CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 40201

Trade Name Hydrocodone Bitartrate and Acetaminophen Tablets USP 7.5mg/500mg and 10mg/500mg

Generic Name Hydrocodone Bitartrate and Acetaminophen Tablets USP 7.5mg/500mg and 10mg/500mg

Sponsor Mallinckrodt Chemical, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 40201

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40201

APPROVAL LETTER

ANDA 40-201

FEB 27 1998

Mallinckrodt Chemical, Inc.
Attention: Marianne Robb
16305 Swingley Ridge Drive
Chesterfield, MO 63017-1777

Dear Madam:

This is in reference to your abbreviated new drug application dated June 28, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/500 mg, and 10 mg/500 mg.

Reference is also made to your amendment dated July 14, 1997.

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/500 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Lortab 7.5/500 Tablets of Mikart Inc.). Additionally, the Division of Bioequivalence has determined your Hydrocodone Bitartrate and Acetaminophen Tablets USP, 10 mg/500 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Lortab 10/500 Tablets of D.M. Graham Laboratories, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same methods 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,

2.27.98

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

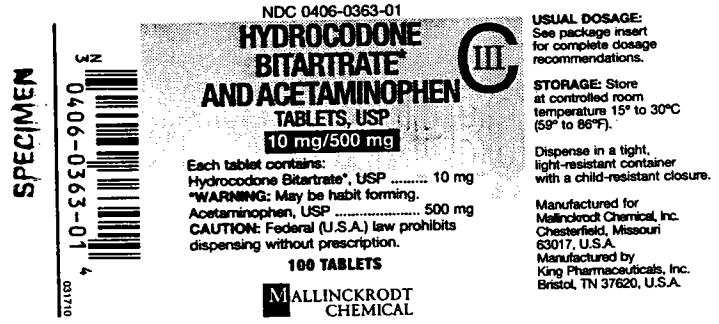
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40201

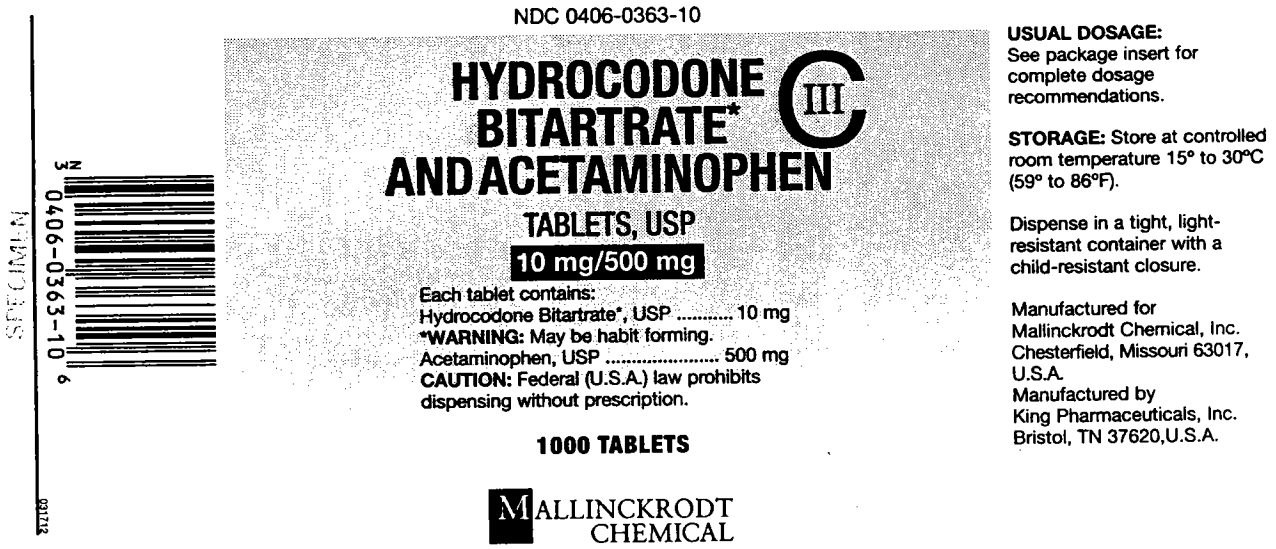
FINAL PRINTED LABELING

Margo

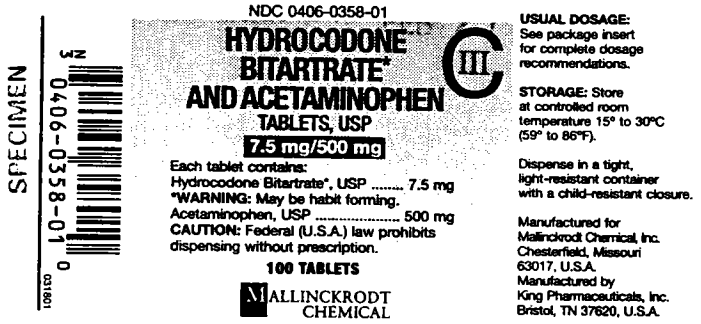
HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP
(10 MG/500 MG)
FINAL PRINTED LABELING - 100 COUNT BOTTLE



HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP
(10 MG/500 MG)
FINAL PRINTED LABELING - 1000 COUNT BOTTLE



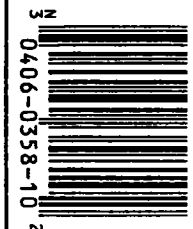
HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP
(7.5 MG/500 MG)
FINAL PRINTED LABELING - 100 COUNT BOTTLE



Margo

HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP (7.5 MG/500 MG) FINAL PRINTED LABELING - 1000 COUNT BOTTLE

SPECIMEN



NDC 0406-0358-10

HYDROCODONE BITARTRATE* AND ACETAMINOPHEN

C III

TABLETS, USP

7.5 mg/500 mg

Each tablet contains:
Hydrocodone Bitartrate*, USP ..... 7.5 mg
***WARNING:** May be habit forming.
Acetaminophen, USP ..... 500 mg
CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

1000 TABLETS

MALLINCKRODT CHEMICAL

USUAL DOSAGE: See package insert for complete dosage recommendations.

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

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

Manufactured for
Mallinckrodt Chemical, Inc.
Chesterfield, Missouri 63017, U.S.A.
Manufactured by
King Pharmaceuticals, Inc.
Bristol, TN 37620, U.S.A.

12

HYDROCODONE BITARTRATE* AND ACETAMINOPHEN TABLETS, USP

10 mg/500 mg

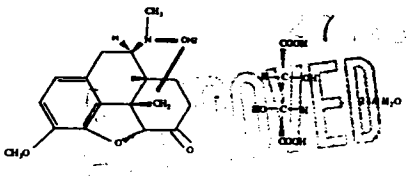
C III

*Warning: May be habit forming.

DESCRIPTION

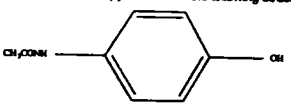
Hydrocodone Bitartrate and Acetaminophen Tablets are supplied in tablet form for oral administration.

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



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

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



$C_8H_9NO_2$ MW = 151.17

Each HYDROCODONE BITARTRATE* AND ACETAMINOPHEN, USP 10 mg/500 mg tablet contains:

Hydrocodone Bitartrate*, USP ..... 10 mg
*(Warning: May be habit forming)
Acetaminophen, USP ..... 500 mg

In addition, each HYDROCODONE BITARTRATE* AND ACETAMINOPHEN, USP 10 mg/500 mg tablet contains the following inactive ingredients: Colloidal Silicon Dioxide NF, Crospovidone NF, Magnesium Stearate NF, Microcrystalline Cellulose NF, Povidone USP, Pregelatinized Starch NF, Stearic Acid NF.

CLINICAL PHARMACOLOGY

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

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

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

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

See OVERDOSAGE for toxicity information.

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

See OVERDOSAGE for toxicity information.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS

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

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

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

PRECAUTIONS

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

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

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

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

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

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

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

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations 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 nonambulatory patients, and some of those 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

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

Signs and Symptoms:

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

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

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

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

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

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

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

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

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

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

The toxic dose for adults for acetaminophen is 10 grams.

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.

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

Each HYDROCODONE BITARTRATE* AND ACETAMINOPHEN, USP 10 mg/500 mg tablet contains Hydrocodone Bitartrate 10 mg *(Warning: May be habit forming) and Acetaminophen 500 mg. It is available as a white, capsule-shaped, bisected tablet debossed with an M 363 identification number.

Bottles of 100 ..... NDC No. 0406-0363-01

Bottles of 1000 ..... NDC No. 0406-0363-10

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

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

A Schedule III Narcotic.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

Manufactured by King Pharmaceuticals, Inc., Bristol, Tennessee 37620, U.S.A.

Manufactured for
Mallinckrodt Chemical, Inc.
Chesterfield, Missouri 63017, U.S.A.

