

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

Approval Package for:

APPLICATION NUMBER:

**40-148/S-002, S-003, S-004, S-005,
and S-011**

Trade Name: Norco 7.5/325

Generic Name: Hydrocodone Bitartrate and
Acetaminophen Tablets, USP

Sponsor: Watson Laboratories

Approval Date: September 12, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

CONTENTS

**40-148/S-002, S-003, S-004, S-005,
and S-011**

Reviews / Information Included in this ANDA Review.

Approval Letter	X
Tentative Approval Letter(s)	
Final Printed Labeling(s)	X
CSO Labeling Review(s)	X
Chemistry Review(s)	X
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	X
Correspondence	X

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

**40-148/S-002, S-003, S-004, S-005,
and S-011**

APPROVAL LETTER

ANDA #40-148/S-002, S-003, S-004, S-005 and S-011

Watson Laboratories
Attention: Ernest Lengle, Ph.D.
311 Bonnie Circle
Corona, CA 91720

SEP 2 2000

Dear Sir:

This is in reference to your supplemental new drug applications dated April 17, 1998 and June 23, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), regarding your abbreviated new drug application for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 10 mg/325 mg, 10 mg/500 mg and 7.5 mg/325 mg (new strength).

Reference is also made to your amendments dated June 23, 1999, February 25 and June 12, 2000.

The supplemental applications provide for:

- S-002: A new dosage strength of 7.5 mg/325 mg.
- S-003: Package additions of 100's and 500's for the new dosage strength.
- S-004: An expiration dating period of 24 months for the new dosage strength in the 100's and 500's packages.
- S-005: Container labels and package insert labeling for the new dosage strength.
- S-011: Package addition of 30's and Physicians samples (2's) for the new dosage strength.

We have completed the review of these supplemental applications as amended, and have concluded that the new 7.5 mg/325 mg strength of the drug product is safe and effective for use as recommended in the submitted labeling. Accordingly, these supplemental applications are approved.

The new strength of Hydrocodone Bitartrate and Acetaminophene Tablets USP, 7.5 mg/325 mg, can be expected to have the same therapeutic effect as that of the listed drug product upon which the Agency relied as the basis of safety and effectiveness.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

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

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

The material submitted is being retained in our files.

Sincerely yours,


Gary Buehler 9/12/00
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

**40-148/S-002, S-003, S-004, S-005,
and S-011**

FINAL PRINTED LABELING(S)

NORCO® 
(Hydrocodone Bitartrate
and Acetaminophen
Tablets, USP)

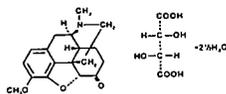
SEP 12 2000

Rx only

DESCRIPTION

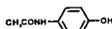
NORCO® (Hydrocodone bitartrate and acetaminophen) is supplied in tablet form for oral administration.

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



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

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



$C_8H_9NO_2$ M. W. = 151.17

NORCO®, for oral administration is available in the following strengths:

	Hydrocodone Bitartrate	Acetaminophen
NORCO® 7.5/325	7.5 mg	325 mg
NORCO® 10/325	10 mg	325 mg

In addition, each tablet contains the following inactive ingredients: croscarmellose sodium, crospovidone, magnesium stearate, microcrystalline cellulose, pregelatinized starch, povidone, and stearic acid; the 7.5 mg/325 mg tablets include FD&C Yellow #6 Aluminum Lake, the 10 mg/325 mg tablets include D&C Yellow #10 Aluminum Lake.

CLINICAL PHARMACOLOGY

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

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

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

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

NORCO® is indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

NORCO® 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, NORCO® 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 NORCO® is used postoperatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all narcotics, may impair the 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 other narcotics, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants (including alcohol) concomitantly with NORCO® 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. NORCO® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not

always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

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

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

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

ADVERSE REACTIONS

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

Other adverse reactions include:

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

Gastrointestinal System: Prolonged administration of NORCO® 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: NORCO® is classified as a Schedule III controlled substance.

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

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly 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 the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

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

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

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

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

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

HOW SUPPLIED

NORCO® 7.5/325 is available as capsule-shaped, light orange tablets bisected on one side and debossed with "NORCO 729" on the other side. Each tablet contains 7.5 mg hydrocodone bitartrate and 325 mg acetaminophen. They are supplied as follows:

Bottles of 30	NDC 52544-729-30
Bottles of 100	NDC 52544-729-01
Bottles of 500	NDC 52544-729-05

NORCO® 10/325 is available as capsule-shaped, yellow tablets bisected on one side and debossed with "NORCO 539" on the other side. Each tablet contains 10 mg hydrocodone bitartrate and 325 mg acetaminophen. They are supplied as follows:

Bottles of 100	NDC 52544-539-01
Bottles of 500	NDC 52544-539-05

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.



Watson Pharma, Inc.
A Subsidiary of
Watson Laboratories, Inc., Corona CA 92880

Revised: Jan 2000

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

**40-148/S-002, S-003, S-004, S-005,
and S-011**

CSO LABELING REVIEW(S)

REVIEW OF PROFESSIONAL LABELING # 1

SUPPLEMENT

DRAFT - Container Labels and Insert Labeling

DATE OF REVIEW: August 24, 1998

ANDA #: 40-148/S-005

NAME OF FIRM: Watson Laboratories, Inc.

NAME OF DRUG: Hydrocodone Bitartrate and Acetaminophen Tablets

DATE OF SUBMISSION: April 17, 1998

COMMENTS:

General Comment:

Your proposed proprietary name "NORCO 7.5/325" is satisfactory.

Container: 100s and 500s

Satisfactory, in draft. We encourage the use of boxing, contrasting colors, or other means to differentiate the strength of this product from other approved and proposed strengths.

Insert:

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

RECOMMENDATIONS:

1. Inform the firm of the above comments.
2. Request the firm revise their insert labeling, then prepare and submit final print container labels and insert labeling.

FOR THE RECORD:

1. Review based on the labeling of the Labeling Guidance

for Hydrocodone Bitartrate and Acetaminophen Tablets
USP, revised April 1994.

2. This labeling supplement is combined with chemistry supplements and is for the addition of a new strength, 7.5 mg/325 mg.
3. The firm has proposed the proprietary name "NORCO 7.5/325" and it has been submitted to the Labeling and Nomenclature Committee for their review and comment.
4. The listing of inactive ingredients is accurate as described in the DESCRIPTION section.

cc: ANDA 40-148
Dup/Division File
HFD-613/AVeZZa/CHoppes (no cc:)
HFD-600/RF
aev/8/24/98|X:\NEW\FIRMSNZ\WATSON\LTRS&REV\40148S05.NAL
Review

**APPEARS THIS WAY
ON ORIGINAL**

REVIEW OF PROFESSIONAL LABELING # 2

SUPPLEMENT

FPL - Container Labels and Insert Labeling

DATE OF REVIEW: September 2, 1999

ANDA #: 40-148/S-005

NAME OF FIRM: Watson Laboratories, Inc.

