CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

40-099/S-002 to S-008

Trade Name: Lortab®

Generic Name: Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5mg/325mg

Sponsor: UCB Pharma, Inc.

Approval Dates: July 13, 1999; February 15, 2000; July 27, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
40-099/S-002 to S-008

CONTENTS

Reviews / Information Included in this ANDA Review.	
Approval Letter	X
Tentative Approval Letter	
ANDAs	
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 Reviews	
Bioequivalence Review(s)	X
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-099/S-002 to S-008

APPROVAL LETTERS

ANDA 40-099/S-002, S-003, S-004, S-005 and S-006

UCB Pharma, Inc.
Attention: Ms. Mary D. Alonso
1950 Lake Park Drive
Smyrna, GA 30080

JUL 13 1999

Dear Ms. Alonso:

This is in reference to your supplemental new drug applications dated August 12, 1998, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug application for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/325 mg (Lortab 5/325).

Reference is also made to your amendment dated June 9, 1999.

The supplemental applications provide: for [redacted] for unit-dose blister packaging using [redacted] blister material as [redacted] and foil lidding as [redacted] (S-002); for a 24-month expiration date for the drug product (S-003); for a control revision (S-004), for [redacted] as a [redacted] (S-005); and for a unit dose blister labeling revision (S-006).

We have completed the review of these supplemental applications and they are approved.

From a labeling perspective the labels and labeling has been satisfactorily revised to reflect the addition of unit dose blister packaging in 100s (4 x 25).

At the time of next printing, please make the following revision to the package insert labeling:

DOSAGE AND ADMINISTRATION - Add the following as the last sentence of this section: - .. [redacted]

This change may be submitted as a Special Supplement Changes Being Effected.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/S/ 7/13/99

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

APPEARS THIS WAY
ON ORIGINAL

ANDA 40-099/S-007

UCB Pharma, Inc.
Attention: Mary Alonso
1950 Lake Park Drive
Smyrna, GA 30080

FEB 15

Dear Mary Alonso:

This is in reference to your supplemental new drug application dated August 10, 1999, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug application for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/325 mg (Lortab 5/325).

The supplemental applications provide for [redacted] as [redacted] using the previously approved [redacted] blister material as [redacted] and foil lidding as [redacted]

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/S/ 2/15/2000

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

ANDA 40-099/S-08

Watson Laboratories, Inc.
Attention: Dorothy A. Frank
417 Wakara Way
Salt Lake City, UT 84108

JUL 27 2001

Dear Madam:

This is in reference to your supplemental new drug application dated February 21, 2001, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Norco® 5 mg/325 mg (Hydrocodone Bitartrate and Acetaminophen Tablets USP 5mg/325 mg).
Refer to amendments dated 2-27-01 and 3-12-01. ms
This supplemental application, submitted as "Changes Being Effected in 30 days" according to section 506A(d) of the Act, provide for the following change:

S-08: To provide for [redacted] 5 mg/325 mg (Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/325 mg).

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/s/ 7/26/01

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-099/S-002 to S-008

Final Printed Labeling

APPROVED
3 1999

ucb Pharma

ucb Pharma

USUAL DOSAGE:
See package insert for complete dosage recommendations.

STORAGE: Store at controlled room temperature 15°-30°C (59°-86°F). Keep tablets in box to protect from light. If dispensed for outpatient use, dispense in a tight, light-resistant container with a child-resistant closure.

This unit-dose package is not child-resistant.

NDC 50474-935-60 100 TABLETS (4 x 25)–Unit Dose

Lortab® 5/325

HYDROCO[illegible]BITARTRATE AND ACETA[illegible]BLETS, USP

5 [illegible] g

Each [illegible] tablet contains:

Hydroc[illegible]tartrate ..... 5 mg
Acetaminoph[illegible] ..... 325 mg

℞ only

Final Printed 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).

NDC 50474-935-01 100 TABLETS

Lortab® 5/325

HYDROCODONE* BITARTRATE AND ACETAMINOPHEN TABLETS, USP

5 mg/325 mg

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

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See package insert for complete dosage recommendations.

FEB 6 1998

APPROVED

N 3 50474-935-01 9

7G14514
Rev. 6/97
Code 667B10

Lot No.:
Exp. Date:

Manufactured for
UCB Pharma, Inc.
Smyrna, GA 30080
by Mikart, Inc.
Atlanta, GA 30318

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).

NDC 50474-935-50 500 TABLETS

Lortab® 5/325

HYDROCODONE* BITARTRATE AND ACETAMINOPHEN TABLETS, USP

5 mg/325 mg

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

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See package insert for complete dosage recommendations.

FEB 6 1998

APPROVED

N 3 50474-935-50 7

7G14518
Rev. 6/97
Code 667B50

Lot No.:
Exp. Date:

Manufactured for
UCB Pharma, Inc.
Smyrna, GA 30080
by Mikart, Inc.
Atlanta, GA 30318

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 or two tablets every four to six hours as needed for pain.

HOW SUPPLIED

Lortab® 5/325 tablets (Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 5 mg/325 mg) contain hydrocodone bitartrate 5 mg and acetaminophen 325 mg. They are supplied as white with orange specks, capsule-shaped, bisected tablets, debossed "ucb/935," in containers of 100 tablets, NDC 50474-935-01, in containers of 500 tablets, NDC 50474-935-50, and in hospital unit-dose packages of 100 tablets [4x25], NDC 50474-935-60.

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

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

A Schedule CIII Narcotic.

ucb Pharma

Manufactured for
UCB Pharma, Inc.
Smyrna, GA 30080

Manufactured by
Mikart, Inc.
Atlanta, GA 30318

Rev. 6/98
Code 667B00
P/N 1002030

50474935

LORTAB® 5/325

HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP

5 mg/325 mg

℞ only

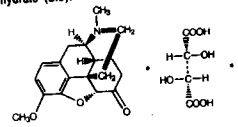
CIII

DESCRIPTION

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

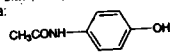
WARNING: May be habit forming (see PRECAUTIONS, Information for Patients, and DRUG ABUSE AND DEPENDENCE).