MALLINCKRODT CHEMICAL

5/97
031713

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40201

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 40-201

3. NAME AND ADDRESS OF APPLICANT
Mallinckrodt Chemical, Inc.
16305 Swingley Ridge Drive
Chesterfield, MO 63017

4. LEGAL BASIS FOR SUBMISSION
Certify to the best of their knowledge there are no patents that claim the listed drug product and referenced listed drug is not entitled to a period of marketing exclusivity.

Listed Product: D. M. Graham - Lortab® 10/500, ANDA 40-100
Mikart - Lortab® 7.5/500, ANDA 89-699

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Anexsia® 10 mg/500 mg

7. NONPROPRIETARY NAME
Hydrocodone Bitartrate and Acetaminophen

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

9. AMENDMENTS AND OTHER DATES:

Firm:
- 6/28/96 - Original.
- 9/30/96 - Response to 8/22/96 letter.
- 10/2/96 - Response to refuse to file letter.
- 7/14/97 - Response to 1st def. letter (chem. & labeling. Subject of this review.

FDA:
- 8/8/96 - Requesting firm to withdraw ANDA 40-202 and submit as amendment to ANDA 40-201
- 8/22/96 - Letter requesting firm to withdraw ANDA 40-202 (7.5 mg/500 mg) and submit as amendment to ANDA 40-201.
- 9/13/96 - Refuse to file letter, basis of submission.
- 9/17/96 - Phone memo, explaining refuse to file and time delay.
- 11/20/96 - Acknowledgment.
- 2/19/97 - Bio. review, acceptable.
- 2/24/97 - Bio. letter, no further questions at this time.
- 5/5/97 - 1st def. letter (chem. & labeling).

10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

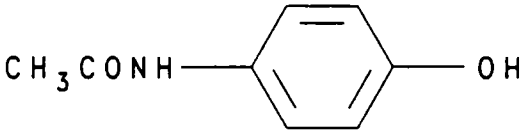
13. DOSAGE FORM
Tablet

14. POTENCY
7.5 mg/500 mg & 10 mg/500 mg

15. CHEMICAL NAME AND STRUCTURE

Acetaminophen USP

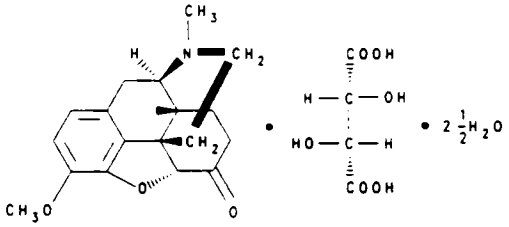
$C_8H_9NO_2$; M.W. = 151.16



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

Hydrocodone Bitartrate USP

$C_{18}H_{21}NO_3.C_4H_6O_6.2½H_2O$; 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
N/A

17. COMMENTS
Method validation not needed, product is USP. DMFs, EER, labeling, and Bio. are satisfactory

18. CONCLUSIONS AND RECOMMENDATIONS
Approval

19. REVIEWER: Norman Gregory
DATE COMPLETED: 1/22/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40201

BIOEQUIVALENCE REVIEW(S)

2.1

ANDA 40-201

Mallinckrodt Chemical, Inc.
Attention: Marianne Robb
16305 Swingley Ridge Drive
Chesterfield, MO 63017-1777

FEB 24 1997

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 Acetaminophen/Hydrocodone Bitartrate Tablets USP, 7.5 mg/500 mg and 10 mg/500 mg.

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

2. 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 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,

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

FEB 19 1997

Acetaminophen/ Hydrocodone Bitartrate	**Mallinckrodt Chemical, Inc.**
500 mg/10 mg & 500 mg/7.5 mg Tablets	Chesterfield, MO
ANDA #40-201	Submission Date:
Reviewer: Sikta Pradhan	September 30, 1996
WP #40201W.996	October 2, 1996

Review of Dissolution Data and Waiver Request

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 produces analgesia and antipyresis.

The combinations of Acetaminophen/Hydrocodone bitartrate are commercially available as 500 mg/5 mg capsule, or 500 mg/2.5 mg, 500 mg/5 mg, 500 mg/7.5 mg, 500 mg/10 mg, 650 mg/7.5 mg, 650 mg /10 mg and 750 mg/7.5 mg tablets.