NAME OF DRUG: Hydrocodone Bitartrate and Acetaminophen Tablets

DATE OF SUBMISSION: June 23, 1999

COMMENTS:

1. Container - 100s and 500s
Satisfactory in final print
2. Sample Pak - 2 Tablets
Satisfactory in final print
3. Insert:

a. GENERAL COMMENT

We note that you have defined Norco® as "Hydrocodone Bitartrate and Acetaminophen" as indicated in your TITLE and in the first paragraph of the DESCRIPTION section, trademarking the "drug substance nonproprietary name" as the proprietary name (i.e., Norco®). Therefore, please be specific with respect to the strength of your products in the following sections as described below and/or comment.

b. DESCRIPTION

- i. Revise to read as follows.
Norco®7.5/325 ...
Norco®10/325 ...
- ii. Delete the term " — " associated with the proprietary name.

c. HOW SUPPLIED

- i. Norco®10/325 is available...
- ii. See comment (ii) under DESCRIPTION. [two instances]

RECOMMENDATIONS:

1. Inform the firm of the above comments.
2. Request the firm revise their insert labeling, then prepare and submit final print insert labeling.

FOR THE RECORD:

1. Review based on the labeling of the Labeling Guidance for Hydrocodone Bitartrate and Acetaminophen Tablets USP, revised April 1994.
2. This labeling supplement is combined with chemistry supplements and is for the addition of a new strength, 7.5 mg/325 mg.
3. The firm has proposed the proprietary name "NORCO® 7.5/325" and it has been submitted to the Labeling and Nomenclature Committee for their review and comment. This proposed proprietary name was found acceptable. We prefer that the firm refer Norco® to the drug substance, not to the whole product name. Refer to the comments in this review.
4. The listing of inactive ingredients is accurate as described in the DESCRIPTION section.

cc: ANDA 40-148/S-005 - *ISI* - 9/13/99.
Dup/Division Fil
HFD-613/CPark/CHoppes (no cc:)
HFD-600/RF
V:\FIRMSNZ\WATSON\LTRS&REV\40148S05.NAL2
Review

ISI 9/13/99
V

REVIEW OF PROFESSIONAL LABELING # 3

SUPPLEMENT

FPL - Container Labels and Insert Labeling

DATE OF REVIEW: March 7, 2000

ANDA #: 40-148/S-005

NAME OF FIRM: Watson Laboratories, Inc.

NAME OF DRUG: Hydrocodone Bitartrate and Acetaminophen Tablets

DATE OF SUBMISSION: February 25, 2000

COMMENTS:

1. Container - 100s and 500s
Satisfactory in final print as of June 23, 1999 submission
2. Sample Pak - 2 Tablets
Satisfactory in final print as of June 23, 1999 submission
3. Insert
Satisfactory in final print as of February 25, 2000 submission

RECOMMENDATIONS:

1. Inform the firm of the above comments.
2. The firm has revised the NDC number for the 30-count bottle of 7.5/325 strength tablets and zip code of the firm's address as indicated in the insert labeling in this submission. The container labels submitted on June 23, 1999 have different NDC number and zip code. The revised container labels reflecting these changes may be submitted in an annual report.

FOR THE RECORD:

1. Review based on the labeling of the Labeling Guidance for Hydrocodone Bitartrate and Acetaminophen Tablets USP, revised April 1994.
2. This labeling supplement is combined with chemistry supplements and is for the addition of a new strength, 7.5 mg/325 mg.
3. The firm has proposed the proprietary name "NORCO® 7.5/325" was found acceptable by the Labeling and Nomenclature Committee in the past. We prefer that the firm refer Norco® to the drug substance, not to the whole product name. Refer to the comments in this review. Now, the firm revised the insert labeling per Agency's request in the last deficiency letter so that Norco® refers to the drug substance only.
4. The listing of inactive ingredients is accurate as described in the DESCRIPTION section.

**CENTER FOR DRUG
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APPLICATION NUMBER:

**40-148/S-002, S-003, S-004, S-005,
and S-011**

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF CHEMISTRY II

SUPPLEMENTAL APPLICATION REVIEW

CHEMIST'S REVIEW NO.

1.

ANDA #

40-148 (10 mg/325 mg & 10 mg/500 mg)

NAME AND ADDRESS OF APPLICANT

Watson Laboratories
Attention: Ron Lapré
311 Bonnie Circle
Corona, CA 91720

LEGAL BASIS FOR SUBMISSION

Reference Listed Drug - Vicodin⁷ (Hydrocodone Bitartrate and Acetaminophen Tablets, 7.5 mg/325 mg) of Knoll Pharmaceutical for the new strength of 7.5 mg/325 mg.

No patents or exclusivity remaining per the firm on pp. 012 and 014 of the supplements.

Suitability Petition for the new dosage strength (Docket No. 87P-0129/CP) by Mikart approved on 6/8/87.

PURPOSE OF AMENDMENT/SUPPLEMENT

S-002: New dosage strength for 7.5 mg/325 mg tablets.

S-003: Package additions.

S-004: Expiration dating.

S-005: Labeling revision.

DATE(S) OF SUBMISSION(S)

S-002, S-003, S-004, S-005: 4/17/98 (Subject of this Review).

PHARMACOLOGICAL CATEGORY

Analgesic for moderate to severe pain.

PROPRIETARY NAME

NORCO 7.5/325 (proposed)

NONPROPRIETARY NAME

Hydrocodone Bitartrate and Acetaminophen

DOSAGE FORM

Tablets

R_x or OTC

R_x

POTENCY

10 mg/325 mg (NORCO Tradename) & 10 mg/500 mg (Generic): Both Strengths

ANDA 40-148
Watson/Hydrocodone Bitartrate & Acetaminophen

2

Already Approved.
7.5 mg/325 mg: Proposed New Dosage Strength.

RECORDS AND REPORTS
N/A

SAMPLES
N/A

STERILIZATION
N/A

RELATED IND/NDA/DMF
DMF
DMF

LABELING

S-005: Proposed insert labeling and container labels (100's and 500's) in draft have been submitted in the supplemental filing. The labels/labeling are essentially the same as those that were approved for the companion dosage strengths. The insert labeling includes the already approved dosage strengths in the HOW SUPPLIED section. The A. Vezza review dated **8/24/98**, indicates revisions that should be made for the labels and labeling, and requests FPL of both with the appropriate revisions.

