CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 40182

Trade Name Hydrocodone Bitartrate and Acetaminophen Elixir 7.5mg/500mg per 15ml

Generic Name Hydrocodone Bitartrate and Acetaminophen Elixir 7.5mg/500mg per 15ml

Sponsor Pharmaceutical Associates, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 40182

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40182

APPROVAL LETTER

ANDA 40-182

MAR 13 1998

Pharmaceutical Associates, Inc.
Attention: Kaye B. McDonald
P.O. Box 128
Conestee, South Carolina 29636

Dear Madam:

This is in reference to your abbreviated new drug application dated February 29, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Hydrocodone Bitartrate and Acetaminophen Elixir, 7.5 mg/500 mg per 15 mL.

Reference is also made to your amendments dated February 25, and November 17, 1997, and January 27, and March 10, 1998.

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

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

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies which may be identified.

Sincerely yours,

3-13-98

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40182

FINAL PRINTED LABELING

NDC 0121-0655-16

Hydrocodone* Bitartrate and Acetaminophen Elixir

CIII

7.5 mg/500 mg per 15 mL

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

CAUTION: Federal law prohibits dispensing without prescription.

16 fl oz (473 mL)

pai Pharmaceutical Associates, Inc.
Greenville, SC 29605

PHARMACIST: Dispense in a tight, light-resistant container with a child-resistant closure.
Store at controlled room temperature, 15°-30°C (59° -86°F).
WARNING: Keep this and all medications out of the reach of children.

USUAL DOSAGE: See Package Insert for Complete Dosage Recommendations.

ADDED

1 3 1998

Lot No.:
Exp. Date:

NDC 0121-0655-04

Hydrocodone* Bitartrate and Acetaminophen Elixir

CIII

7.5 mg/500 mg per 15 mL

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

CAUTION: Federal law prohibits dispensing without prescription.

4 fl oz (118 mL)

pai Pharmaceutical Associates, Inc.
Greenville, SC 29605

PHARMACIST: Dispense in a tight, light-resistant container with a child-resistant closure.
Store at controlled room temperature, 15°-30°C (59°-86°F).
WARNING: Keep this and all medications out of the reach of children.

USUAL DOSAGE: See Package Insert for Complete Dosage Recommendations.

ADDED

1 3 1998

Lot No.:
Exp. Date:

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR
10 x 15 mL

1 3 1998

Hydrocodone Bitartrate and Acetaminophen Elixir

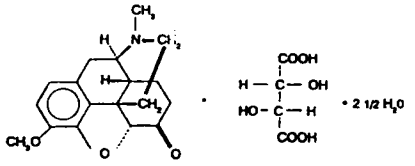
CIII

7.5 mg/500 mg per 15 mL

DESCRIPTION

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

Hydrocodone bitartrate is an opioid analgesic and antitussive which 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:



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$ M.W. 494.50

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

$C_8H_9NO_2$ M.W. 151.16

Hydrocodone Bitartrate and Acetaminophen Elixir contains:

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

In addition Hydrocodone Bitartrate and Acetaminophen Elixir contains the following inactive ingredients: citric acid, glycerin, methylparaben, propylene glycol, purified water, saccharin sodium, sorbitol solution, sucrose, with D&C Yellow #10 as coloring and natural and artificial flavoring.

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics: The behavior of the individual components is described below.

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6-α- and 6-β-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 Elixir is indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

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

WARNINGS

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

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

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

Pregnancy:

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

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

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

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

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

ADVERSE REACTIONS

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory 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 Elixir may produce constipation.

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

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on 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

Hydrocodone Bitartrate and Acetaminophen Elixir is classified as a Schedule III controlled substance.

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

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly larger 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 and 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 the pain and the response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one tablespoonful (15 mL) every four to six hours as needed for pain. The total 24 hour dose should not exceed 6 tablespoonfuls.

HOW SUPPLIED

Hydrocodone Bitartrate and Acetaminophen Elixir is a yellow-colored, fruit flavored liquid containing 7.5 mg hydrocodone* bitartrate (*WARNING: May be habit forming), and 500 mg acetaminophen per 15 mL, with 7% alcohol. It is supplied in containers of 4 fl oz (118 mL), NDC 0121-0855-04, in containers of 16 fl oz (473 mL), NDC 0121-0855-16, and unit dose containers of 15 mL NDC 0121-0855-15.