II. Objective:

Mallinckrodt Chemical, Inc. has informed the Agency that they have purchased three applications for various strengths of Acetaminophen/Hydrocodone Bitartrate Tablets, USP (Anexsia : ANDA #89-160 (500mg/5mg), ANDA #89-725 (650mg/7.5mg) and ANDA #40-084 (750mg/7.5mg) from King Pharmaceutica Company. In this application, the firm has requested a waiver of the in vivo bioequivalence requirements for its Acetaminophen/Hydrocodone Bitartrate, 500 mg/10 mg and 500 mg/7.5 mg Tablets USP. The firm has further informed the Agency that these test products will be manufactured, processed, packaged, labeled, and tested for release and stability by King Pharmaceutical, Inc., Bristol, Tennessee. The packaged product will be released, held, and distributed by Mallinckrodt Chemical, Inc., St. Louis, Missouri. In support of this waiver request, the firm has submitted the compositions and the dissolution testing data of the test products. Acetaminophen/Hydrocodone Bitartrate Tablets are coded AA on various strengths in the Orange Book.

III. Dissolution Testing:

The firm conducted dissolution testing on its test products, Acetaminophen/Hydrocodone Bitartrate, 500mg/10mg and 500mg/7.5mg tablets comparing them with Lortab^{R}, 500mg/10mg Tabtets (owned by Graham and approved on January 26, 1996) and Acetaminophen/ Hydrocodone Bitartrate Tablets, 500mg/7.5mg (owned by Mikart and

approved on August 25, 1989), respectively. The dissolution testing results are shown in Table I.

Table I. In Vitro Dissolution Testing

Drug (Generic Name): Acetaminophen Tablets /Hydrocodone Bitartrate
Dose Strength: 500 mg/10 mg
ANDA No.: 40-201
Firm: Mallinckrodt Chemical, Inc.
Submission Dates: September 30, 1996 & October 2, 1996
File Name:40201W.996

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL of phosphate buffer pH 5.8
Specifications:NLT in 30 minutes for each component
Reference Drug: Lortab® (Graham) 500 mg/10 mg Tablet
Assay Methodology:

II. Results of In Vitro Dissolution Testing:Hydrocodone Bitartrate

Sampling Times (Minutes)	Test Product Lot #PLT-259 Strength(mg) 10			Reference Product Lot #WL109655A Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%CV
5	99.3		1.5	100.3		0.9
10	100.0		1.5	101.5		1.0
20	99.8		1.6	101.6		0.8
30	100.1		1.8	101.7		0.8

Acetaminophen

Sampling Times (Minutes)	Test Product Lot #PLT-259 Strength(mg) 500			Reference Product Lot #WL109655A Strength(mg) 500		
	Mean %	Range	%CV	Mean %	Range	%CV
5	97.7		1.0	98.4		0.9
10	99.0		0.6	99.6		0.9
20	99.4		0.9	99.9		0.8
30	99.4		0.7	100.1		0.8

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL of phosphate buffer pH 5.8
Specifications: NLT in 30 minutes for each component
Reference Drug: Acetaminophen/Hydrocodone Bitartrate Tablets, 500 mg/7.5 mg Tablet (Mikart)
Assay Methodology:

II. Results of In Vitro Dissolution Testing: Hydrocodone Bitartrate

Sampling Times (Minutes)	Test Product Lot #PLT-257 Strength(mg) 7.5			Reference Product Lot #930994K Strength(mg) 7.5		
	Mean %	Range	%CV	Mean %	Range	%CV
10	95.5		0.7	98.0		1.8
20	96.2		0.8	99.7		1.3
30	95.8		0.8	100.0		1.3

Acetaminophen

Sampling Times (Minutes)	Test Product Lot #PLT-257 Strength(mg) 500			Reference Product Lot #930994K Strength(mg) 500		
	Mean %	Range	%CV	Mean %	Range	%CV
10	94.2		1.6	97.3		1.6
20	97.2		1.1	99.3		1.0
30	98.1		1.1	99.7		0.8

The dissolution testing results for the test products met the USP specifications.

IV. Formulation:

The formulations of the test products are shown below:

	Acetaminophen/Hydrocodone Bitartrate	
	500mg/7.5mg	500mg/10mg
Tablet Component	mg/Tablet	mg/Tablet
Starch, NF	40.0	40.0
Microcrystalline Cellulose, NF		
Hydrocodone Bitartrate, USP		
Acetaminophen USP		
Silicon Dioxide, NF		
Stearic Acid, NF		
Magnesium Stearate, NF		
	731.26 mg	733.76 mg