According to the review, the proposed tradename "NORCO 7.5/325" is satisfactory. The approval of the tradename NORCO for the 10 mg/325 mg dosage strength in this ANDA has been referenced.

Watson will update the supplemental application for the new dosage strength if the tradename is acceptable with the following revised documents bearing the tradename:

- a.
- b. SPEC. and QA REPORT to reflect new appearance.
- c. FPL for insert labels and container labels.

BIOEQUIVALENCY STATUS

In vitro dissolution data are found on pp. 53 ff., and a request for a waiver of *in vivo* bioequivalence study requirements to this dosage strength has been made on p. 74. The J. Lee review dated **7/31/98**, recommends that the dissolution testing be included in the manufacturing controls and stability program, and that "The test product should meet the following specification: Not less than $\frac{1}{2}$ of the labeled amount of both components of the drug in the tablet is dissolved in 30 minutes", and "The Division of Bioequivalence finds that the information provided by the sponsor demonstrates that the test product falls under 21 CFR 320.22(c) of Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of an *in vivo* bioavailability study be granted". The Watson dissolution procedure and specs. comply with the requirements of the compendium monograph and the DOB (i.e., NLT $\frac{1}{2}$ (Q) in 30 min.).

ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION

A categorical exclusion under 21 CFR 312.24(c)(1) has been claimed for the manufacture of the new dosage strength.

ESTABLISHMENT INSPECTION

EER=s for Watson as part of 40-094/S-001 and S-002 for additional suppliers of the ds=s were acceptable on 6/11/97, per M. Egas (HFD-322). Watson manufactured the exhibit batch with approved sources of the ds=s, and all firms involved in the manufacture/testing of the respective new dosage strengths were satisfactory for the original approval of ANDA 40-148 and 40-094/S-001 and S-002. A new EER may not be necessary.

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

S-002: The applicant proposes to manufacture a new dosage strength containing 7.5 mg/325 mg of the active ingredients. Raw materials controls, manufacturing and processing instructions, in-process controls, c/c information, controls for the finished dosage form, mv of the in-house methods to be used for the drug product, and stability information and data have been provided.

COMPONENTS AND COMPOSITION

	<u>Tablet</u>	<u>Tablets</u>	<u>Tablets</u>
	<u>mg</u>	<u>Batch (kg)</u>	<u>Batch (kg)</u>
Hydrocodone Bitartrate USP	7.5	_____	_____
— Acetaminophen USP ¹	_____	_____	_____
Croscarmellose Sodium NF	_____	_____	_____
Microcrystalline Cellulose NF	_____	_____	_____
Magnesium Stearate NF	_____	_____	_____
FD&C Yellow # 6 Alum. Lake	_____	_____	_____
Total	425.0	_____	_____
(Actual)	(425.0)	_____	_____

¹ This ingredient _____ bears the tradename _____ contains _____, Acetaminophen USP, Pregelatinized Starch NF, Povidone NF, Crospovidone NF, and Stearic Acid NF. The amount/tablet is equivalent to 325.0 mg of Acetaminophen NF.

The tablets will be 0.250" x 0.550", capsule-shaped light orange, scored on the lower punch, and debossed "Watson 729" on the upper punch.

The firm proposed a trade name for this product, and the punches would have different embossing (or debossing) characters that would be used to identify the product. The documents, punch description, etc. have not been

ANDA 40-148

Watson/Hydrocodone Bitartrate & Acetaminophen
submitted at this time.

The site at which the manufacturing, processing, packaging, labeling, and testing (in-process, drug product, and stability testing) will be performed is located at:

Watson Laboratories, Inc.
132 Business Center Drive
Corona, CA 91720

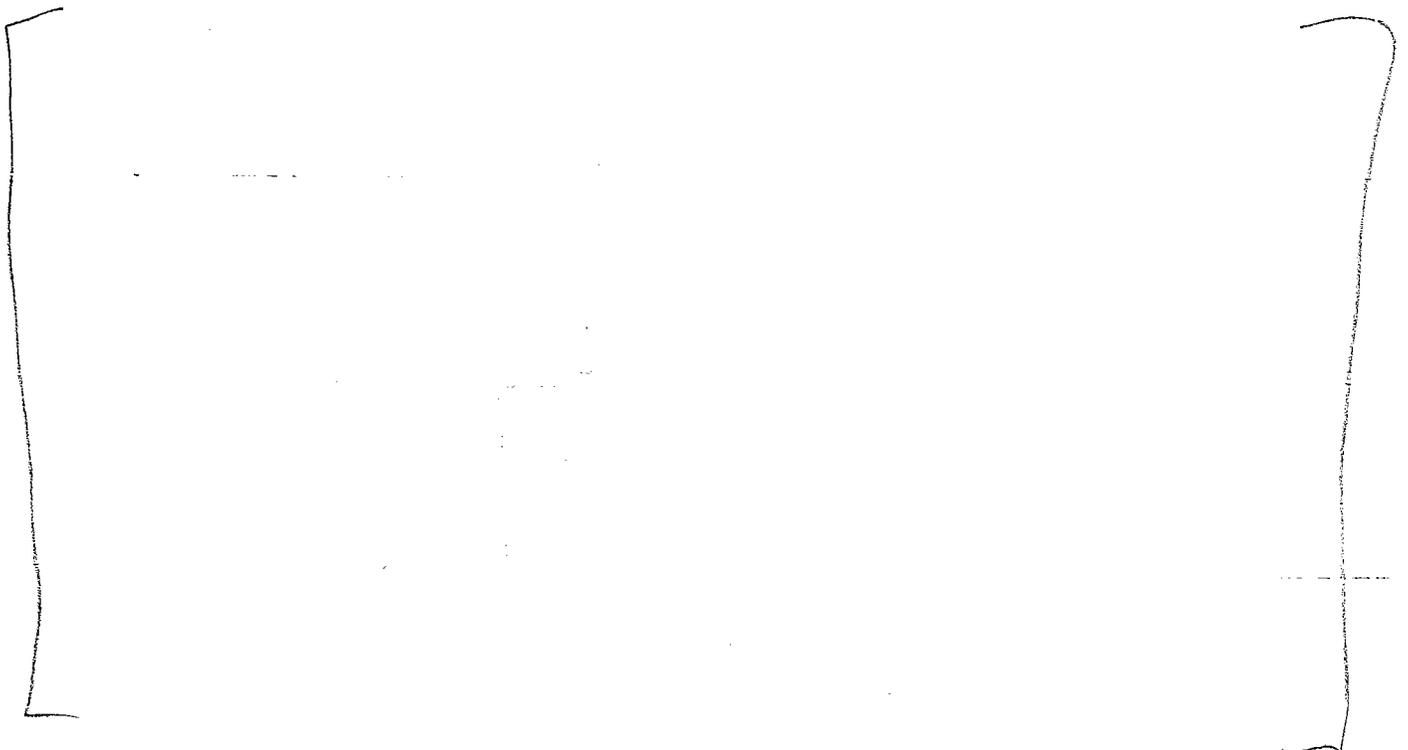
Storage and shipping of the drug product will be undertaken at the facility located at:

Watson Laboratories, Inc.
311 Bonnie Circle
Corona, CA 91720

Receiving and storage of chemicals and components will be undertaken at the facility located at:

Watson Laboratories, Inc.
341 Bonnie Circle
Corona, CA 91720

RAW MATERIAL CONTROLS



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7

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Supplemental Application Review

ANDA #40-148 (10 mg/325 mg, 10 mg/500 mg and 7.5 mg/325 mg-new strength).

NAME AND ADDRESS OF APPLICANT

Watson Laboratories
Attention: Ron Lapré
311 Bonnie Circle
Corona, CA 91720

PURPOSE OF AMENDMENT/SUPPLEMENT

- S-002: A new dosage strength of 7.5 mg/325 mg.
- S-003: Package additions of 100's and 500's for the new dosage strength.
- S-004: An expiration dating period of 24 months for the new dosage strength in the 100's and 500's packages.
- S-005: Container labels and package insert labeling for the new dosage strength.
- S-011: Package addition of 30's and Physicians samples (2's).

DATE(S) OF SUBMISSION(S)

Firm:

April 17, 1998 - Original submission
June 23, 1999 - Major amendment (subject of this review)
June 23, 1999 - S-011 original submission (subject of this review).

Agency:

July 31, 1998 - Bioequivalence review #1 (J. Lee)
August 25, 1998 - Labeling review #1 (A. Vezza)
March 16, 1999 - Chemistry Review #1 (R. Permisohn)
March 19, 1999 - Major deficiencies forwarded to the applicant
September 13, 1999 - Labeling review #2 (C. Park)

<u>PHARMACOLOGICAL CATEGORY</u>	<u>TRADE NAME</u>	<u>NONPROPRIETARY NAME</u>
Narcotic Analgesics	Norco®7.5/325	Hydrocodone Bitartrate and Acetaminophen Tablets, USP

<u>DOSAGE FORM</u>	<u>POTENCY</u>	<u>R OR OTC</u>
Tablets-Oral	10 mg/325 mg 10 mg/500 mg	R

7.5 mg/325 mg (New strength)

<u>SAMPLES</u>	<u>RELATED IND/NDA/DMF</u>	<u>STERILIZATION</u>
N/A	DMF # _____ (Approved Source).	N/A
	DMF _____ (Approved Source).	
	DMF # _____	

LABELING Unsatisfactory

The DESCRIPTION and HOW SUPPLIED section of the insert labeling will be modified as requested on C. Park's labeling review #2 (9/13/99).

BIOEQUIVALENCY STATUS

A waiver of *in vivo* bioequivalence study requirements was requested (p. 73) and granted by the division of Bioequivalence (J. Lee, 7/31/98).

ESTABLISHMENT INSPECTION

A Facility Update Request will be placed for the laboratory located at 311 Bonnie Circle.

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS (_____)



Components and Composition

Ingredient	Tablet (mg)	Demonstration Batch _____	Production Batch _____
		Tablets, kg)	Tablets, kg)
Hydrocodone Bitartrate USP	7.5		

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**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Supplemental Application Review**

ANDA #40-148/S-002, 003, 004, 005, & 011 (10 mg/325 mg, 10 mg/500 mg and 7.5 mg/325 mg-new strength).

Review # 3

NAME AND ADDRESS OF APPLICANT

Watson Laboratories
Attention: Ernest E. Lengle
311 Bonnie Circle
Corona, CA 91720

PURPOSE OF AMENDMENT/SUPPLEMENT

- S-002: A new dosage strength of 7.5 mg/325 mg.
- S-003: Package additions of 100's and 500's for the new dosage strength.
- S-004: An expiration dating period of 24 months for the new dosage strength in the 100's and 500's packages.
- S-005: Container labels and package insert labeling for the new dosage strength.
- S-011: Package addition of 30's and Physicians samples (2's).

DATE(S) OF SUBMISSION(S)

Firm:

April 17, 1998 - Original submission
June 23, 1999 - Major amendment
June 23, 1999 - S-011 original submission
February 25, 2000 - Minor amendment (Subject of this review).

Agency:

July 31, 1998 - Bioequivalence review #1 (J. Lee)
August 25, 1998 - Labeling review #1 (A. Vezza)
March 16, 1999 - Chemistry Review #1 (R. Permisohn)
March 19, 1999 - Major deficiencies forwarded to the applicant
September 13, 1999 - Labeling review #2 (C. Park)
March 7, 2000 - Labeling review #3 (C. Park)

<u>PHARMACOLOGICAL CATEGORY</u>	<u>TRADE NAME</u>	<u>NONPROPRIETARY NAME</u>
Narcotic Analgesics	Norco®7.5/325	Hydrocodone Bitartrate and Acetaminophen Tablets, USP

<u>DOSAGE FORM</u>	<u>POTENCY</u>	<u>R OR OTC</u>
Tablets-Oral	10 mg/325 mg 10 mg/500 mg 7.5 mg/325 mg (New strength)	R

<u>SAMPLES</u>	<u>RELATED IND/NDA/DMF</u>	<u>STERILIZATION</u>
N/A	DMF # _____ /Approved Source).	N/A
	DMF # _____ /Approved Source).	

- DMF # _____

LABELING Satisfactory
Acceptable on 3/10/00.

BIOEQUIVALENCY STATUS
A waiver of *in vivo* bioequivalence study requirements was requested (p. 73) and granted by the division of Bioequivalence (J. Lee, 7/31/98).

ESTABLISHMENT INSPECTION

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS (



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13

Page(s) of trade

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confidential

commercial

information

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs

Abbreviated New Drug Supplemental Application Review

ANDA #40-148 (10 mg/325 mg, 10 mg/500 mg and 7.5 mg/325 mg-new strength).

