CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040134

Trade Name : HYDROCODONE BITARTRATE AND ACETAMINOPHEN 7.5mg/650mg

Generic Name: Hydrocodone Bitartrate and Acetaminophen 7.5mg/650mg Tablets

Sponsor : UCB Pharma, Inc.

Approval Date: November 21, 1996

ANDA 40-134

UCB Pharma, Inc.
Attention: Patricia A. Fritz
1950 Lake Park Drive
Smyrna, Georgia 30080

Dear Madam:

This is in reference to your abbreviated new drug application dated December 27, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/650 mg.

Reference is also made to your amendments dated April 30 and September 20, 1996 and October 18, 1996.

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 Tablets USP, 7.5 mg/650 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/650 mg, 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 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.

Sincerely yours,

D. L. Sporn 11/21/96

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

1. CHEMISTRY REVIEW NO #3

2. ANDA 40-134 (7.5 mg/650 mg)

3. NAME AND ADDRESS OF APPLICANT
UCB Pharma, Inc.
Attention: P. A. Fritz
1950 Lake Park Drive
Smyrna, Georgia 30080

4. LEGAL BASIS FOR SUBMISSION- 314.94 (a) (3)
Mikart Inc.- 7.5 mg/650 mg Hydrocodone Bitartrate and Acetaminophen Tablets. Lorcet Plus Tablets. Patent has expired and there is no exclusivity.

Response to #1:
Revised information submitted to the Agency on June 6, 1995. Satisfactory.

Signed application form (section I), Basis for ANDA submission (section II), Patent Certification and Exclusivity statement(section III), Comparison between generic drug and reference listed drug (section IV), Labeling (section V), Bioavailability/Bioequivalence requests for waiver of in-vitro study (section VI) should be resubmitted based on the appropriate reference drug listed in the orange book. See amendment#2 on June 6, 1995.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5/650

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

9. AMENDMENTS AND OTHER DATES:
Firm:
December 27, 1994: Original submission.
May 10, 1995: Amendment#1
June 6, 1995: Amendment#2
August 25, 1995: Amendment#3
November 27, 1995: Amendment#4
December 13, 1995: Amendment#5
January 11, 1996: Amendment
April 30, 1996: Amendment
September 20, 1996: Amendment

FDA:
May 5, 1995: Acknowledgement letter.
June 14, 1995: Deficiency letter.
April 23, 1996: Deficiency letter.

10. PHARMACOLOGICAL CATEGORY
Narcotic analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

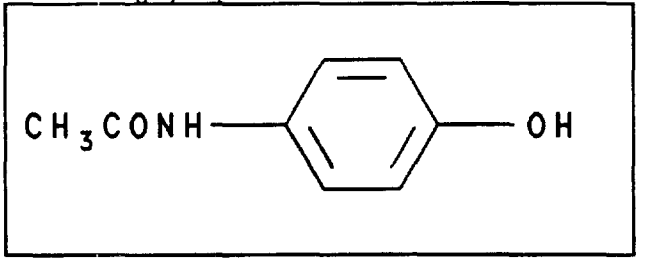
13. DOSAGE FORM
Tablets

14. POTENCY
7.5 mg/650 mg

15. CHEMICAL NAME AND STRUCTURE

Acetaminophen USP

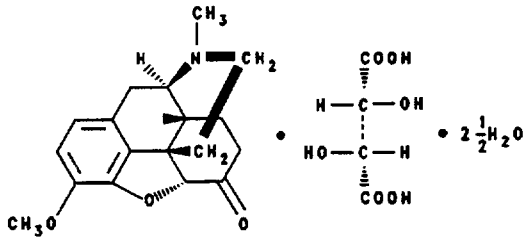
$C_8H_9NO_2$; M.W. = 151.17



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

Hydrocodone Bitartrate USP

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

16. RECORDS AND REPORTS
Memorandum from B.Russell on January 26, 1995.
Memorandum from P. Rickman on April 26, 1995.
Memorandum from W. Russell on April 27, 1995.

17. COMMENTS
The following deficiencies are found:
None

18. CONCLUSIONS AND RECOMMENDATIONS
The application is considered as approvable. The approval letter will be issued based on the revised final printed labeling.

19. REVIEWER: DATE COMPLETED:
Sema Basaran, Ph.D. 10-2-96
10-25-96 (Labeling)

ucb Pharma

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

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

Lot No.:
Exp. Date:

Manufactured for
UCB Pharma, Inc.
Smyrna (Atlanta), GA 30080
by D.M. Graham Laboratories, Inc.
Hobart, NY 13788

NDC 50474-975-50 **500 TABLETS**

HYDROCODONE* BITARTRATE AND ACETAMINOPHEN TABLETS, USP 7.5 mg/650 mg

*Warning: May be habit forming.