V. Recommendations:

1. The dissolution testings conducted by Mallinckrodt Chemical, Inc. on its Acetaminophen/Hydrocodone Bitartrate, 500 mg/10 mg and 500 mg/7.5 mg Tablets, lot #PLT-259 and lot #PLT-257, respectively, are acceptable. The waiver of the in vivo bioequivalence study requirements is granted for the test product Acetaminophen/Hydrocodone Bitartrate, 500mg/10 mg and 500mg/7.5 mg Tablets based on 21 CFR 320.22 (c). The Division of Bioequivalence deems Acetaminophen/Hydrocodone Bitartrate, 500mg/10mg and 500mg/7.5mg Tablets, manufactured by King Pharmaceutical, Inc. for Mallinckrodt Chemical, Inc. to be bioequivalent to Lortab® 500 mg/10 mg Tablets of Graham Laboratories, Inc. and Acetaminophen/Hydrocodone Bitartrate, 500mg/7.5mg Tablets of Mikart Laboratories, Inc., respectively.

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 amounts of both acetaminophen and hydrocodone bitartrate in the dosage form are dissolved in 30 minutes.

The firm should be informed of the above recommendations.

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG 2/19/97

Concur: _____ Date: 2/19/97
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

cc: ANDA # 40-201 (original, duplicate), HFD-652 (Huang, Pradhan), Drug File, Division File

SP/1-29-97/02-3-97/2-18-97//X:\wpfile\Pradhan\40201W.996

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #40-201 **SPONSOR :Mallinckrodt Chemical, Inc.**

DRUG & DOSAGE FORM : Acetaminophen/Hydrocodone Bitartrate Tablet
STRENGTH (s) : 500 mg/10 mg & 500 mg/7.5 mg
TYPE OF STUDY: Waiver

STUDY SITE: CLINICAL & ANALYTICAL: N/A

STUDY SUMMARY : **Waiver acceptable on the basis of:**
1) Similar Compositions &
2) Acceptable Dissolution

DISSOLUTION CONDITIONS:

USP Dissolution condition-
Test product met USP XXIII dissolution specifications of Q = of the labeled amounts of both acetaminophen and hydrocodone bitartrate in the tablet is dissolved in 30 minutes. The in vitro dissolution testing data are acceptable.

PRIMARY REVIEWER : Sikta Pradhan **BRANCH : I**

INITIAL : _____ **DATE :** 2/23/98

BRANCH CHIEF : Yih Chain Huang **BRANCH : I**

INITIAL : _____ **DATE :** 2/23/98

DIRECTOR : Dale P. Conner
DIVISION OF BIOEQUIVALENCE

INITIAL : _____ **DATE :** 2/23/98

DIRECTOR : Douglas L. Sporn
OFFICE OF GENERIC DRUGS

INITIAL : _____ **DATE :** _____

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40201

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA: 40-201 FIRM: Mallinckrodt Chemical, Inc.

DRUG PRODUCT: Hydrocodone Bitartrate and Acetaminophen

DOSAGE FORM: Tablets STRENGTH: 7.5 mg/500 mg & 10 mg/500 mg

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable for all on 9/10/97.

BIO STUDY: Dissolution testing (Lot #PLT-257, 7.5 mg/500 mg and Lot #PLT-259, 10 mg/500 mg) are acceptable and waiver of bioequivalence study requirements granted on 2/19/97 by Sikta Pradhan.

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

Active Ingredients: N/A, product is compendial refer to memo dated 11/14/90 regarding Compliance Program Guidance Manual # 7346.832, code 52832 for ANDAs and AADAs.

Finish Dosage Form: N/A, product is compendial refer to memo dated 11/14/90 regarding Compliance Program Guidance Manual # 7346.832, code 52832 for ANDAs and AADAs.

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

Protocol: Satisfactory

Exp.Date: 24 months - 40°C, 75% R.H., 3 months and 12 months R.T. (25°C-30°C), smallest and largest container/ closure system, one lot each strength (Lot #PLT-257, 7.5 mg/500 mg and Lot #PLT-259 10 mg/500 mg)

Container/Closure systems are the same.

LABELING: Container: Satisfactory in FPL.
Insert: Satisfactory in FPL.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):
Lot #PLT-257, 7.5 mg/500 mg) and
, Lot #PLT-259, 10 mg/500 mg), source of NDSs acceptable (Mallinckrodt Chemical, Inc. for both).

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):
Lot #PLT-257, 7.5 mg/500 mg) and units
, Lot #PLT-259, 10 mg/500 mg).

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:
7.5 mg/500 mg) and
kg, 10 mg/500 mg).

