule-shaped, scored tablets. Debossed with b/898 on one side and plain on the other side (need in stability data report).

Dissolution:

a. Hydrocodone Bitartrate:
pH 5.8 buffer, 900 mL, USP 2, 50 rpm, assay, NLT dissolved in 30 mins.
b. Acetaminophen:
pH 5.8 buffer, 900 mL, USP 2, 50 rpm, assay, NLT dissolved in 30 mins.

Assay:

a. Hydrocodone Bitartrate: 90.0% - 110.0% of label claim
b. Acetaminophen: 90.0% - 110.0% of label claim

Impurities/degradants:

Water:

LABELING: Acceptable 11/10/99.

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH:

Bio-waiver was granted based on in-vitro dissolution data obtained on the exhibit batch.

SIZE OF STABILITY BATCHES:

The executed batch records can be found on the following pages:

2.5 mg/500 mg:

a. executed batch #7T89601 [#7C869BI]), p. 12-0005-12-00073)
b. (blank batch record), p. 11-00011-11-00057

7.5 mg/500 mg:

a. (executed batch #7T89702 #[71897BB]) p.12-00074-12-000184
b. (blank batch record), p. 11-00058-11-000133

7.5 mg/650 mg:

a. executed batch #7T89501 [#7E897BB]), p.12-0185-12-00265)
b. atch record), p.11-00134-11-000187.

10 mg/650 mg:

a. (executed batch #7T89801 [#7E898BC]), p.12-0266-12-00369)
b. blank batch record), p.11-00188-11-00268. 281-295.

PROPOSED PRODUCTION BATCH:

The proposed production batch sizes for the strengths indicated above are , respectively.

RECOMMENDATION: Approve.

SIGNATURE: DATE: 7/24/00
7/27/00

Page(s) ~~0~~ 5

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

Div. Rev. 7/24/00

composition
specification
lab controls

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

ANDA Number: 40-307, 40-308, 40-309

Date of Submissions: April 13, 1998 (40-307)
April 14, 1998 (40-308)
April 15, 1998 (40-309)

Applicant's Name: Barr Laboratories, Inc.

Established Name: Hydrocodone Bitartrate and Acetaminophen Tablets USP
(40-307) 2.5 mg/500 mg, 7.5 mg/500 mg, 7.5 mg/650 mg, 10 mg/650 mg
(40-308) 5 mg/500 mg, 7.5 mg/750 mg
(40-309) 10 mg/500 mg

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. Please note that since ANDAs 40-307, 40-308 and 40-309 share a common insert that these applications must be approved at the same time or the insert must be revised accordingly.

   b. Section 126 of Title I of the FDA Modernization Act of 1997, amends Section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act to require, at a minimum, that prior to dispensing, the label of prescription products contain the symbol "Rx only". A GUIDANCE FOR INDUSTRY entitled "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 Elimination of Certain Labeling Requirements", was revised July 1998 and posted at Internet site: **http://www.fda.gov/cder/guidance/index.htm.** Please note that Section IV, "Frequently Asked Questions" offers guidance on placement of the symbol on all labels and labeling.

c. The FDA Modernization Act of 1997 has deleted the requirement for the presence of the statement "WARNING: May be habit-forming." throughout the labels and labeling of scheduled drugs. You may remove this statement and accompanying asterisk from your labels and labeling.

2. CONTAINER 100s and 500s (all strengths)

a. Satisfactory, however see GENERAL COMMENTS (b) and (c) above.

b. The changes as mentioned in (b) and (c) above may be done post-approval for the container labels.

3. INSERT

a. DESCRIPTION

i. Revise the structural formula of hydrocodone bitartrate as follows:

$2\frac{1}{2}H_2O$ rather than 5/2 H_2O

ii. Third paragraph, last sentence - "It has ..." Rather than "Its has ...".

iii. Revise the molecular weight of acetaminophen to read 151.17 as seen in USP 23.

iv. See GENERAL COMMENT (c) above.

b. HOW SUPPLIED

i. You have described the 10 mg/500 mg tablet as "light beige mottled" yet on page 15.00006 of ANDA 40-309 it states "light brown" with no mention of "mottled". Please comment and/or revise.

ii. See GENERAL COMMENT (b) above.

Please revise your insert labeling, as instructed above, and submit in final print.

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

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

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

ANDA 40-307

Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970-0519

MAY 21 1998

Dear Madam:-

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

Reference is made to the telephone conversation dated April 28, 1998 and your correspondence dated May 11, 1998.