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



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$ 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 Lortab 5/325 tablet contains:

Hydrocodone Bitartrate	5 mg
Acetaminophen	325 mg

In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, crospovidone, microcrystalline cellulose, povidone, pregelatinized starch, stearic acid and sugar spheres which are composed of starch derived from corn, sucrose, and FD&C Yellow #6.

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

Lortab 5/325 tablets (Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 5 mg/325 mg) 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, Lortab 5/325 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 Lortab 5/325 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 Lortab 5/325 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. Lortab 5/325 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 Lortab 5/325 tablets 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 Lortab 5/325 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: Lortab 5/325 tablets (Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 5 mg/325 mg) 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, Lortab 5/325 tablets should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when Lortab 5/325 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:

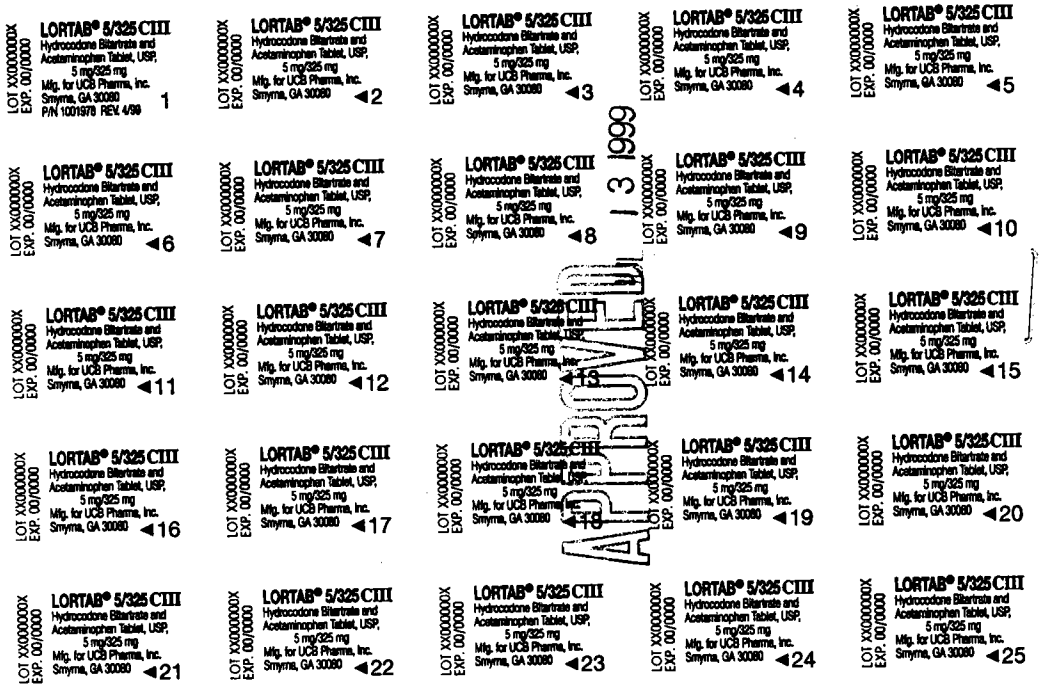
Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis) extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia 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.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LORTAB® 5/325 CIII
Hydrocodone Bitartrate and
Acetaminophen Tablet, USP,
5 mg/325 mg
Mfg. for UCB Pharma, Inc.
Smyrna, GA 30080
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APPROVED
JAN 13 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-099/S-002 to S-008

CHEMISTRY REVIEW(S)

ANDA 40-099/S-007 CHEMISTRY REVIEW NO. 1

NAME AND ADDRESS OF APPLICANT:
UCB Pharma, Inc.
Attention: Mary Alonso
1950 Lake Park Drive
Smyrna, GA 30080
Phone-(770)437-5621

PURPOSE OF AMENDMENT/SUPPLEMENT
Provide for [redacted] using the previously approved [redacted] blister material as [redacted] and foil lidding as [redacted]

DATE OF SUBMISSION
August 10, 1999- Original submission

PHARMACOLOGICAL CATEGORY	TRADE NAME
Narcotic analgesic	Lortab 5/325

NONPROPRIETARY NAME
Hydrocodone Bitartrate and Acetaminophen Tablets, USP

DOSAGE FORM	POTENCY	RX OR OTC
Oral Tablets	5 mg/325 mg	Rx

SAMPLES	RELATED IND/NDA/DMF	STERILIZATION
N/A	None	N/A

LABELING
N/C

BIOEQUIVALENCY STATUS
N/A

ESTABLISHMENT INSPECTION
EER for [redacted] was reported as acceptable dated 8/13/99. A CGMP Certification is included (p 3).

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS
N/A

PACKAGING
LORTAB 5/325 tablets will be [redacted] for [redacted] foil [redacted] blister packages. The foil is [redacted] and the [redacted] The unit dose blister package configuration was previously approved. CGMP certification from [redacted] is included.

STABILITY
A commitment to place the first production lot of the unit dose

blister, on long term room temperature stability study, [redacted] at the proposed facility is included. The approved stability protocol will be followed. Data obtained will be submitted in Annual Reports.

REMARKS AND CONCLUSION
Recommend approvable letter to issue.