CHEMIST: Norman Gregory DATE: 1/22/98

SUPERVISOR: U.V. Venkataram, Ph.D. DATE: 1/22/98

2/13/98

RECORD OF TELEPHONE CONVERSATION

Mallinckrodt was issued refuse to file letters on ANDA 40-201 on Sept.13, 1996, and ANDA 40-202 on Aug.22, 1996. The RTF letters requested the firm to compress both ANDAs into a single application (ANDA 40-201). The firm called to complain about the timing of the RTF letters and that they were unaware that a newly approved application, Loratab by UCB, ANDA 40-100 was designated a reference listed drug. The UCB approval in January 1996 changed OGD's position on compressing these drug products into a single application. The RTF letters should of gone together but for some reason with holiday/vacations they were almost a month apart in issuing. I apologized for the delay, but it would not change the RTF or the filing date of either application.

The firm plans to answer the RTF issue regarding in-vitro dissolution profile for ANDA 40-201 and withdraw ANDA 40-202 and amend it to other application.

DATE
Sept. 17, 1996

APPLICATION NUMBER
40-201 (10/500)
40-202 (7.5/500)

IND NUMBER

TELECON

INITIATED BY **MADE**
X APPLICANT/ SPONSOR **_ BY TELE.**
FDA ** IN PERSON**

PRODUCT NAME
Hydrocodone Bitartarte & Acetaminophen
10 mg/500 mg
7.5 mg/500 mg

FIRM NAME
Mallinckrodt

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Mary Ann Robb
Regulatory Affairs Associate

TELEPHONE NUMBER
314-530-2258

SIGNATURE
Harvey Greenberg

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40201

CORRESPONDENCE

ANDA 40-201

Mallinckrodt Chemical, Inc.
Attention: Marianne Robb
16305 Swingley Ridge Drive
Chesterfield, MO 63017-1777

NOV 20 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 September 13, 1996, and your amendments dated September 30,1996, and October 2, 1996.

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

DATE OF APPLICATION: June 28, 1996

DATE OF RECEIPT: July 10, 1996

DATE ACCEPTABLE FOR FILING: October 8, 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) 594-0305

Sincerely yours,

11/20/96

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

MALLINCKRODT
CHEMICAL

AMENDMENT TO PENDING APPLICATION ANDA 40-201

Mallinckrodt Chemical, Inc.
16305 Swingley Ridge Drive
Chesterfield, Missouri 63017-1777
Telephone (314) 530-2000

October 2, 1996

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

ORIG AMENDMENT

RE: Hydrocodone Bitartrate and Acetaminophen Tablets, USP (10 mg/500 mg)

Dear Madame or Sir:

In response to an September 13, 1996 Agency letter (Attached), Mallinckrodt Chemical, Inc. hereby submits an amendment to pending application ANDA 40-201, Hydrocodone Bitartrate and Acetaminophen Tablets, USP (10 mg/500 mg) which provides a revised Form 356h that cites the reference listed drug as described in Approved Drug Products with Therapeutic Equivalence, 16th Edition, Cumulative Supplement #5. Hydrocodone Bitartrate and Acetaminophen Tablets, USP are a Schedule III prescription drug indicated for the relief of moderate to moderately severe pain.

In addition, Mallinckrodt Chemical, Inc hereby waives the right to an informal conference with the agency under 21 CFR §314.101(a)(3).

In December 1995, Mallinckrodt Chemical, Inc. purchased from King Pharmaceutical, Inc. three applications for various strengths of Hydrocodone Bitartrate and Acetaminophen Tablets, USP (Anexsia®): ANDA 89-160 (5 mg/500 mg), ANDA 89-725 (7.5 mg/650 mg), and 40-084 (7.5 mg/750 mg). Hydrocodone Bitartrate and Acetaminophen Tablets, USP (10 mg/500 mg) will be manufactured, processed, packaged, labeled, and tested for release and stability by King Pharmaceutical, Inc. at 505 Fifth Street in Bristol, Tennessee. The packaged product will be released, held, and distributed by Mallinckrodt Chemical, Inc. at Mallinckrodt & Second Streets in St. Louis, Missouri.

This application consists of one volume containing the amended Sections I through VII of the original application and a signed Field Copy Certification. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder. A separate copy of the bioequivalence section is being submitted in an orange folder. This also certifies that, concurrently with the filing of this ANDA, true copies of the technical sections of the ANDA were sent to the local district offices. These "field copies" were contained in burgundy folders.

For more detailed information on the organization of this application, please refer to the "Executive Summary" which is included immediately following the Table of Contents.

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Chemical, Inc. 16305 Swingley Ridge Dr., Chesterfield, Missouri 63017.