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See package insert for complete dosage recommendations.

NOV 21 1996

N 3 50474-975-50 3

Rev. 10/96
FDA Sub. 3

ucb Pharma

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

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

Lot No.:
Exp. Date:

Manufactured for
UCB Pharma, Inc.
Smyrna (Atlanta), GA 30080
by D.M. Graham Laboratories, Inc.
Hobart, NY 13788

NDC 50474-975-01 **100 TABLETS**

HYDROCODONE* BITARTRATE AND ACETAMINOPHEN TABLETS, USP 7.5 mg/650 mg

*Warning: May be habit forming.

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See package insert for complete dosage recommendations.

NOV 21 1996

N 3 50474-975-01 5

Rev. 10/96
FDA Sub.3

tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

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

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

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

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

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

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

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

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

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

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

HOW SUPPLIED

Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 7.5 mg/650 mg, contain hydrocodone bitartrate 7.5 mg (Warning: May be habit forming) and acetaminophen 650 mg. They are supplied as white capsule-shaped, bisected tablets, debossed, "Whitby/975," in containers of 100 tablets NDC 50474-975-01 and 500 tablets NDC 50474-975-50.

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 CIII Narcotic.

Manufactured for:
UCB Pharma, Inc.
Smyrna (Atlanta), Georgia 30080

Manufactured by:
D.M. GRAHAM LABORATORIES, INC.
Hobart, New York 13788

Revised 9/96
FDA Sub.3

49750996

HYDROCODONE* BITARTRATE AND ACETAMINOPHEN TABLETS, USP 7.5 mg/650 mg

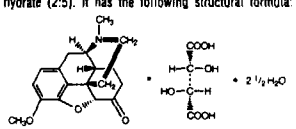
CIII

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

DESCRIPTION

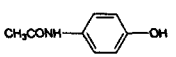
Hydrocodone bitartrate and acetaminophen is supplied in tablet form for oral administration.

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:



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

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



$C_8H_9NO_2$ MW = 151.17

Each tablet contains:

Hydrocodone Bitartrate (Warning: May be habit forming)	7.5 mg
Acetaminophen	650 mg

In addition each tablet contains the following inactive ingredients: croscarmellose sodium, microcrystalline cellulose, colloidal silicon dioxide, starch (corn), stearic acid, pregelatinized starch, povidone, and crospovidone.

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.

NOV 21 1996

Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6-α- and 6-β-hydroxymetabolites.

See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See OVERDOSAGE for toxicity information.

INDICATIONS AND USAGE

Hydrocodone bitartrate and acetaminophen tablets are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

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

WARNINGS

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

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

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

PRECAUTIONS

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

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when hydrocodone bitartrate and acetaminophen tablets are used postoperatively and in patients with pulmonary disease.

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

Other adverse reactions include:

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

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

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

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

Dermatological: Skin rash, pruritus.

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

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Hydrocodone bitartrate and acetaminophen tablets are classified as a Schedule III controlled substance.

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

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms:

Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis) extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal

Copy 12 - continued

AUG 8 1995

Hydrocodone Bitartrate/
Acetaminophen
7.5 mg/650 mg Tablets
ANDA #40-134
Reviewer: Moheb H. Makary
WP #40134W.595

Whitby Pharmaceuticals, Inc.
Richmond, Virginia
Submission Date:
December 27, 1994
June 6, 1995

Review of a Dissolution Data

I. Introduction:

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

II. Objective:

The firm has requested a waiver of the *in vivo* bioequivalence requirements for its Hydrocodone Bitartrate/Acetaminophen Tablets, 7.5 mg/650 mg. In the May 10, 1995 submission, the firm conducted dissolution testing on its test product comparing it to Boehringer Mannheim's Anexsia[R], Hydrocodone Bitartrate/ Acetaminophen Tablets, 7.5 mg/650 mg. On June 6, 1995, the firm submitted additional dissolution testing results comparing its test product to the FDA designated reference product Lorcet® Plus, Hydrocodone Bitartrate/Acetaminophen Tablets 7.5 mg/650 mg, manufactured by Mikart.

Acetaminophen/Hydrocodone Bitartrate Tablets are coded AA on various strengths in the Orange Book.

III. Dissolution Testing:

The following USP 23 conditions were used:

Apparatus:	2 (paddle) at 50 rpm
Medium:	900 mL phosphate buffer pH 5.8
Test product:	Whitby's Hydrocodone Bitartrate/Acetaminophen Tablets 7.5 mg/650 mg , lot #EXPT 9432.
Reference products:	Boehringer Mannheim' s Anexsia[R], Hydrocodone Bitartrate/Acetaminophen Tablets 7.5 mg/650 mg, lot #AR3220, Exp. 9/96. Mikart's Lorcet® Plus, Hydrocodone Bitartrate/Acetaminophen Tablets 7.5 mg/650 mg, lot #940466D, Exp. 3/97.