Reviewer
Edwin Ramos

Date
January 12, 2000

2/2/00

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-090/S-002 to S-008

ADMINISTRATIVE DOCUMENTS

ANDA 40-099/S-002, S-003, S-004, S-005, and S-006

NAME AND ADDRESS OF APPLICANT:
UCB Pharma, Inc.
Attention: Mary D. Alonzo
1950 Lake Park Drive
Smyrna, GA 30080
Phone-(770)437-5621

PURPOSE OF AMENDMENT/SUPPLEMENT
S-002: Provide for Hospital Unit Dose (Blister) [redacted] using [redacted] blister material as [redacted] and foil lidding as [redacted]

S-003: Provide for a 24-month expiration date for product.

S-004: Control revision.

S-005: [redacted]

S-006: Unit Dose Blister labeling revision.

DATE OF SUBMISSION
August 12, 1998- Original sub[illegible]
March 3, 1999-
June 9, 1999-

PHARMACOLOGICAL CATE[illegible] [illegible]
Narcotic analgesic [illegible]25

NONPROPRIETARY NAME
Hydrocodone Bitartra[illegible] Tablets, USP

DOSAGE FORM	POTENCY	RX OR OTC
Oral Tablets	5 mg/325 mg	Rx

SAMPLES	RELATED IND/NDA/DMF	STERILIZATION
N/A	DMF# [redacted]	N/A
	DMF# [redacted]	
	DMF# [redacted]	

LABELING
Satisfactory dated June 15, 1999.

BIOEQUIVALENCY STATUS
N/A

ESTABLISHMENT INSPECTION
EER for [redacted]
(Filed on 1-13-99). CGMP Certification for [redacted] is provided in Attachment 5 on page 27, Satisfactory. EER was

Redacted 2

pages of trade secret and/or confidential commercial information

Blister packaging components are now specified in the stability report form as [redacted] foil and [redacted]

REMARKS AND CONCLUSION
Recommend approvable letter to issue.

Reviewer
Edwin Ramos

Date
June 25, 1999
/S/ 7/12/99

ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt Yes

Spot---No

APPEARS THIS WAY
ON ORIGINAL

Redacted _____

pages of trade secret and/or confidential commercial information

REVIEW OF PROFESSIONAL LABELING # 2

Amendment to supplement (FPL)

DATE OF REVIEW: June 15, 1999

ANDA #: 40-099/S-006

NAME OF FIRM: UCB Pharma, Inc.

NAME OF DRUG: Lortab® 5/325 (Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/325 mg)

DATE OF SUBMISSION: June 9, 1999

COMMENTS

1. From a labeling perspective the labels and labeling has been satisfactorily revised to reflect the addition of unit dose blister packaging in 100s (4 x 25).

2. At the time of next printing, please make the following revision to the package insert labeling:

   DOSAGE AND ADMINISTRATION - Add the following as the last sentence of this section: - ...

   This change may be submitted as a Special Supplement - Changes Being Effected.

RECOMMENDATIONS:

Inform the firm of the above comments only if there are chemistry comments, otherwise please notify labeling reviewer.

FOR THE RECORD:

1. Review based on the labeling of Lortab® 5/325, approved February 6, 1998.

2. This supplement is in conjunction with the chemistry supplements to reflect for addition of Hospital Unit dose (blister) Packaging of 100's (4 x 25).

cc: ANDA 40-099/S-006
Dup/Division File
HFD-613/AVezza/CHoppes /(no cc: /S/ 6/17/99
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Review

/S/ 6/18/99

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trade secret and/or

confidential

commercial

information

ANDA 40-099/S-002, S-003, S-004, S-005, and S-006

NAME AND ADDRESS OF APPLICANT:
UCB Pharma, Inc.
Attention: Mary D. Alonzo
1950 Lake Park Drive
Smyrna, GA 30080
Phone-(770)437-5621

PURPOSE OF AMENDMENT/SUPPLEMENT

S-002: Supplemental application is provided for Hospital Unit Dose (Blister) [redacted] using [redacted] blister material as [redacted] and foil lidding as [redacted]

S-003: 24 month expiration date for product.

S-004: Control revision.

S-005: [redacted]

S-006: Unit Dose Blister labeling revision.

DATE OF SUBMISSION
August 12, 1998: Original submission

PHARMACOLOGICAL CATEGORY	TRADE NAME
Narcotic analgesic	Lortab 5/325

NONPROPRIETARY NAME
Hydrocodone Bitartrate and Acetaminophen Tablets, USP

DOSAGE FORM	POTENCY	RX OR OTC
Oral Tablets	5 mg/325 mg	Rx

SAMPLES	RELATED IND/NDA/DMF	STERILIZATION
N/A	DMF# [redacted]	N/A
	DMF# [redacted]	
	DMF# [redacted]	

LABELING- Unsatisfactory
Labeling is unsatisfactory per C.Park on 1-28-99.

BIOEQUIVALENCY STATUS
N/A

REMARKS AND CCONCLUSION
These supplements are considered as not approvable. The deficiencies will be considered as a minor amendment. The letter will be issued.

RECALLS
N/A

Reviewer
Sema Basaran, Ph.D.

ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt Yes__X__
No_____

If no, explain reason(s) below.

Spot Yes_____ No____x____

cc: ANDA 40-099
Division File
Field Copy

Endorsements:

HFD-647/S.Basaran/1-6-98. /S/ 2/8/99
HFD-647/U.Venkataram/1-12-98. /S/ 2/26/99.
Ms/code 40099S02rsb.Doc
V:new\frmsnz\UCB\lettter&rev\40099S02RSB.Doc
F/T by PAH/1-?-98.
NA Minor

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 40099/002**
Stamp: **13-AUG-1998** Regulatory Due:
Applicant: **UCB PHARMA**
1950 LAKE PARK DR
SMYRNA, GA 30080

Priority:
Org Code: **600**
Action Goal:
District Goal: **13-JAN-1999**
Brand Name:
Established Name: **HYDROCODONE BITARTRATE;ACETAMINOPHEN**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **5 MG/325 MG**

FDA Contacts: **S. BASARAN** **(HFD-647)** **301-827-5849 , Review Chemist**

Overall Recommendation:

ACCEPTABLE on 13-JAN-1999 by S. FERGUSON (HFD-324) 301-827-0062

Establishment: [redacted]

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **13-JAN-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING # 1

supplement (Draft)

DATE OF REVIEW: January 14, 1999

ANDA #: 40-099/S-006

NAME OF FIRM: UCB Pharma, Inc:

NAME OF DRUG: Lortab® 5/325 (Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/325 mg)

DATE OF SUBMISSION: August 12, 1998

COMMENTS

1. Unit dose blister

   Satisfactory in draft

2. Unit dose carton (100's)

   a. Revise to include the following beneath the established name on each panel.