Sincerely,

Marianne Robb
Manager, Regulatory Affairs
(314) 530-2258
Fax (314) 530-2496

MAY 5 1997

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-201 APPLICANT: Mallinckrodt Chemical, Inc.

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

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. Please revise and resubmit your Form 356h

2. Regarding Active Ingredients:

3. Regarding Inactive Ingredients:

4. Regarding Other Firms:

5. Regarding Manufacturing and Processing:

6. Regarding Container/Closure:

7. Regarding Packaging and Labeling:

8. Regarding Laboratory Controls (In-process):

9. Regarding Laboratory Controls (Finished Dosage Form):

10. Regarding Stability:

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Your is satisfactory. However, since the subject product is an official article in the United States Pharmacopeia (USP), approval to use an analytical procedure that differs from that in the USP does not release you from the obligations to comply with the methods and procedures in the USP. Therefore, in the event of dispute, only the results obtained by the official methods and procedures in the USP will be considered conclusive.

Sincerely yours,

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 40-201

Mallinckrodt Chemical, Inc.
Attention: Charles H. Smith
16305 Swingley Ridge Drive
Chesterfield, MO 63017-1777

SEP 13 1996

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated June 28, 1996, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 10 mg/500 mg.

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:

Please note that your application can not use as the basis of submission an acceptable ANDA Suitability Petition, since the drug product is now the subject of an approved application.

Please provide a revised Form FDA 356h that cites the correct reference listed and application holder. Please refer to the Approved Drug Products with Therapeutic Equivalence Evaluations, 16th Edition, Cumulative Supplement #5, Jan'96-May'96, for information regarding the correct reference listed drug. In addition, please submit new 505(j)(2)(A) information including a new labeling comparison to reflect the reference listed drug.

You must also submit *in vitro* comparative dissolution profiles comparing your proposed drug product against the corresponding reference listed drug. Comparative dissolution profiles should include individual tablet data as well mean, range, and standard deviation at each time point for twelve tablets.

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
Project Manager
(301) 594-0315

Sincerely yours,

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

MALLINCKRODT CHEMICAL

RECEIVED
JUL 10 1996
GENERIC DRUGS

Mallinckrodt Chemical, Inc.
16305 Swingley Ridge Drive
Chesterfield, Missouri 63017-1777
Telephone (314) 530-2000

June 28, 1996

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

RECEIVED
GENERIC DRUGS

RE: ANDA for Anexsia® 10/500 (Hydrocodone Bitartrate and Acetaminophen Tablets, USP) 10 mg/500 mg - New Application

Dear Madam or Sir,

Mallinckrodt Chemical, Inc. hereby submits this Abbreviated New Drug Application (ANDA) under 21 C.F.R. § 314.92 (a)(1). This ANDA is for Hydrocodone Bitartrate and Acetaminophen Tablets, USP (10 mg/500 mg), a Schedule III prescription drug indicated for the relief of moderate to moderately severe pain. Mallinckrodt Chemical, Inc. (MC) is concurrently submitting an application for Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5 mg/500 mg).

In December 1995, Mallinckrodt Chemical, Inc. purchased from King Pharmaceuticals, Inc. these applications for various strengths of Hydrocodone Bitartrate and Acetaminophen Tablets, USP (Anexsia®): ANDA 89-160 (5 mg/500 mg), ANDA 89-725 (7.5 mg/650 mg), and 40-084 (7.5 mg/750 mg) and (5 mg/500 mg). This product is currently contract manufactured for Mallinckrodt Chemical, Inc. by King Pharmaceuticals, Inc. The active ingredients and container/closure systems, labeling, analytical methods, specifications, controls, and personnel are similar for the above applications as in this proposed product. The reference listed drug for this proposed product is the same as was used for the previously approved products. The most significant difference in the products is that the previously approved products are manufactured
proposed product will be

Hydrocodone Bitartrate and Acetaminophen Tablets, USP (10 mg/500 mg) will be manufactured, processed, packaged, labeled, and tested for release and stability by King Pharmaceuticals, Inc. at 501 Fifth Street in Bristol, Tennessee. The packaged product will

be released, held, and distributed by Mallinckrodt Chemical, Inc. at Mallinckrodt & Second Streets in St. Louis, Missouri.

To support the filing of this application, an exhibit lot of tablets was manufactured. The active and inactive ingredients are compendial or derived from compendial sources. The operations during the manufacture of the stability lot were performed by production personnel according to CGMP. The operations were monitored by Quality Assurance personnel. The process, equipment and controls will be the same for the commercial lots as used for the exhibit lot. The proposed commercial batch size is tablets

The stability studies were performed in the proposed container/closure systems. All data are acceptable through three months of storage under labeled and accelerated conditions. An expiration dating period of twenty-four months is requested.