NAME OF DRUG: Hydrocodone Bitartrate and Acetaminophen Tablets USP, 2.5 mg/500 mg, 7.5 mg/500 mg, 7.5 mg/650 mg and 10 mg/650 mg

DATE OF APPLICATION: April 13, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: April 14, 1998

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

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

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-307

CORRESPONDENCE

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

July 11, 2000

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

REFERENCE: **TELEPHONE AMENDMENT**
ANDA 40-307
HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP
2.5 MG/500 MG, 7.5 MG/500 MG, 7.5 MG/650 MG & 10 MG/650 MG

Reference is made to our Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Tablets, USP 2.5 mg/500 mg, 7.5 mg/500 mg, 7.5 mg/650 mg and 10 mg/650 mg, submitted on April 13, 1998.

Reference is also made to a discussion between Christine Mundkur of Barr Laboratories Inc. and Andrew Langowski of the Office of Generic Drugs on July 6, 2000. As requested by Mr. Langowski, we are providing updated Raw Materials Specification and Test Records for, Acetaminophen, USP and Hydrocodone Bitartrate, USP, to conform to USP 24.

Barr has also tightened the stability specification of [redacted] for Hydrocodone Bitartrate and Acetaminophen Tablets, USP. Copies of the revised Acceptance Tests for In-Process and Finished Products and Marketed Product Stability Specifications and Test Records are provided.

Identical copies of this amendment have also been submitted to the New Jersey and Baltimore District Offices. If you have any questions concerning this correspondence, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely

BARR LABORATORIES, INC.

Christine Mundkur,
Regulatory Counsel and Vice President of
Regulatory Affairs

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

April 12, 2000

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

REFERENCE: **FACSIMILE AMENDMENT**
ANDA 40-307
HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP 2.5 MG/500 MG, 7.5 MG/500 MG, 7.5 MG/650 MG, AND 10 MG/650 MG

Reference is made to our Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Tablets, USP 2.5 mg/500 mg, 7.5 mg/500 mg, 7.5 mg/650 mg and 10 mg/650 mg submitted on April 13, 1998.

Reference is also made to a facsimile deficiency received on January 18, 2000. Following are the deficiencies identified by the Agency in bold print followed by Barr's response.

Chemistry Deficiencies:

1. **Regarding the components and composition:**

RESPONSE

OGD

Page(s) 2

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

4/12/00

3.

Sincerely

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

Document Certification

In accordance with 21 CFR 314.96 (b), Barr Laboratories, Inc. hereby certifies that field copies of this Amendment have been submitted to the New Jersey and Baltimore district offices of the FDA. Barr Laboratories, Inc. further certifies that the field copies are true copies of the material submitted to the Agency.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

April 12, 2000
Date

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

July 13, 1999

TPC
NDA ORIG AMENDMENT
AC

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

REFERENCE: **MAJOR AMENDMENT**
ANDA 40-307
HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP 2.5 MG/500 MG, 7.5 MG/500 MG, 7.5 MG/650 MG, AND 10 MG/650 MG

Reference is made to our Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Tablets, USP 2.5 mg/500 mg, 7.5 mg/500 mg, 7.5 mg/650 mg and 10 mg/650 mg submitted on April 13, 1998.

Reference is also made to a deficiency letter received on November 30, 1998. Following are the deficiencies identified by the Agency in bold print followed by Barr's response.

Chemistry Deficiencies:

1. **Regarding the components and composition:**

RESPONSE

...ed in

Page(s) 9

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

7/13/99

ANDA 40-307
HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP
2.5 MG/500 MG, 7.5 MG/500 MG, 7.5 MG/650 MG, AND 10 MG/650 MG

Labeling Deficiencies:

1. **GENERAL COMMENTS**

   a. **Please note that since ANDAs 40-307, 40-308 and 40-309 share a common insert that these applications must be approved at the same time or the insert must be revised accordingly.**

   b. **Section 126 of Title I of the FDA Modernization Act of 1997, amend Section 503 (b) (4) of the Federal Food, Drug and Cosmetic Act to require, at a minimum, that prior to dispensing, the label of prescription products contain the symbol "Rx only". A GUIDANCE FOR INDUSTRY entitled "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 Elimination of Certain Labeling Requirements", was revised July 1998 and posted at Internet site: http://www.fda.gov/cder/guidance/index.htm. Please note that Section IV, " Frequently Asked Questions " offer guidance on placement of the symbol on all labels and labeling.**

   c. **The FDA Modernization Act of 1997 has deleted the requirement for the presence of the statement "WARNING: May be habit-forming." throughout the labels and labeling of scheduled drugs. You may remove this statement and accompanying asterisk from your labels and labeling**

   RESPONSE

   We acknowledge Agency's comment regarding the common insert, "Rx only" symbol and WARNING statement. Please refer to our response to Comments 2 and 3.