      Each tablet contains:

      Hydrocodone Bitartrate ----- 5 mg
      Acetaminophen---------- 325 mg

   b. We encourage the inclusion of the following statement:

      If dispensed for out patient use, dispense in a tight, light-resistant container with a child-resistant closure.

3. Insert labeling

   We encourage the inclusion of "Rx only" statement to appear beneath the established name.

Revise the labeling as instructed above and submit 12 copies in final print.

RECOMMENDATIONS:

Inform the firm of the above comments.

FOR THE RECORD:

1. Review based on the labeling of Lortab® 5/325, approved February 6, 1998.

2. This supplement is in conjunction with the chemistry supplements to reflect for addition of Hospital Unit dose (blister) Packaging of 100's (4 x 25).

cc: ANDA 40-099/S-006
Dup/Division File
HFD-613/CPark/CHoppes V (no cc:)
V:\FIRMSNZ\UCBPHARM\LTRS&REV\40099S06.ael
Review

/S/ 1/15/99

/S/ 1/28/99

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 40099/007**
Stamp: **10-AUG-1999** Regulatory Due:
Applicant: **UCB PHARMA**
1950 LAKE PARK DR
SMYRNA, GA 30080

Priority:
Org Code: **600**
Action Goal:
District Goal: **10-JAN-2000**
Brand Name:
Established Name: **HYDROCODONE BITARTRATE;ACETAMINOPHEN**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **5 MG/325 MG**

FDA Contacts:			
T. AMES	**(HFD-640)**	**301-827-5849**	**, Project Manager**
E. RAMOS	**(HFD-645)**	**301-827-5849**	**, Review Chemist**
G. SMITH	**(HFD-647)**	**301-827-5849**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 13-AUG-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment: [redacted]

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **13-AUG-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

APPEARS THIS WAY
ON ORIGINAL

ANDA 40-099/S-008

NAME AND ADDRESS OF APPLICANT:
Watson Laboratories, Inc.
Attention: Dorothy Frank
417 Wakara Way
Salt Lake City, UT 84018

PURPOSE OF AMENDMENT/SUPPLEMENT
S-008: Facility addition

DATE OF SUBMISSION
February 21, 2001: Original submission
February 27, 2001: Amendment to CBE supplement dated February 21, 2001
March 12, 2001: Amendment 2 to CBE Supplement dated February 21, 2001

PHARMACOLOGICAL CATEGORY
Narcotic analgesic

TRADE NAME
[redacted]

NONPROPRIETARY NAME
Hydrocodone Bitartrate and Acetaminophen Tablets, USP

DOSAGE FORM	POTENCY	RX OR OTC
Oral Tablets	5 mg/325 mg	Rx

SAMPLES	RELATED IND/NDA/DMF	STERILIZATION
N/A		N/A

LABELING

BIOEQUIVALENCY STATUS
N/A

ESTABLISHMENT INSPECTION
Acceptable March 22, 2001

APPEARS THIS WAY
ON ORIGINAL

Redacted _____ | _____

pages of trade secret and/or confidential commercial information

RECALLS
N/A

Reviewer
Mahnaz Farahani, Ph.D.

ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt Yes__X__
No_____

If no, explain reason(s) below.

Spot Yes_____ No____x____

cc: ANDA 40-099/S-009
Division File

V:\FIRMSNZ\WATSON\LTRS&REV\40099s009AE.LABELING.doc

ENDORSEMENTS: HFD-613/CPARK, 10/24/02 /S/ 11/12/02
HFD-613/LGOLSON

Approvable Letter - Single Supplement

FOR THE RECORD

1. The comments are based on the new drug division's response to our consult on Vicodin ES® (7.5 mg/750 mg), ANDA 89-736/S-013 and Vicodin (5 mg/500 mg), ANDA 88058/S-027. See file folder for detail.

2. The following is the letter issued to the owner of Vicodin, Abbott Co. on July 31, 2002 regarding this issue.

Dear Sir:

We acknowledge receipt on July 01, 2002, of your annual report dated June 28, 2002, submitted pursuant to the provisions of 21 CFR 314.81(b)(2) and Section 505(k) of the Federal Food, Drug, and Cosmetic Act, for Vicodin® (hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/500 mg)

We have reviewed the labels and labeling submitted and have the following comments:

To date, we have not received a response to the February 22, 2002 letter the Agency issued to the former owner of this application, Knoll Pharmaceutical Company. In that letter, we asked Knoll to revise the "Special Sense" subsection of the ADVERSE REACTIONS section and to submit supporting data for the proposed "Geriatric Use" subsection of the PRECAUTIONS section that was submitted in the supplemental application dated April 6, 2001. A copy of the letter is enclosed for your convenience.

Since Abbott Laboratories is now the owner of this application and your product is the reference listed drug, a prompt response is requested.

Please be advised that the instruction described above also applies to your applications for ANDA 89-736 (Vicodin ES®) and 40-117 (Vicodin HP®).