Review # 4

NAME AND ADDRESS OF APPLICANT

Watson Laboratories
Attention: Ron Lapré
311 Bonnie Circle
Corona, CA 91720

PURPOSE OF AMENDMENT/SUPPLEMENT

- S-002: A new dosage strength of 7.5 mg/325 mg.
- S-003: Package additions of 100's and 500's for the new dosage strength.
- S-004: An expiration dating period of 24 months for the new dosage strength in the 100's and 500's packages.
- S-005: Container labels and package insert labeling for the new dosage strength.
- S-011: Package addition of 30's and Physicians samples (2's).

DATE(S) OF SUBMISSION(S)

Firm:

April 17, 1998 - Original submission
June 23, 1999 - Major amendment
June 23, 1999 - S-011 original submission
February 25, 2000 - Minor amendment
June 12, 2000 - Minor amendment

Agency:

July 31, 1998 - Bioequivalence review #1 (J. Lee)
August 25, 1998 - Labeling review #1 (A. Vezza)
March 16, 1999 - Chemistry Review #1 (R. Permisohn)
March 19, 1999 - Major deficiencies forwarded to the applicant
September 13, 1999 - Labeling review #2 (C. Park)
December 6, 1999 - Chemistry review #2 (M. Piñeiro-Sánchez)
March 7, 2000 - Labeling review #3 (C. Park)
May 2, 2000 - Chemistry review #3 (M. Piñeiro-Sánchez)

<u>PHARMACOLOGICAL CATEGORY</u>	<u>TRADE NAME</u>	<u>NONPROPRIETARY NAME</u>
Narcotic Analgesics	Norco®7.5/325	Hydrocodone Bitartrate and Acetaminophen Tablets, USP

<u>DOSAGE FORM</u>	<u>POTENCY</u>	<u>R OR OTC</u>
Tablets-Oral	10 mg/325 mg 10 mg/500 mg 7.5 mg/325 mg (New strength)	R

<u>SAMPLES</u>	<u>RELATED IND/NDA/DMF</u>	<u>STERILIZATION</u>
N/A	DMF # _____ /Approved Source).	N/A
	DMF # _____ /Approved Source).	

- DMF # _____

LABELING (Satisfactory)

The DESCRIPTION and HOW SUPPLIED section of the insert labeling appear accurate except for the NDC number and zip code which C. Park suggested be submitted in an annual report (3/7/00).

BIOEQUIVALENCY STATUS

A waiver of *in vivo* bioequivalence study requirements was requested (p. 73) and granted by the division of Bioequivalence (J. Lee, 7/31/98).

ESTABLISHMENT INSPECTION

Pending as on 6/28/00.

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS



Redacted

14

Page(s) of trade

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**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

**40-148/S-002, S-003, S-004, S-005,
and S-011**

**ADMINISTRATIVE
DOCUMENTS**

**PAGE(S) HAVE BEEN REDACTED IN
FULL FROM THIS DOCUMENT**

REASON:

_____ b(2) 'low'

_____ b(4) CCI

_____ b(4) TS

 2 b(5) Deliberative Process; Attorney
Client and Attorney Work Product Privilege

_____ b(6) Personal Privacy

_____ b(7) Law Enforcement Records

Electronic Mail Message

Date: 1/19/00 6:00:30 PM
From: Patricia Alcock (ALCOCKP)
To: See Below
Subject: ANDA # 40-148/s-005 - Watson, CA

Glen,

Just a quick heads-up. The above mentioned application will be "returned" by the District with a _____ based on the pending injunction. OC sent a memo, which included the injunction memo, on 9/24/99, and referenced ANDA's # 75-203, 75-238, 75-647. Due to the pending injunction, OC will not forward any additional pending applications to the District office.

If you need further information, please call me at 70064.

Thanks,

Pat Alcock

To: Glen Smith (SMITHGL)
To: Jeen Min (MINJ)
To: Robert West (WESTR)
To: Pat Beers-Block (BEERSBLOCKP)
Cc: Janine Davis-D'Ambrogio (DAMBROGIOJ)
Cc: Bruce W. Hartman (HARTMANB)
Cc: Shirnette Ferguson (FERGUSONS)
Cc: Monica Caphart (CAPHARTM)

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 9/12/00 8:31:00 AM
From: Timothy Ames (AMEST)
To: Jeen Min (MINJ)
To: Glen Smith (SMITHGL)
To: MAYRA L PINEIRO SANCHEZ (NOMAIL) (PAPERMAIL@A1 @NONODE)
Cc: Nasser Mahmud (MAHMUDN)
Subject: FWD: Re: ANDA 40-148/s-002, s-003, s-004, s-005 and s-011

Jeen, et. al.,

I've forwarded the attached as the ANDA is in your branch.

tim

**APPEARS THIS WAY
ON ORIGINAL**

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: ANDA 40148/002
Stamp: 20-APR-1998 Regulatory Due:
Applicant: WATSON LABS
311 BONNIE CIR
CORONA, CA 92880

Priority:
Action Goal: District Goal: 20-SEP-1998
Brand Name:
Established Name: HYDROCODONE
BITARTRATE; ACETAMINOPHEN

Generic Name:
Dosage Form: TAB (TABLET)
Strength: 10MG/325MG & 10MG/500MG

FDA Contacts: J. MIN (HFD-617) 301-827-5761 , Project Manager
G. SMITH (HFD-647) 301-827-5849 , Team Leader

Overall Recommendation:

ACCEPTABLE on 31-JUL-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 2024830
WATSON LABORATORIES
132A BUSINESS CENTER DR
CORONA, CA 91720

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 31-JUL-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE OTHER
TESTER

APPEARS THIS WAY
ON ORIGINAL

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

**40-148/S-002, S-003, S-004, S-005,
and S-011**

CORRESPONDENCE

M



A Subsidiary of Watson Pharmaceuticals, Inc.

June 12, 2000

Gary Buehler, R.Ph.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Minor Amendment
Additional Strength of 7.5 mg/325 mg
S-002, 003, 004, 005, 011

**Re: Hydrocodone Bitartrate and Acetaminophen Tablets, USP
ANDA 40-148**

Dear Mr. Buehler:

This amendment is in response to your May 4, 2000 deficiency letter regarding Hydrocodone Bitartrate and Acetaminophen Tablets (ANDA 40-148). On June 9, 2000, Mr. Bob West, Director of Labeling and Program Support, informed Watson Laboratories, Inc., that the Division of Manufacturing and Product Quality (DMPQ), Office of Compliance had recommended approval of ANDA 40-148.

We certify that except for administrative issues and/or items of clarification which can be reported in an Annual Report, the conditions under which this drug product was reviewed regarding final-printed labeling, chemistry, manufacturing, and controls have not changed. We believe that we have responded to all issues raised by FDA in the May 4th letter and request approval of this application at this time.