2. **CONTAINER 100s and 500s (all strengths)**

   a. **Satisfactory, however see GENERAL COMMENTS (b) and (c) above.**

   b. **The changes as mentioned in (b) and (c) above may be done post-approval for the container labels.**

ANDA 40-307
HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP
2.5 MG/500 MG, 7.5 MG/500 MG, 7.5 MG/650 MG, AND 10 MG/650 MG

Labeling Deficiencies (Continued):

RESPONSE

Barr will revise its container labels to replace the caution statement with the "Rx only" symbol during printing of the next production quantities.

3. **INSERT**

a. **DESCRIPTION**

i. **Revise the structural formula of hydrocodone bitartrate as follows: 2 ½ H_2O rather than 5/2 H_2O**

ii. **Third paragraph, last sentence – "It has ..." Rather than "Its has ...".**

iii. **Revise the molecular weight of acetaminophen to read 151.17 as seen in USP 23.**

iv. **See GENERAL COMMENT (c) above.**

RESPONSE

The insert has been revised according to the above comments. The revised final printed insert is provided in Attachment L.

b. **HOW SUPPLIED**

i. **You have described the 10 mg/500 mg tablet as " light beige mottled" yet on page 15.00006 of ANDA 40-309 it states " light brown" with no mention of "mottled". Please comment and /or revise.**

RESPONSE

The description of 10 mg/500 mg tablet "light beige mottled" as it appears in the HOW SUPPLIED section is the correct description. Page 15-00006 of ANDA 40-309 is the executed finished product specification and test record that had the improper description. The finished product specification for 10 mg/500 mg tablet has been revised with proper tablet description and is provided in the Amendment to ANDA 40-309.

ANDA 40-307
HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP
2.5 MG/500 MG, 7.5 MG/500 MG, 7.5 MG/650 MG, AND 10 MG/650 MG

Labeling Deficiencies (Continued):

ii. **See GENERAL COMMENT (b) above.**

RESPONSE

The insert has been revised according to the GENERAL COMMENT (b) above.

Please revise your insert labeling, as instructed above, and submit in final print.

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

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

RESPONSE

The insert has been revised according to the above comments. The revised final printed insert is provided in Attachment L. A side-by-side comparison of revised insert with our last submission is provided in Attachment M with all differences annotated and explained.

Please note that Barr was just informed that during August 1997 to February 1998 Celsis Laboratory Group, one of Barr's outside contract laboratory, has relocated their New Jersey testing site to 165 Fieldcrest Avenue, Edison, New Jersey 08837. Appropriate CGMP statement and Debarment certification is provided in Attachment N.

If you have any questions concerning this correspondence, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality
and Regulatory Counsel

Barr Laboratories, Inc.

Document Certification

In accordance with 21 CFR 314.96 (b), Barr Laboratories, Inc. hereby certifies that field copies of this correspondence have been submitted to the New Jersey and Baltimore district offices of the FDA. Barr Laboratories, Inc. further certifies that the field copies are true copies of the material submitted to the Agency.

Christine Mundkur
Vice President, Quality
and Regulatory Counsel

JUL 13 1999

Date

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

Labeling reviewed drafted 8/21/98 A. Vega

April 13, 1998

505(j)(2)(A) OK 5/14/98

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

We are submitting herewith, in duplicate, an Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Tablets, USP 2.5 mg/500 mg, 7.5 mg/500 mg, 7.5 mg/650 mg, and 10 mg/650 mg.

The application is provided both as an archival copy and a review copy. The archival copy of the application is contained in blue binders and consists of 5 volumes. The review copy is divided into two parts. The chemistry, manufacturing and controls part of the review copy is contained in red binders and consists of 5 volumes. The bioequivalence part of the review copy is contained in orange binders and consists of 1volumes.

The format of this application is in accordance with Office of Generic Drugs, Policy and Procedure Guide #30-91. The contents of this application have been compiled in accordance the October 14, 1994 communication from Dr. Janet Woodcock, Director (CDER) and Mr. Ronald Chesemore (ORA). Numerous SOPs are no longer submitted in the application; however, these procedures are kept current and are available for inspection by the FDA District Field Investigators.

Included in this application, and in accordance with the Generic Drug Enforcement Act of 1992, a Debarment Certification Statement with a List of Convictions Statement is provided in this application. In addition, in accordance with the FDA's Final Rule (Federal Register, Vol. 58, No. 172, September 8, 1993), a "Field Copy" of this application has been forwarded to the Baltimore, and New Jersey District Offices.

Please note that Barr is also submitting two other applications for Hydrocodone Bitartrate and Acetaminophen Tablets, USP 5 mg/500 mg, and 10 mg/500 mg, and 7.5 mg/750 mg strengths, respectively, at the same time.

Your earliest acknowledgment to this application will be very much appreciated.

Sincerely

BARR LABORATORIES, INC.

Christine Mundkur,
Regulatory Counsel and Director of
Regulatory Affairs

CM:cad
Enclosures