Enclosure: A copy of the letter of February 22, 2002.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-099/S-002 to S-008

CORRESPONDENCE

ANDA 40-099/S-009

NOV 13 2002

Watson Laboratories, Inc.
Attention: Margaret Choy
311 Bonnie Circle
Corona, California 92880

Dear Madam:

This is in reference to your supplemental new drug application dated October 11, 2002, submitted pursuant to 21 CFR 314.70(c) "Special Supplement - Changes Being Effected" regarding your abbreviated new drug application for ——— (Hydrocodone Bitartrate and Acetaminophen Tablets, USP), 5 mg/325 mg.

The supplemental application provides for revised package insert labeling reflecting the changes in the CONTRAINDICATIONS, PRECAUTIONS, and ADVERSE REACTIONS sections found in the labeling for the reference listed drug, Vicodin®.

We have completed the review of this supplemental application and it is approvable. However, before the supplement application may be approved, it is necessary that you supply sufficient information to show that the changes proposed in your labeling have been approved for the reference listed drug, Vicodin®. Submit this information as an amendment to this supplement application.

Sincerely yours,

/S/ 11/12/02

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ARCHIVAL COPY

WATSON Laboratories, Inc.

A Subsidiary of Watson Pharmaceuticals, Inc.

October 11, 2002

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

Labeling Supplement
Changes Being Effected (CBE-0)

NDA NO. 40-099 REF NO. 91-009-AI
NDA SUPPL FOR Labeling Rev.

RE: ANDA 40-099
_____® (Hydrocodone Bitartrate and Acetaminophen Tablets, USP)
5 mg/325 mg

Including Final Printed Labeling

FPL

Dear Mr. Buehler:

In accordance with the FDA Guidance to Industry, "Changes to an Approved NDA or ANDA," Section X.C., November 1999, Watson Laboratories Inc. hereby submits this Labeling Supplement - Changes Being Effected (CBE-0) for review for ANDA 40-099 _____ Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 5 mg/325 mg. This supplement is being provided to include new information for the **CONTRAINDICATIONS, PRECAUTIONS,** and **ADVERSE REACTIONS** sections. Watson's labeling has been revised in accordance with the current Reference Listed Drug (RLD) labeling, VICODIN® (hydrocodone bitartrate and acetaminophen tablets, USP) Tablets, which are manufactured by Knoll Laboratories, revised July 2000.

The changes to the insert include the addition of new information in the following sections: added second paragraph to **CONTRAINDICATIONS,** added subsections for **Geriatric Use** under **PRECAUTIONS,** and **Special Senses** under **ADVERSE REACTIONS**. Other modifications were made to update molecular weights per USP, changed revision date, and editorial changes to reflect current Watson format.

Please find attached twelve copies of our proposed final printed package insert labeling, eleven (11) archival copies and one (1) review copy of this supplement (See **Exhibit 1**).

In order to facilitate review of the submission and in accordance with 314.94 (a)(8)(iv), we have provided a side-by-side comparison of our revised package insert labeling, Code 667C00, revised June 2002, which incorporates the above listed changes with the RLD labeling (See **Exhibit 2**).

RECEIVED
OCT 15 2002
OGD/CDER

311 Bonnie Circle, Corona, CA 92880 • Tel: (800) 249-5499 • Fax: (909) 493-5802 • Website: www.watsonpharm.com

We trust the information provided is satisfactory for your review of this Labeling Supplement - Changes Being Effected. Should you require additional information, please contact me by phone at (909) 493-5449 or by fax at (909) 493-5806.

Sincerely,

Margaret Choy, BSc., RAC
Director, Regulatory Affairs

SM/nl

APPEARS THIS WAY
ON ORIGINAL

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

March 12, 2001

SCBO & AC
CURTL ATTACHMENT

Mr. Gary Buehler, R.Ph.
Acting Director,
Office of Generic Drugs
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Amendment 2 to CBE
Supplement Dated
February 21, 2001

Re: ANDA 40-099, [redacted] 5 mg/325 mg Tablets
(Hydrocodone Bitartrate and Acetaminophen tablets, USP 5 mg/325 mg)

Dear Mr. Buehler,

On February 21, 2001, Watson Laboratories, Inc. submitted a supplement for an [redacted] change for [redacted] 5 mg/325 mg (Hydrocodone Bitartrate and Acetaminophen tablets, USP 5 mg/325 mg). Watson amended this supplement on February 27, 2001, by changing it to a Supplement – Changes Being Effected in 30 Days, effective as of March 23, 2001. Watson would like to further amend this supplement by specifying that [redacted] in question, has had a satisfactory FDA inspection. [redacted] was inspected by the FDA from May 2 to May 10, 2000.

We have enclosed one (1) archival and one (1) review copy of this supplement and, in accordance with 21 CFR 314.50(k)(3), one field copy of this supplement will be forwarded to the Denver District Office, FDA.

Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical sections contained in the archival and review copies of this supplement.

If you have any questions regarding the information provided, please contact me by phone at (801) 588-6200 or by fax at (801) 583-8135.

Sincerely,

Cheri D. Fehr for

Dorothy A. Frank, M.S., R.A.C
Director, Regulatory Affairs

CENTER FOR DRUG
RECD
MAR 13 2001
OGD
EVALUATION AND RESEARCH

Research Park, 417 Wakara Way, Salt Lake City, UT 84108 • Tel: 801/588-6200 • Fax: 801/583-6042

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

NDA SUPP AMEND
SCB-00[illegible] /AC

February 27, 2001

Mr. Gary Buehler, R.Ph.
Acting Director,
Office of Generic Drugs
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Amendment to CBE
Supplement Dated
February 21, 2001

Re: ANDA 40-099, [redacted] 5 mg/325 mg Tablets
(Hydrocodone Bitartrate and Acetaminophen tablets, USP 5 mg/325 mg)

Dear Mr. Buehler,

On February 21, 2001, Watson Laboratories, Inc., submitted a supplement as a Special Supplement – Changes Being Effected in accordance with 21 CFR 314.70(c), PAC-ATLS: Post-approval Changes – [redacted] April 1998. This supplement provides for an [redacted] for [redacted] 5 mg/325 mg (Hydrocodone Bitartrate and Acetaminophen tablets, USP 5 mg/325 mg). Watson wishes to amend this supplement by changing it to a Supplement – Changes Being Effected in 30 Days in accordance with the Guidance for Industry: Changes to an Approved NDA or ANDA, November 1999. The change will be effective as of March 23, 2001.