We have enclosed one (1) archival and one (1) review copy of this amendment. In accordance with 21 CFR § 314.94 (d)(5), one (1) field copy of this amendment will be forwarded to the LA District Office. Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical section contained in the archival and review copies of this amendment.

Please contact me by phone at (909) 270-1400 or by fax at (909) 278-0967 if you have any questions or if I can assist you with the review of this application.

Sincerely,

A handwritten signature in cursive script that reads "Ernest Lengle".
Ernest Lengle, Ph.D.
Sr. Director
Regulatory Affairs

311 Bonnie Circle, P.O. Box 1900, Corona, California 92878-1900 • Tel: 909/270-1400 • Fax: 909/270-1096



A Subsidiary of Watson Pharmaceuticals, Inc.

June 12, 2000

District Director
Food & Drug Administration
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

Minor Amendment
Additional Strength of 7.5 mg/325 mg
S-002, 003, 004, 005, 011

RE: **Field Copy**
ANDA 40-148
Hydrocodone Bitartrate and Acetaminophen Tablets, USP

Dear Sir/Madam:

Watson Laboratories, Inc. has submitted to the Office of Generic Drug a minor amendment to its Hydrocodone Bitartrate and Acetaminophen Tablets application (ANDA 40-148). Watson is hereby providing the enclosed Field Copy (1 volume) of the application to the Los Angeles District Office. Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application.

Should you require additional information, please contact me at (909) 270-1400.

Sincerely,

Ernest Lengle
Ernest Lengle, Ph.D.
Senior Director,
Regulatory Affairs

ARCHIVAL COPY



A Subsidiary of Watson Pharmaceuticals, Inc.

June 12, 2000

Gary Buehler, R.Ph.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Minor Amendment
Additional Strength of 7.5 mg/325 mg
S-002, 003, 004, 005, 011

SCA 002, SCA 03, 04, 05
NDA SUPPL AMENDMENT SCA 011 *AM*

**Re: Hydrocodone Bitartrate and Acetaminophen Tablets, USP
ANDA 40-148**

Dear Mr. Buehler:

This amendment is in response to your May 4, 2000 deficiency letter regarding Hydrocodone Bitartrate and Acetaminophen Tablets (ANDA 40-148). On June 9, 2000, Mr. Bob West, Director of Labeling and Program Support, informed Watson Laboratories, Inc., that the Division of Manufacturing and Product Quality (DMPQ), Office of Compliance had recommended approval of ANDA 40-148.

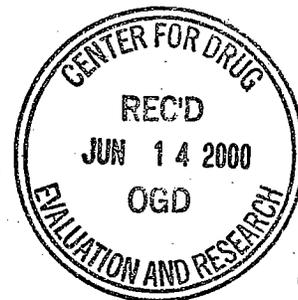
We certify that except for administrative issues and/or items of clarification which can be reported in an Annual Report, the conditions under which this drug product was reviewed regarding final- printed labeling, chemistry, manufacturing, and controls have not changed. We believe that we have responded to all issues raised by FDA in the May 4th letter and request approval of this application at this time.

We have enclosed one (1) archival and one (1) review copy of this amendment. In accordance with 21 CFR § 314.94 (d)(5), one (1) field copy of this amendment will be forwarded to the LA District Office. Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical section contained in the archival and review copies of this amendment.

Please contact me by phone at (909) 270-1400 or by fax at (909) 278-0967 if you have any questions or if I can assist you with the review of this application.

Sincerely,

Ernest Lengle
Ernest Lengle, Ph.D.
Sr. Director
Regulatory Affairs



NW
12-16-00

ANDA 40-148/S-002, S-003, S-004, S-005

Watson Laboratories, Inc.
Attention: Ron Lapré
311 Bonnie Circle
P.O. Box 1900
Corona, CA 91718-1900

Dear Sir:

This is in reference to your supplemental new drug applications dated April 17, 1998, submitted pursuant to 21 CFR 314.70, regarding your abbreviated new drug applications for Hydrocodone Bitartate and Acetaminophen Tablets USP, 10 mg/325 mg and 10 mg/500 mg.

The supplemental applications provide for:

- S-002: A new dosage strength of 7.5 mg/325 mg.
- S-003: Package additions of 100's and 500's for the new dosage strength.
- S-004: An expiration dating period of 24 months for the new dosage strength in the 100's and 500's packages.
- S-005: Container labels and package insert labeling for the new dosage strength.

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

A. Chemistry Deficiencies

1. The proposed proprietary name of NORCO 7.5/325 is satisfactory. Please submit the revised documents that are enumerated on p. 2 of the cover letter for these supplemental applications.
- 2.a. The Watson Certificate of Analysis (COA), blank SPECIFICATION AND QUALITY ASSURANCE REPORT, and manufacturing instructions for the executed batch declare the item Acetaminophen _____ without the tradename _____. Since the constituents of Acetaminophen _____, may vary from one source

Watson/Hydrocodone Bitartrate & Acetaminophen

to another, it is recommended that the tradename be included in any record in which this ingredient appears. Please revise the documents to include the tradename/grade designation for this ingredient.

- b. The Watson COA on p. 81 for the Hydrocodone Bitartrate drug substance (ds) indicates that "Full test" was/should be performed, but, the COA on p. 78 requires reduced testing for Acceptance Criteria. Please clarify and declare the tests that will be performed.
 - c. Blank SPECIFICATION AND QUALITY ASSURANCE REPORT's for Hydrocodone Bitartrate USP, Croscarmellose Sodium NF, and Magnesium Stearate NF have not been submitted. It is recommended that these blank forms declare the "Acceptance Criteria" (i.e., reduced testing or full testing) and tests to be performed in-house or by an outside contract testing laboratory. Please provide this documentation.
 - d. The blank SPECIFICATION AND QUALITY ASSURANCE REPORT's for the Acetaminophen _____ ds and Microcrystalline Cellulose NF / _____ do not declare the "Acceptance Criteria" for each lot of these items to be tested. Please revise and resubmit.
 - e. In the Composition Statement, the weight of a tablet is 425.0 mg. However, in the executed and MASTER batch records, the weight of each tablet is either 425.00 mg, 0.425 g, or 425 mg. Also, the amounts of ingredients per tablet and per batch are expressed from 1 to as many as 5 significant figures. Any actual or theoretical weights that are reported should be reflective of the degree of accuracy to which each can be weighed (or otherwise measured). Please correct as necessary and resubmit.
- 3.a. The proposed Manufacturing Batch Record has eliminated instructions for which samples were taken for homogeneity determinations. Please explain the reason(s).
 - b. The executed batch record does not cite the Acetaminophen _____ as ' _____ See comment 2.a. above.
 - c. It is noted that samples taken from each of the _____

*

pg 3

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2. Container: 100s and 500s.