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

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

CAUTION: Federal law prohibits dispensing without prescription.

A schedule III Controlled Substance.

Manufactured by:

Pai Pharmaceutical Associates, Inc.
Greenville, SC 29605

R 1/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40182

CHEMISTRY REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VI
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 40-182

3. NAME AND ADDRESS OF APPLICANT
Pharmaceutical Associates, Inc.
Delaware Street at Perimeter Road
P.O. Box 128
Contestee, SC 29636

4. LEGAL BASIS FOR SUBMISSION
Lortab® Elixir, 7.5 mg/500 mg per 15 mL
Mikart, Inc.
2090 Marietta Boulevard, N.W.
Atlanta, GA 30318

There are no current patents or exclusivities.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Hydrocodone Bitartrate
USP and Acetaminophen USP

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

9. AMENDMENTS AND OTHER DATES:
Firm:
2/29/96 Original Submission.
4/23/96 Response to Agency's Refusal to File letter of 4/10/96.
2/25/97 Amendment - Response to Agency's letter of 11/27/96.
11/17/97 Amendment.
FDA:
4/10/96 Issuance of Refusal to File Letter.
5/14/96 Receipt acknowledged - Acceptance for Filing.
9/6/96 Issuance of Bioequivalence No Further Questions Letter.
11/27/96 Issuance of Not Approvable letter.

10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesics

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA #81-051 001 - Mikart

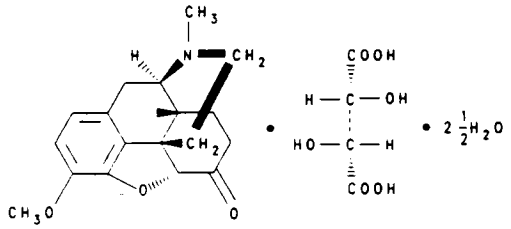
13. DOSAGE FORM
Oral Elixir

14. POTENCY
7.5 mg/15 mL Hydrocodone Bitartrate
500 mg/15 mL Acetaminophen

15. CHEMICAL NAME AND STRUCTURE

Hydrocodone Bitartrate USP

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



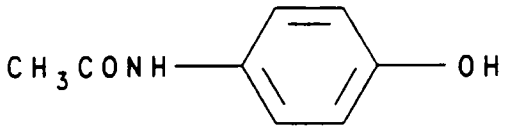
4,5α-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). CAS [34195-34-1; 6190-38-1]

USP: Fine, white crystals or a crystalline powder. Is affected by light. Soluble in water; slightly soluble in alcohol; insoluble in ether and in chloroform.

Merck: Needles, mp 146 - 148 ° (dry). (This melting range is reported but actual tests do not confirm it.) One gram dissolves in 16 mL water, in 150 g 95% ethanol. Almost insol in ether, chloroform. pH of a 2% aq soln ~3.6. LD_{50} s.c. in mice (Hydrocodone): 8.57 mg/kg.

Caution: May be habit forming. This is a controlled substance (opiate) listed in the U.S. Code of Federal Regulations, Title 21 Parts 329.1 and 1308.12 (1985).

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



4'-

Hydroxyacetanilide. CAS [103-90-2]

A white, odorless crystalline powder, possessing a slightly bitter taste. Large monoclinic prisms from water, mp 169 - 170.5°C. d_4^{21} 1.293. uv max (ethanol): 250 nm (ε 13,800). Very slightly sol in cold water, considerably more sol in hot water. Sol in methanol, ethanol, dimethylformamide, ethylene dichloride, acetone, ethyl acetate. Slightly sol in ether. Practically insol in petr ether, pentane, benzene. LD_{50} in mice (mg/kg): 338 orally, 500 i.p.

16. RECORDS AND REPORTS
8/14/96 - Labeling review, C. Hoppes.
8/27/96 - Bioequivalence waiver, M. Park.
9/30/96 - Chemistry review #1, G.J. Smith.
5/9/97 - Labeling review, C. Holquist.

17. COMMENTS
The firm has resolved all major questions concerning the chemistry, manufacturing, and controls section of the application.

Labeling was found to be satisfactory.

The request for bioequivalence waiver was granted by the Division of Bioequivalence.

An acceptable EIR was issued by the Office of Compliance.

Methods Validation for the drug product pending.

The DMF's for both drug substances remain satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS
The application may be Approved, pending acceptable Method Validation report.