We have enclosed one (1) archival and one (1) review copy of this supplement and, in accordance with 21 CFR 314.50(k)(3), one field copy of this supplement will be forwarded to the Denver District Office, FDA.

Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical sections contained in the archival and review copies of this supplement.

Research Park, 417 Wakara Way, Salt Lake City, UT 84108 • Tel: 801/588-6200 • Fax: 801/583-6042

If you have any questions regarding the information provided, please contact me by phone at (801) 588-6200 or by fax at (801) 583-8135.

Sincerely,

Dorothy A. Frank

Dorothy A. Frank, M.S., R.A.C
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

EER submitted
Jan 3/21/01

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

February 21, 2001

NDA NO. 40099 REF NO. SCB-008
NDA SUPPL FOR Facility Addition
AT

Mr. Gary Buehler, R.Ph.
Acting Director,
Office of Generic Drugs
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PAC-ATLS
SPECIAL SUPPLEMENT-
Changes Being Effected

Re: ANDA 40-099, ——— 5 mg/325 mg Tablets
(Hydrocodone Bitartrate and Acetaminophen tablets, USP 5 mg/325 mg)

Dear Mr. Buehler,

This Special Supplement – Changes Being Effected is submitted in accordance with 21 CFR 314.70(c), PAC-ATLS: Post-approval Changes – ———————— ——, April 1998. This supplement provides for an ———————— change for —— 5 mg/325 mg (Hydrocodone Bitartrate and Acetaminophen tablets, USP 5 mg/325 mg).

This supplement covers the transfer of ———————— of Hospital Unit Dose Packages (HUD) on ——— from ———————— was approved for ——— ——of HUD units on August 13, 1999 —— is currently the approved manufacturer and lab of release and stability testing for the bottled ——, 5 mg/325 mg product.

We have enclosed one (1) archival and one (1) review copy of this supplement and, in accordance with 21 CFR 314.50(k)(3), one field copy of this supplement will be forwarded to the Denver District Office, FDA.

Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical sections contained in the archival and review copies of this supplement.

CENTER FOR DRUG
RECD
FEB 23 2001
OGD
EVALUATION AND RESEARCH

Research Park, 417 Wakara Way, Salt Lake City, UT 84108 • Tel: 801/588-6200 • Fax: 801/583-6042

If you have any questions regarding the information provided, please contact me by phone at (801) 588-6200 or by fax at (801) 583-8135.

Sincerely,

Dorothy A. Frank

Dorothy A. Frank, M.S., R.A.C
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

EER requested
(acceptable on 8/13) 8/12
1st. Amend

UCB Pharma

UCB Pharma, Inc. - 1950 Lake Park Drive - Smyrna, Georgia 30080

August 10, 1999

Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2, Room 204 (HFD-630)
7500 Standish Place
Rockville, Maryland 20855

NDA NO. 40099 REF NO. SUB-007
NDA SUPPL FOR Facility Addition
SI

Granted
1st 8/12/99

ANDA #40-099 Lortab® 5/325 C III
(Hydrocodone Bitartrate and Acetaminophen Tablets, USP 5 mg/325 mg)
SUPAC IR - SPECIAL SUPPLEMENT CHANGES BEING EFFECTED REQUEST

Dear Sir or Madam:

Reference is made to UCB Pharma, Inc.'s Abbreviated New Drug Application (ANDA) #40-099 for Lortab® 5/325 approved June 25, 1997, and a supplement that provided for a unit-dose blister pack approved June 9, 1999. The approved supplement specifies [redacted]

Provided herein, in duplicate, is a supplement to add [redacted] This supplement is being submitted in accordance with the "Stand Alone Packaging Operations Site Changes" section of the Letter to Industry from the Center for Drug Evaluation and Research dated February 18, 1997 as a SUPAC IR - SPECIAL SUPPLEMENT CHANGES BEING EFFECTED REQUEST.

[redacted] has provided written certification stating that it is in conformance with cGMPs. The last FDA inspection of [redacted] which covered the [redacted] was concluded on May 11, 1999 and resulted in three 483 citations which were corrected at the time of inspection. A copy of the 483 citation and the [redacted] esponse are attached for your review.

The same container/closure described in the approved application, [redacted] and [redacted] will be employed for all [redacted] The [redacted] at [redacted] is of the same design and operating principle as the equipment used at [redacted]

UCB Pharma, Inc. commits to place an initial production lot of the unit dose product [redacted] on-long-term stability study using the current stability protocol and provide updates in Annual Reports through the approved expiry.

If you have any questions regarding this application, please contact the undersigned at (770)-437-5621 or by facsimile at (770)-437-5507.