Satisfactory in draft. We encourage the use of boxing, contrasting colors, or other means to differentiate the strength of this product from other approved and proposed strengths.

3. Insert:

The FDA Modernization Act of 1997 has deleted the requirement for the presence of the statement "Warning: May be habit-forming." throughout the labels and labeling of scheduled drugs. You may remove this statement from the DESCRIPTION and HOW SUPPLIED sections.

Please revise your insert labeling, then prepare and submit final print container labels and insert labeling.

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 the supplemental applications. Your amendment should respond to all deficiencies listed. A partial reply will not be considered for review, nor will the review clock be activated until all deficiencies have been addressed. The response to this letter will be considered as a MINOR amendment 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,

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

ANDA 40-148/S-002, 003, 004, 005, and 011

MAY 4 2000

Watson Laboratories, Inc.
Attention: Ernest E. Lengle
311 Bonnie, CA 91720
Corona, CA 91720

Dear Sir:

This is in reference to your abbreviated new drug application dated April 17, 1998 and June 23, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 10 mg/325 mg and 10 mg/500 mg.

Reference is also made to your amendments dated June 23, 1999 and February 25, 2000.

We have completed the review of this abbreviated application and have concluded that this application is deficient and, therefore, not approvable under 21 CFR 314.124 (b)(13) because the Center for Drug Evaluation and Research (CDER) is unable to find that the methods used in, and the facilities and controls used for, the manufacture, processing, packaging or holding of the drug product, Hydrocodone Bitartrate and Acetaminophen Tablet, by Watson Laboratories, Inc., comply with current good manufacturing practice (CGMP) regulations. Our conclusion is based upon the findings revealed during an initial inspection of Watson Laboratories, Inc. by representatives of the United States Food and Drug Administration from January 23 through March 12, 1999. Upon review of the inspector's report and observations noted during this inspection, we have received a recommendation from our Division of Manufacturing and Product Quality (DMPQ), Office of Compliance, to withhold approval of your abbreviated application.

Until such time as it can be determined to the Agency that the CGMP-related issues associated with Watson Laboratories, Inc.'s manufacture of Hydrocodone Bitartrate and Acetaminophen Tablets have been corrected and the Agency's concerns are otherwise satisfied, your application cannot be approved. We note that arrangements are currently being made by the Office of Compliance to reinspect the facility.

You should amend this application when the CGMP-related issues have been satisfactorily resolved. Your amendment to this letter will be considered a MINOR AMENDMENT and should be plainly marked as such in your cover letter. If, as a result of follow-up inspections related to the ongoing evaluation of this or other applications, it is necessary for you to significantly revise your procedures, controls or practices to correct the deficiencies, then the amendment will be considered to represent a MAJOR AMENDMENT.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

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



WATSON
Laboratories, Inc.

ARCHIVAL COPY

A Subsidiary of Watson Pharmaceuticals, Inc.
February 25, 2000

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place Room 150
Rockville, MD 20855-2773

SUPL AMENDEMENT

SCA 002

SC 003

SC 004

SL 005

SCA 011

} AM

Minor Amendment to Supplement
Additional Dosage Strength of 7.5 mg/325 mg
S-002, 003, 004, 005, 011

Re: **ANDA 40-148**
Hydrocodone Bitartrate and Acetaminophen Tablets, USP
10 mg/325 mg and 10 mg/500 mg

INCLUDE FINAL PRINTED LABELING

Dear Mr. Sporn:

This is in response to a FDA deficiency letter dated June 23, 1999 regarding Hydrocodone Bitartrate and Acetaminophen Tablets, ANDA 40-148 (copy attached). For ease of review, FDA's comments are in bold typeface followed by our responses.

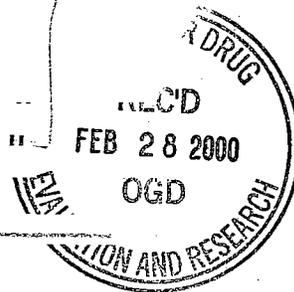
1.

[]

2.a. **Regarding your in-process controls:**

[]

Watson Laboratories, Inc. commits to perform in-process testing of all commercial batches as recommended by the Agency.



Cont'd.../2

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Labeling

1. **Container – 100s and 500s**
Satisfactory in final print
2. **Sample Pak – 2 Tablets**
Satisfactory in final print
- 3.a. **Insert:**
GENERAL COMMENT

We note that you have defined Norco® as “Hydrocodone Bitartrate and Acetaminophen” as indicated in your TITLE and in the first paragraph of the DESCRIPTION section, trademarking the “drug substance nonproprietary name” as the proprietary name (*i.e.*, Norco®). Therefore, please be specific with respect to the strength of your products in the following sections as described below and/or comment.

3.b. DESCRIPTION

- i. **Revise to read as follows.**

Norco®7.5/325 ...

Norco®10/325 ...

- ii. **Delete the term “ — ” associated with the proprietary name.**

3.c. HOW SUPPLIED

- i. **Norco®10/325 is available...**
- ii. **See comment (ii) under DESCRIPTION. [two instances]**

We have revised our packaging insert labeling to include all the changes as requested by the Agency.

We have attached a total of twelve (12) copies of the final printed package insert labeling, eleven (11) inserts are included in the archival copy and one (1) insert is included in the review copy of the application (see Exhibit 10).

In order to facilitate review of the submission and in accordance with 21 CFR §314.94(a)(8)(iv); we have provided a side-by-side comparison of our revised



Hydrocodone Bitartrate and Acetaminophen Tablets
ANDA 40-148
Minor Amendment for Supplemental Application 7.5 mg/325 mg
Page 5 of 5

final printed labeling (January 2000) to the packaging insert labeling that was submitted on 6/23/1999 (April 1999) with all the differences annotated and explained (see Exhibit 11).

We have enclosed one volume each of (1) archival, one (1) review copy, and in accordance with 21 CFR § 314.96 (5) (d), one (1) field copy of this amendment will be forwarded to the FDA Los Angeles District Office. Watson Laboratories, Inc. certifies that the Field copy is a true copy of the technical section contained in this amendment.

We believe we have addressed all issues of concern to FDA. If I can assist with the review of this application, please contact me by phone at (909) 270-1400 or by fax at (909) 278-0967.