The dissolution testing results are shown in Table I.

IV. Formulation:

The formulation of the test product is shown below:

Component	mg/Tablet
Starch NF	
Microcrystalline Cellulose NF	
Hydrocodone Bitartrate USP	7.5
Acetaminophen USP	722.2
Croscarmellose Sodium NF	
Colloidal Silicon Dioxide NF	
Stearic Acid NF	
	========
	964.1 mg

V. Comments:

1. The dissolution testing results for the test product met the USP specifications.

2. In the May 10, 1995 submission, the firm conducted the dissolution testing on December 1, 1994. There was no designated reference listed product for Hydrocodone Bitartrate/Acetaminophen Tablets 7.5 mg/650 mg in the 14th edition of Approved Drug Product (1994) (FDA Orange Book). Hydrocodone Bitartrate/Acetaminophen Tablets 7.5 mg/650 mg, manufactured by Mikart is the FDA designated reference product in the 15th edition of Approved Drug Product (1995) (FDA Orange Book).

3. In future comparative dissolution testing, the firm is advised to use Hydrocodone Bitartrate/Acetaminophen Tablets, 7.5 mg/650 mg, manufactured by Mikart as the FDA designated reference product.

VI. Recommendations:

1. The dissolution testing conducted by Whitby Pharmaceuticals, Inc., on its Hydrocodone Bitartrate/Acetaminophen, 7.5 mg/650 mg Tablets, lot #EXPT 9432, is acceptable. The waiver of the in vivo bioequivalence study requirements is granted for the test product Hydrocodone Bitartrate/Acetaminophen, 7.5 mg/650 mg Tablets based on 21 CFR 320.22 (c).

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of phosphate buffer pH 5.8,

at 37 °C using USP 23 apparatus 2 (paddle) at 50 rpm.
The test product should meet the following specifications:

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

The firm should be informed of the comment #3 and recommendations.

Moheb H. Makary

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

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE Mo Park for

Concur: _____ Date: 8/8/95

Keith Chan, Ph.D.
Director
Division of Bioequivalence

MMakary/8-2-95 wp 40134W.595
cc: ANDA #40-134, (original, HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-658 (Mhatre, Makary), Drug File.

Table I. In Vitro Dissolution Testing

Drug (Generic Name):Hydrocodone Bitartrate/Acetaminophen Tablets
Dose Strength:7.5 mg/650 mg
ANDA No.:40-134
Firm:Whitby Pharmaceuticals, Inc.
Submission Date: May 10, 1995
File Name:40134W.595

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL of phosphate buffer pH 5.8
Specifications:NLT in 30 minutes for both products
Reference Drug: Anexsia (Boehringer Mannheim)7.5 mg/650 mg Tablet
Assay Methodology

II. Results of In Vitro Dissolution Testing:Hydrocodone Bitartrate

Sampling Times (Minutes)	Test Product Lot #EXPT 9432 Strength(mg) 7.5			Reference Product Lot #AR3220 Strength(mg) 7.5		
	Mean %	Range	%CV	Mean %	Range	%CV
10	100.4		0.8	100.0		1.3
20	99.4		0.9	100.5		1.3
30	98.4		0.8	99.1		1.3
45	97.7		1.2	98.2		1.2

Acetaminophen

Sampling Times (Minutes)	Test Product Lot #EXPT 9432 Strength(mg) 650			Reference Product Lot # AR3220 Strength(mg) 650		
	Mean %	Range	%CV	Mean %	Range	%CV
10	93.8		0.1	90.7		2.0
20	93.3		2.1	96.4		1.0
30	93.2		2.3	96.7		1.1
45	93.9		2.3	96.6		1.1

II. Results of In Vitro Dissolution Testing: Hydrocodone Bitartrate

Sampling Times (Minutes)	Test Product Lot # EXPT 9432 Strength(mg) 7.5			Reference Product Lot # 940466D Strength(mg) 7.5		
	Mean %	Range	%CV	Mean %	Range	%CV
10	100.0		2.0	101.5		2.4
20	99.6		2.1	100.4		1.4
30	98.1		1.7	100.0		1.7
45	98.0		2.1	99.0		1.8

Acetaminophen

Sampling Times (Minutes)	Test Product Lot # EXPT 9432 Strength(mg) 650			Reference Product Lot # 940466D Strength(mg) 650		
	Mean %	Range	%CV	Mean %	Range	%CV
10	97.2		1.2	97.5		2.0
20	96.4		1.2	96.6		1.6
30	95.5		1.2	96.3		1.1
45	94.4		1.3	95.5		1.0