19. REVIEWER: Glen Jon Smith
DATE COMPLETED: 17 December 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40182

BIOEQUIVALENCE REVIEW(S)

ANDA 40-182

Pharmaceutical Associates, Inc.
Attention: Kaye B. McDonald
Delaware Street at Perimeter Road
P.O. BOX 128
Contestee SC 29636

SEP 6 1996

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Elixir 7.5 mg/500 mg per 15 mL.

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

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

for Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

AUG 27 1995

Hydrocodone Bitartrate and Acetaminophen Elixir	Pharmaceutical Associates
7.5 mg/500 mg per 15 mL	Conestee, SC
ANDA #40182	Submission Dates:
Reviewer: Moo Park	February 29, 1996
Filename: 40182w.296	April 23, 1996

Review of a Waiver Request

I. Objectives

Review of Pharmaceutical Associates' waiver request for its Hydrocodone/Acetaminophen Elixir, 7.5 mg/500 mg. Reference listed drug product is Whitby's Lortab^{R} elixir, 7.5 mg/500 mg per 15 mL (Mikart is the manufacturer.)

II. Background

The original submission dated 2/29/96 was refused to be filed by OGD due to the additional unit dose packages (5 and 10 mL) the firm included in the ANDA. The firm revised the ANDA to include only 15 ml unit dose in the resubmitted ANDA dated 4/23/96.

III. Comments

1. Hydrocodone/Acetaminophen Elixir is an AA rated drug products and dosage form is an oral solution. ✓

2. Formulation of the test product is shown in Table 1. The reference product contains citric acid anhydrous, ethyl maltol, glycerin, methylparaben, propylene glycol, propylparaben, purified water, saccharin sodium, sorbitol solution, sucrose, colors and flavors besides the active ingredients. The test formulation is acceptable.

Table 1. Test Formulation

Ingredient	Amount, mg/15 mL
Acetaminophen	500
Hydrocodone Bitartrate	7.5
Alcohol USP	
Methylparaben	
Sodium Saccharin	
Sucrose NF	
Propylene Glycol	
Glycerin	
Sorbitol Solution USP	
D&C Yellow NO. 10 0.001% w/v	
Mixed Fruit Flavor 0.5% v/v	
Purified Water	
Total volume	15 mL

3. The waiver of *in vivo* bioequivalence study requirements is granted for the test product.

XI. Recommendations

The Division of Bioequivalence agrees that the information submitted by Pharmaceutical Associates demonstrate that Hydrocodone Bitartrate/Acetaminophen Elixir, 7.5 mg/500 mg per 15 mL, falls under 21 CFR Section 320.22 (b) of the Bioavailability/ Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test Hydrocodone Bitartrate/Acetaminophen Elixir, 7.5 mg/500 mg per 15 mL, to be bioequivalent to Mikart's Lortab® elixir, 7.5 mg/500 mg per 15 mL.

Moo Park, Ph.D.
Review Branch III
The Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRF 8/19/96

Concur: _____ Date: 8/27/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA # 40-182, HFD-630(OGD), HFD-604(Hare), HFD-658 (Mhatre, Park), HFD-22 (Hooton), HFC-130/JAllen, Drug File

File history: Draft (7/30/96); Final (8/14/96)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40182

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA: 40-182

DRUG PRODUCT: Hydrocodone Bitartrate and Acetaminophen

FIRM: Pharmaceutical Associates
Delaware Street at Perimeter Road
P.O. Box 128
Contestee, SC 29636

DOSAGE FORM: Oral Elixir
STRENGTH: 7.5 mg/500 mg per 15 mL

CGMP STATEMENT/EIR UPDATE STATUS:

CGMP statement (p. 1815) and Section 306(k) certification (pp. 4, 5) in original submission.

EIR acceptable for drug product manufacturer and drug substance manufacturer,

Facilities included:

Manufacturing, packaging, labeling, testing:

Pharmaceutical Associates, Inc.
Division of Beach Products, Inc.
201 Delaware Street
Greenville, SC 29605.

Drug Substance Manufacturer: Acetaminophen USP

Drug Substance Manufacturer: Hydrocodone Bitartrate USP

BIO STUDY:

The firm requested a waiver from the requirement for the submission of evidence demonstrating the *in vivo* bioavailability of the drug product per 21 CFR 320.22(b)(3). A waiver of *in vivo* bioequivalence study was granted by the Division of Bioequivalence, M. Park, 8/27/96.