Sincerely,

Mary D. Alonso

Mary D. Alonso
Sr. Regulatory Affairs Associate

ucb Pharma
UCB Pharma, Inc. - 1950 Lake Park Drive - Smyrna, Georgia 30080

labeling reviewed
drafted 6/15/99
CVezza

June 9, 1999

Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2, Room 204 (HFD-630)
7500 Standish Place
Rockville, Maryland 20855

NDA SUPP AMEND
SC 002
SC 003
SC 004
SC 005 } AM
SL 006

ANDA #40-099
Lortab® 5/325 C III
(Hydrocodone Bitartrate and Acetaminophen Tablets, USP 5 mg/325 mg)

Minor Amendment
to
Supplements S-003, S-004, S-005, and S-006

Dear Sir or Madam:

Reference is made to UCB Pharma's Abbreviated New Drug Application (ANDA) #40-099 for Lortab® 5/325 (hydrocodone bitartrate and acetaminophen tablets, USP 5 mg/325 mg) approved on June 25, 1997 and supplements (S-003, S-004, S-005, and S-006) providing for unit dose _____ filed on August 12, 1998. Reference is also made to a deficiency letter received from the Food and Drug Administration dated March 3, 1999 which outlined specific "minor" deficiencies within the pending supplements.

Herewith submitted in duplicate, is a minor amendment to address the FDA's deficiencies as outlined in the March 3, 1999 letter.

Should you have any additional questions, please feel free to contact the undersigned at (770)-437-5621 by telephone or (770)-437-5507 by facsimile.

Sincerely,

Mary D. Alonso

Mary D. Alonso
Senior Regulatory Affairs Associate

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 10 1999
OGD

ANDA 40-099/S-002, S-003, S-004, S-005, and S-006

UCB Pharma, Inc.
Attention: Mary D. Alonso
1950 Lake Park Drive
Smyrna, GA 30080
Phone-(770)437-5555

MAR 3 1999

Dear Madam:

This is in reference to your supplemental new drug applications dated August 12, 1998, submitted pursuant to 21 CFR 314.70, regarding your abbreviated new drug application for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/325 mg (Lortab 5/325).

The supplemental applications provide for:

S-002: Supplemental application is provided for Hospital Unit Dose (Blister) [redacted] using [redacted] blister material as [redacted] and foil lidding as [redacted]

S-003: 24 month expiration date for product.

S-004: Control revision.

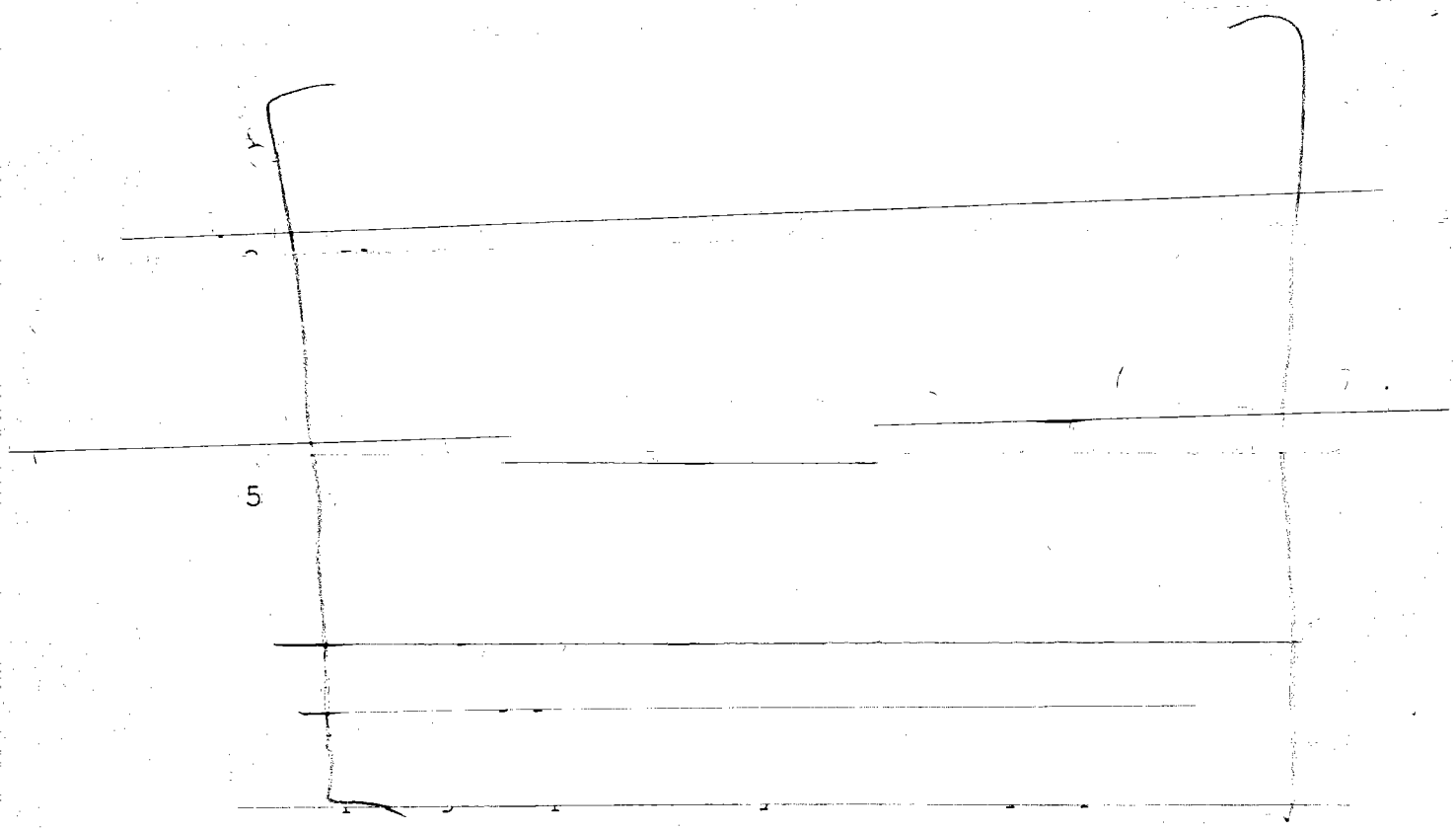
S-005: [redacted]

S-006: Unit Dose Blister labeling revision.