Sincerely,

for *M. Choy*
Ernest E. Lengle, Ph.D.
Senior Director
Regulatory Affairs



WATSON
Laboratories, Inc.

A Subsidiary of Watson Pharmaceuticals, Inc.

February 25, 2000

District Director
Los Angeles District
Food & Drug Administration
19900 MacArthur Blvd.
Irvine, CA 92612

*Minor Amendment to Supplement
Additional Dosage Strength of 7.5 mg/325 mg
S-002, 003, 004, 005, 011*

**Re: Field Copy
ANDA 40-148
Hydrocodone Bitartrate and Acetaminophen Tablets, USP
10 mg/325 mg and 10 mg/500 mg**

Dear Sir/Madam:

Watson Laboratories, Inc. has submitted to the Office of Generic Drugs a minor amendment to its Hydrocodone Bitartrate and Acetaminophen Tablets application (ANDA 40-148). Watson is hereby providing the enclosed Field Copy (1 volume) of the application to the Los Angeles District Office. Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application.

Should you require additional information, please contact me at (909) 270-1400.

Sincerely,

Ernest E. Lengle
Ernest E. Lengle, Ph.D.
Senior Director
Regulatory Affairs

ANDA #40-148/S-002, S-003, S-004, S-005, S-011

Watson Laboratories
Attention: Ron Lapré
311 Bonnie Circle
Corona, CA 91720

JAN 6 2000

Dear Sir:

This is in reference to your supplemental new drug applications dated April 17, 1998 and June 23, 1999, submitted pursuant under section 505(j) of the Federal Food, Drug and Cosmetic Act, regarding your abbreviated new drug application for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 10 mg/325 mg, 10 mg/500 mg and 7.5 mg/325 mg(new strength).

Reference is also made to your amendment dated June 23, 1999.

The supplemental applications provides for:

- S-002: A new dosage strength of 7.5 mg/325 mg.
- S-003: Package additions of 100's and 500's for the new dosage strength.
- S-004: An expiration dating period of 24 months for the new dosage strength in the 100's and 500's packages.
- S-005: Container labels and package insert labeling for the new dosage strength.
- S-011: Package addition of 30's and Physicians samples (2's) for the new dosage strength.

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

Chemistry Deficiencies:

[]

Redacted _____ /

Page(s) of trade

secret and /or

confidential

commercial

information

Labeling Deficiencies:

1. Container - 100s and 500s

Satisfactory in final print

2. Sample Pak - 2 Tablets

Satisfactory in final print

3. Insert:

a. GENERAL COMMENT

We note that you have defined Norco® as "Hydrocodone Bitartrate and Acetaminophen" as indicated in your TITLE and in the first paragraph of the DESCRIPTION section, trademarking the "drug substance nonproprietary name" as the proprietary name (*i.e.*, Norco®). Therefore, please be specific with respect to the strength of your products in the following sections as described below and/or comment.

b. DESCRIPTION

i. Revise to read as follows.

Norco®7.5/325 ...

Norco®10/325 ...

ii. Delete the term — associated with the proprietary name.

c. HOW SUPPLIED

i. Norco®10/325 is available...

ii. See comment (ii) under DESCRIPTION. [two instances]

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 response to this letter will be considered a **MINOR** amendment 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,

151
ff *F. Fang* *15100*

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



File ANDA 40-148/S-002

Memorandum

SEP 24 1999

From

CSO, Investigations and Preapproval
Compliance Branch, HFD-324

Subject

Recommendation to Withhold Approval
ANDAs 75-203, 75-238 and 75-647

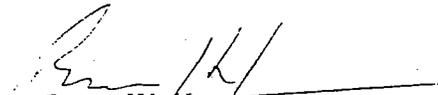
Appl: Watson Laboratories
Corona, CA 91720
CFN: 2024830

To

Patricia Beers Block, HFD-617
Office of Generic Drugs

The Division of Manufacturing and Product Quality (DMPQ) has completed review of the January 26 through March 12, 1999 inspection report and the subsequent injunction recommendation related to the subject firm. The injunction recommendation was approved on August 25, 1999. Also, please reference our February 5, 1999 withhold recommendation. The February 5 withhold recommendation was based on an inspection that was completed in December 1998. The December 1998 inspection resulted in the issuance of a warning letter to Watson. Both the warning letter and the injunction are official regulatory actions taken by the agency because significant GMP compliance problems exist that touch on all activities by the subject firm.

The February 5, 1999 recommendation withheld all pending applications that had been submitted to DMPQ for compliance evaluation up to that point. Applications referenced in this memo were submitted to DMPQ for evaluation since the February withhold recommendation to the present. All applications and supplements submitted by the subject firm will be considered unacceptable until existing compliance problems are resolved. We are requesting that EERs for applications which require compliance evaluations not be submitted for evaluation until Watson notifies you that problems are corrected and they are prepared for comprehensive GMP and preapproval coverage by the field.


Bruce W. Hartman

attachment



WATSON
Laboratories, Inc.

A Subsidiary of Watson Pharmaceuticals, Inc.

June 23, 1999

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place Room 150
Rockville, MD 20855-2773

**ARCHIVAL
COPY**

NDA SUPPL AMENDMENT

SCA 002, S C003, 004 / AC
SLC05AL

*Major Amendment to Supplement
Additional Dosage Strength of 7.5 mg/325 mg*

Re: **ANDA 40-148**
Hydrocodone Bitartrate and Acetaminophen Tablets, USP
10 mg/325 mg and 10 mg/500 mg

NDA NO. 40-148 REF NO. SCA-011
NDA SUPPL FOR Packaging
Addition

INCLUDE FINAL PRINTED LABELING

Dear Mr. Sporn:

Pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act and 21 CFR § 314.96, Watson Laboratories is submitting this major amendment to provide a complete response to the comments included in the FDA letter dated March 19, 1999 pertaining to the referenced ANDA (copy attached). Our responses are given in the order in which the comments appear in the letter. In addition, we have provided CMC information for an additional package size of 30's and physician samples that we request to be included in this application

We have enclosed one volume each of (1) archival, one (1) review copy, and in accordance with 21 CFR § 314.96 (5) (d), one (1) field copy of this amendment will be forwarded to the FDA Los Angeles District Office.

Watson Laboratories, Inc. certifies that the Field copy is a true copy of the technical section contained in this amendment.

We trust this information is sufficient for this amendment to be evaluated. If I can assist with the review of this application, please contact me by phone at (909) 270-1400 or by fax at (909) 278-0967.

Sincerely,

Ernest E. Lengle, Ph.D.
Senior Director
Regulatory Affairs