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Drug substances are compendial. Methods for drug product pending update request of 12/11/97.

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

Stability for the following included:

Dosage	Lot #	Batch Size	Sample	Test Conditions
7.5 mg/ 500 mg per 15 mL	13315		15 mL Unit	40°C/75% RH/3 months 25° - 30°C/3, 10, 22 months
			4 oz PET	40°C/75% RH/3 months 25° - 30°C/3, 10, 22 months
			16 oz PET	40°C/75% RH/3 months 25° - 30°C/3, 10, 22 months
			16 oz HDPE	40°C/75% RH/3 months 25° - 30°C/3, 10, 22 months

Container/Closure system:

473 mL/container - 16 oz Amber PET bottle, 28-400 White Fine-Ribbed Polypropylene closure with pulp/vinyl liner; 473 mL/container - 16 oz Brown HDPE bottle, 28-400 White Fine-Ribbed Polypropylene closure with pulp/vinyl liner; 118 mL/container - 4 oz Amber PET bottle, White Fine-Ribbed Clic-Loc II closure with pulp/vinyl liner.

Unit dose cups - 45 mL unit dose HDPE cup, aluminum laminate lid with heat seal coating, containing 15 mL.

All container/closure systems are as described in the Container/Closure section.

Expiration date: 24 months for PET and HDPE bottles, 18 months for unit dose cups, based on accelerated/room temperature data.

LABELING:

Description in package insert satisfactory for molecular structure, molecular formula, formula weight, inactive ingredients, product description and package size.

Professional labeling - satisfactory, J. White, 12/11/97.

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

Bio waiver batch: 7.5 mg/500 mg per 15 mL product, Lot #13315, bulk batch size stability data included.

satisfactory, L.Tang, 4/18/97, no amendments since then.

satisfactory, L. Tang, 4/18/97, no amendments since.

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?:

Executed batch records for the 7.5 mg/500 mg per 15 mL batch bulk Lot #13315 (bio waiver/stability batch) included. Six blank batch records were submitted in the application: bulk solutions. All scale-ups consistent with current Office policy. Proposed manufacturing processes are the same as the bio/stability batches.

CHEMIST: GSmith DATE: 1/12/97; 1/14/98 2/6/98

SUPERVISOR: Uvenkatarar DATE: 1/14/98 2/10/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40182

CORRESPONDENCE

pai Pharmaceutical Associates, Inc.

FA

FASCIMILE AMENDMENT

November 17,1997

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

(N/FA)

RECEIVED
NOV 19 1997
GENERIC DRUGS

Re: ANDA 40-182 Hydrocodone
Bitartrate and Acetaminophen Elixir 7.5mg/500mg per 15ml

Dear Sirs:
This Facsimile Amendment is in response to your communication dated October 23, 1997.

A. Deficiencies:

1. Your final product specifications for the unit dose cup erroneously show the upper fill/delivery limit as Please submit a corrected copy of the final product specification.

Response:

A corrected copy of the final product specifications is included on pages 1-2.

2. Your most recent stability specifications do not contain Microbial Limits Testing as was shown in the original submission. They also fail to include testing fill/delivery volume. Please revise your stability protocol and specification to include these tests, to be conducted at least on an annual basis and at expiration.

Response:

A revised stability specification and protocol is included on pages 3-5.

3. The room temperature stability data submitted in support of your expiration dating was not conducted at the testing stations 0, 3, 6, 9, 12, 18, and 24 months as indicated in your proposed stability protocol.

a. Please explain why stability testing was not conducted according to the proposed protocol.

Response:

The stability protocol refers to production batches. At the time the pilot batch was manufactured, we were not testing experimental lots except for accelerated stability. We now perform shelf stability testing as well as accelerated.

b. Please submit any data obtained for the exhibit lots tested according to the original protocol schedule.

Response:

The available stability data is included on pages 6 -9. The Hydrocodone degradant method has been revised recently in order to detect lower levels of degradant. The earlier method did not detect any peaks, however, the revised method was used on shelf sample which were approximately 30 months old. This data is included on pages 10 - 12.

c. Please confirm that stability testing will be conducted according to the approved protocol.

Response:

Stability testing on the product will be performed per the original stability schedule.

Labeling

1. Container (1 pint, 4 fl oz., and 15 mL unit dose)

   For computer generated labels to be acceptable as final print, they must be of true size, color and clarity. Please assure that these criteria are met prior to submitting final print.