The supplemental applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies:

[redacted]



B. Labeling Deficiencies:

B. Labeling Deficiencies:

1. Unit dose blister

   Satisfactory in draft

2. Unit dose carton (100's)

   a. Revise to include the following beneath the established name on each panel.

      Each tablet contains:

      Hydrocodone Bitartrate ----- 5 mg
      Acetaminophen---------- 325 mg

   b. We encourage the inclusion of the following statement:

      If dispensed for out patient use, dispense in a tight, light-resistant container with a child-resistant closure.

3. Insert labeling

We encourage the inclusion of "Rx only" statement to appear beneath the established name.

Revise the labeling as instructed above and submit 12 copies in final print.

The file on these supplemental applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw these supplemental applications. 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 responses to this letter will be considered as MINOR amendments and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving these supplemental applications, you may request an opportunity for a hearing.

Sincerely yours,

/S/ for

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

APPEARS THIS WAY
ON ORIGINAL

UCB Pharma

UCB Pharma, Inc. - 1950 Lake Park Drive - Smyrna, Georgia 30080

NDA NO. _____ REF NO. SC-006
NDA SUPPL FOR Label Rev

August 12, 1998

NDA NO. _____ REF NO. SC-002
NDA SUPPL FOR Packaging change

Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2, Room 204 (HFD-630)
7500 Standish Place
Rockville, Maryland 20855

NDA NO. 40-099 REF NO. SC-003
NDA SUPPL FOR Exp Date

NDA NO. 40-099 REF NO. SC-004
NDA SUPPL FOR Control Lab

ANDA #40-099 Lortab® 5/325 C III
(Hydrocodone Bitartrate and Acetaminophen Tablets, USP 5 mg/325 mg)

NDA NO. 40-099 REF NO. SC-005
NDA SUPPL FOR Facility Add.

Dear Sir or Madam:

Reference is made to UCB Pharma, Inc.'s Abbreviated New Drug Application (ANDA) #40-099 for Lortab® 5/325.

Provided herein, in duplicate, is a supplemental application for HUD _____ using _____ blister material as _____ and foil lidding as _____. The data included demonstrate satisfactory stability for the product in the proposed package for up to three months at 40°C/75% RH and justify a 24-month expiry for product stored at room temperature.

UCB Pharma, Inc. commits to place an initial production lot of the unit dose product _____ on long-term stability study using the current stability protocol and provide updates in Annual Reports through the approved expiry.

If you have any questions regarding this application, please contact the undersigned at (770)-437-5621 or by facsimile at (770)-437-5507.

Sincerely,

Mary D. Alonso

Mary D. Alonso
Senior Regulatory Affairs Associate

RECEIVED
AUG 13 1998
GENERIC DRUGS

ucb Pharma
UCB Pharma, Inc. - 1950 Lake Park Drive - Smyrna, Georgia 30080

August 18, 1997

NDA NO. _____ REF. NO. 5 LOV/
NDA SUPPL. FOR Label Rev
labels + labeling submitted
satisfactory - approval
letter drafted
2/3/98

Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2, Room 204 (HFD-630)
5600 Standish Place
Rockville, Maryland 20857

ANDA # 40-099
Lortab® 5/325 (Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 5 mg/325 mg)

Dear Sir,

Reference is made to UCB Pharma, Inc.'s Abbreviated New Drug Application (ANDA) # 40-099 for Lortab® 5/325 (Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 5 mg/325 mg), approved June 25, 1997. Reference is also made to telephone contacts with the Division of Labeling and Program Support on June 12, 1997 and June 23, 1997, regarding changes requested to the Final Printed Package Insert.

Herewith submitted, in duplicate, is a side-by-side comparison of the Final Printed Labeling submitted on January 31, 1996 and the revised Final Printed Labeling with the changes requested and other minor changes. Twelve copies of the revised labeling are also included.

Should you have any questions, please feel free to contact the undersigned at (770) 437-5559 or Patty Fritz, Associate Director, Regulatory Affairs, at (770) 437-5555

Sincerely,

Diane F. Vandeputte, Ph.D.
Assistant Manager, Regulatory Affairs

ANDA 40-099/S-001

UCB Pharma, Inc.
Attention: Diane F. Vandeputte, Ph.D.
1950 Lake Park Drive
Smyrna, GA 30080

FEB 6 1998

Dear Madam:

This is in reference to your supplemental new drug application dated August 18, 1997, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug application for Lortab® 5/325 (Hydrocodone Bitartrate and Acetaminophen Tablets. USP, 5 mg/325 mg).

The supplemental application provides for revisions to the DESCRIPTION, DOSAGE AND ADMINISTRATION, and HOW SUPPLIED sections of the package insert labeling and the changing of the address of the distributor on the container label and insert labeling.

We have completed the review of this supplemental application and it is approved.

However, due to the FDA Modernization Act of 1997, please make the following revisions:

1. Delete the "[redacted]" statement throughout your labels and labeling.

2. Replace the "[redacted]" statement with the symbol "Rx only" throughout your labels and labeling.

The revisions above may be made and reported with your next annual report, provided that the changes are described in full.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/S/ 2/5/98

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

cc: ANDA 40-099/S-001
Division File
HFD-92/with labeling
HFD-600/Reading File
HFD-610/JPhillips
Field Copy
aev/2/3/98|X:\NEW\FIRMSNZ\UCBPHARM\LTRS&REV\40099S01.APL
APPROVAL LETTER - SINGLE SUPPLEMENT

Endorsements:
HFD-613/AVezz /S/ 2/5/98
HFD-613/CHoppes

/S/ 2/5/98

APPEARS THIS WAY
ON ORIGINAL