The basis for this abbreviated new drug application for ANEXSIA®10/500 (Hydrocodone Bitartrate and Acetaminophen Tablets, USP) is a Citizen's Petition #87 P-0170/CP filed by LuChem Pharmaceuticals, Inc for the 10 mg/500 mg strength and approved July 7, 1987. The Citizen's Petition references VICODIN® 5/500. Application 88-058 for VICODIN® was approved on January 7, 1983. Copies of the Citizen's Petition and the relevant pages of the 16th Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations follow.

Correspondence related to this submission should be addressed to Official Correspondent, Mallinckrodt Chemical, Inc. 16305 Swingley Ridge Dr., Chesterfield, Missouri 63017.

Sincerely,

Charles H. Smith

Charles H. Smith
Official Correspondent
(314) 530-2128
Fax (314) 530-2496

MALLINCKRODT
CHEMICAL

AMENDMENT TO PENDING APPLICATION ANDA 40-201

Mallinckrodt Chemical, Inc.
16305 Swingley Ridge Drive
Chesterfield, Missouri 63017-1777
Telephone (314) 530-2000

September 30, 1996

BIOAVAILABILITY
ORIG AMENDMENT
N/AC

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

RE: Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5 mg/500 mg)

Dear Madame or Sir:

Mallinckrodt Chemical, Inc. hereby withdraws ANDA 40-202 without prejudice to refile under 21 CFR §314.65 and waives the right to an informal conference with the agency under 21 CFR §314.101(a)(3) in response to an August 22, 1996 Agency letter (Attached).

Under 21 CFR §314.60 (a) Mallinckrodt Chemical, Inc. hereby resubmits the information originally contained in ANDA 40-202 as an amendment to the pending application ANDA 40-201. This amendment is for the additional strength of Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5 mg/500 mg) which was originally submitted June 28, 1996 and designated ANDA 40-202. Hydrocodone Bitartrate and Acetaminophen Tablets, USP are a Schedule III prescription drug indicated for the relief of moderate to moderately severe pain.

In December 1995, Mallinckrodt Chemical, Inc. purchased from King Pharmaceutical, Inc. three applications for various strengths of Hydrocodone Bitartrate and Acetaminophen Tablets, USP (Anexsia®): ANDA 89-160 (5 mg/500 mg), ANDA 89-725 (7.5 mg/650 mg), and 40-084 (7.5 mg/750 mg). Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5 mg/500 mg) will be manufactured, processed, packaged, labeled, and tested for release and stability by King Pharmaceutical, Inc. at 505 Fifth Street in Bristol, Tennessee. The packaged product will be released, held, and distributed by Mallinckrodt Chemical, Inc. at Mallinckrodt & Second Streets in St. Louis, Missouri.

This application consists of two volumes. An archival copy is being filed in blue folders and a technical review copy is being filed in red folders. A separate copy of the bioequivalence section is being submitted in an orange folder. For more detailed information on the organization of this application, please refer to the "Executive Summary"which is included immediately following the Table of Contents.

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Chemical, Inc. 16305 Swingley Ridge Dr., Chesterfield, Missouri 63017.

Sincerely,

Marianne Robb
Manager, Regulatory Affairs
(314) 530-2258
Fax (314) 530-2496

MALLINCKRODT

Improving Healthcare and Chemistry

MAJOR AMENDMENT

Mallinckrodt
16305 Swingley Ridge Drive
Chesterfield. Missouri 63017-1777
Telephone (314) 530 2000

AMENDMENT
N/AC

July 14, 1997

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

RE: ANDA 40-201: Hydrocodone Bitartrate and Acetaminophen Tablets, USP (10 mg/500 mg & 7.5 mg/500 mg)

Dear Madame or Sir:

The following information is provided in response to a May 5, 1997 chemistry deficiency letter and a request for final printed labeling from the Agency. For ease of review, a copy of the May 5 letter is attached and the Agency's comments have been repeated.

This amendment consists of one volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder. This also certifies that, concurrently with the filing of this Major Amendment, true copies of the technical sections of the ANDA were sent to the local district offices. These "field copies" are contained in burgundy folders.

If there are any questions concerning this information, please contact myself or Robert Lake, Ph.D. at (314) 530-2125.

Sincerely,

Marianne Robb
Manager, Regulatory Submissions
Responsible Agent
Telephone: (314) 530-2258