Response:

Included on pages 13 – 24 are 2X12 copies of final printed container labels for the 16 0z. 4 oz, and 15 mL unit dose.

2. Carton (10 x 15 mL)

The 15 mL unite dose tray labels will be exactly as they appear in the amendment dated February 25, 1997 on pages 140 – 141. The ends will be stamped as those included on pages 25 - 26 of this amendment.

At the request of the inspector during a pre-approval inspection in August of this year, additional work was done on the degradation testing for Hydrocodone. A copy of this work is included on pages 27 – 46.

During a follow-up inspection in October, additional work was requested on the Hydrocodone degradants. The sample preparation was adjusted for the degradation testing to improve the detection of the low-level degradents. This work and the revised method are included on pages 47 – 96. Shelf samples (approximately 30 months) were tested using the revised procedure. These results are included on pages 10 – 12.

We have answered all questions to the best of our knowledge. If you have further questions, please call (864) 277-7282 ext. 30.

Sincerely,

PHARMACEUTICAL ASSOCIATES, INC.

Kaye B. McDonald

Kaye B. McDonald
Director of Scientific Affairs

pai Pharmaceutical Associates, Inc.

February 25, 1997

NDA ORIG AMENDMENT
N/Ic PL

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-273

RE: ANDA 40-182 Hydrocodone Bitartrate and Acetaminophen Elixir, 7.5 mg/500 mg per mL

Enclosed is Form 356H applying for a MAJOR amendment to our pending ANDA 40-182 Hydrocodone Bitartrate and Acetaminophen Elixir, 7.5 mg/500 mg per 15 mL. This is in response to your communication dated November 27, 1996.

A. Chemistry Deficiencies

PAGES 2-5

CHEMISTRY DEFICIENCIES REDACTED

GENERIC DRUGS

B. Labeling Deficiencies

1. General

Our labeling is in compliance with 21 CFR 1302.03, 1302.04 and 1302.05 regarding the controlled substance symbol.

2. Container

We have revised our container labeling incorporating all of your comments. Included in this amendment are 2 x 12 copies of final print container labels for 1 pint on pages 129 - 134, 4 fl oz on page 135 - 138 and 15 mL unit dose on page 139.

3. Carton

Included on pages 142 - 147 of this amendment are 2 x 12 copies of final print for tray labels and tray ends. All of your comments have been incorporated into the revision.

4. Insert

We have revised the insert incorporating all of your comments and have included 2 x 12 copies of final print on pages 150 - 162.

A side-by-side comparison of our proposed labeling with our last submission is included on pages 150 - 162 of this amendment.

We have responded to all your questions and comments. If further information is needed, please let us know. Our fax number is (864) 277-8045.

Sincerely,

Kaye B. McDonald

Kaye B. McDonald

Scientific Affairs Manager

ANDA 40-182

Pharmaceutical Associates, Inc.
Attention: Kaye B. McDonald
Delaware Street at Perimeter Road
P.O. Box 128
Contestee, SC 29636

NOV 27 1996

Dear Madam:

This is in reference to your abbreviated new drug application dated February 29, 1996 and accepted for filing April 24, 1996 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, for Hydrocodone Bitartrate and Acetaminophen Elixir, 7.5 mg/500 mg per 15 mL.

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

A. Chemistry Deficiencies

1. Components and Composition

PAGES 2-4
CHEMISTRY DEFICIENCIES
REDACTED

B. Labeling Deficiencies

1. GENERAL

a. We acknowledge the comments in your letter of April 23, 1996, that you have requested that reference to
be deleted.

b. We refer you to 21 CFR 1302.03, 1302.04, and 1302.05, regarding the requirements for the controlled substance symbol to appear on the labeling for your product. Please ensure that your labeling is in compliance with these regulations.

2. CONTAINER (1 pint, 4 fl oz, and 15 mL unit dose)

a. See second GENERAL comment.

b. Make the following revisions on the container label for the 1 pint and 4 oz sizes:

i. Revise the established name of your product as follows, "**HYDROCODONE***...", (include an asterisk).

ii. Revise your USUAL DOSAGE statement as follows:

USUAL DOSAGE: See package insert for complete dosage recommendations.

c. Revise the Warning statement on the 1 pint container label as follows, "...children.", (period rather than comma).

d. For your 15 mL size:

i. See second GENERAL comment.

ii. Place an asterisk on "hydrocodone", (two places) and on the "Warning: May Be...", statement.

iii. Revise to read, "Each 15 mL...", rather than, "Each 5 mL...".

3. CARTON (15 mL, 10s)

a. See second GENERAL comment and comment 2(d)(iii).

b. Include the "Warning: May Be...", statement as it is to appear on your container labels.

4. INSERT

a. See second GENERAL comment.

b. Please revise your insert labeling to be in accord with the enclosed marked up labeling guidance.

c. DESCRIPTION

i. Alphabetize your listing of inactive ingredients.

ii. Spelling of "citric acid".

iii. Revise the molecular weight of acetaminophen to read, "151.17", to be in accord with USP 23.

d. HOW SUPPLIED

i. See first GENERAL comment.

ii. We note that the NDC numbers as listed differ from those seen on your draft container labels. Please revise or comment.

Please prepare and submit final print container labels and package insert and carton labeling. You may submit draft insert labeling if you prefer.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon further 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.

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.

11/26/96

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

Enclosure: Package Insert

ANDA 40-182

Pharmaceutical Associates, Inc.
Attention: Kaye B. McDonald
Delaware Street at Perimeter Road
P.O. Box 128
Conestee, SC 29636

MAY 14 1996

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 also made to our "Refuse to File" letter dated April 10, 1996, and your amendment dated April 23, 1996.

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

DATE OF APPLICATION: February 29, 1996

DATE OF RECEIPT: March 1, 1996

DATE ACCEPTABLE FOR FILING: April 24, 1996

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) 594-0350

Sincerely yours,

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

ANDA 40-182

Pharmaceutical Associates, Inc.
Attention: Kaye B. McDonald
Delaware Street at Perimeter Road
P.O. Box 128
Conestee, SC 29636

APR 10 1996

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated February 29, 1996, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Elixir 7.5 mg/500 mg per 15 mL.

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

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

> You have proposed to package 15 mL unit dose containers. Please note that the labeling of the reference listed drug does not support a dose less than 15 mL. In addition, there is no approved packaging configurations of the reference listed drug which would support Please withdraw these .rom your application.

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

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3)If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Harvey Greenberg
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

4/10/96

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

ANDA 40-182
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Sup. CSO _____ 3/26/96 date
HFD-615/HGreenberg/CSO _____ date
HFD-647/JSimmons,Sup.Chem. _____ date
File x:\new\firmnz\pharma.Assoc.\ltrs&rev\~~92~~40182.rtf
F/T File hrw 3-25-96
ANDA Refuse to File!

Pharmaceutical Associates, Inc.
Delaware St. at Perimeter Rd. ▪ P.O. Box 128 ▪ Conestee, South Carolina 29636 ▪ 803/277-7282 ▪ 800/845-8210 ▪ FAX: 803/277-8045

RECEIVED
MAR 0 1 1996
GENERIC DRUGS

February 29, 1996

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA Hydrocodone Bitartrate and Acetaminophen Elixir
7.5 mg/500 mg per 15 mL

Dear Sir:

Enclosed is the abbreviated new drug application for the drug product Hydrocodone Bitartrate and Acetaminophen Elixir in 16 oz. containers, a 4 oz container and 15 mL unit dose containers.

We have answered comprehensively, responsibly, and to the best of our ability all required items on Form FDA 356h and have to the best of our knowledge replied to the requirements of 21 CFR Section 314.50 and 314.94 where applicable.

The Table of Contents explains the organization of the application which consists of three volumes. Volume 1 consists of Sections I-XII, Volume 2 consists of Sections XIII - XV and Volume 3 consists of Sections XVI - XXI. Each separate section of the ANDA is split off by labeled dividers that contain both the section number of that section and brief description of the section's subject matter (e.g., I. Basis). These dividers correspond to the sections listed in the Table of Contents.

Pharmaceutical Associates, Inc. is filing an archival copy (in blue folder) that contains all the information required in the ANDA and a technical review copy (in red folder) which contains all the information in the archival copy. In addition, we are also providing, in gray folders, three additional copies of the methods validation portion of the ANDA.

I certify that a true copy of this application has been provided to the Atlanta District Office.

Thank you for your consideration in this matter.

Sincerely yours,

PHARMACEUTICAL ASSOCIATES, INC.

Kaye B. McDonald

Kaye B. McDonald
Scientific Affairs Manager