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CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

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September 26, 2001

OVERNIGHT DOCUMENT 9/26/01

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

The undersigned, on behalf of a client, submits this petition in quadruplicate pursuant to Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act ("the FDC Act"), 21 U.S.C. § 355(j)(2)(C), and 21 C.F.R. §§ 10.20, 10.30, and 314.93 to request that the Commissioner of Food and Drugs make a determination that an Abbreviated New Drug Application (ANDA) may be submitted for Hydrocodone Bitartrate and Acetaminophen Tablets, USP 10 mg / 300 mg.

A. Action Requested

The petitioner requests that the Commissioner of Food and Drugs make a determination that a Hydrocodone Bitartrate and Acetaminophen Tablets, 10 mg / 300 mg combination drug product is suitable for submission as an ANDA. The reference-listed drug product upon which this petition is based is NORCO® (Hydrocodone Bitartrate and Acetaminophen Tablet, 10 mg / 325 mg) manufactured by Watson Laboratories. Therefore, this petition requests a change in the strength of one of the active ingredients (Acetaminophen) from 325 mg to 300 mg per tablet. Because thjs request involves a change in strength, the provisions of the Pediatric Final' Rule are not applicable to the evaluation of this petition.

B. Statement of Grounds

Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act provides for the submission of an ANDA for a new drug that differs in strength from a listed drug, provided that the FDA has approved a petition seeking permission to file such an application. This petition requests a change in the strength of one of the active ingredients, Acetaminophen, from 325 mg per tablet which is found in the listed drug, NORCO®, manufactured by Watson Laboratories, to 300 mg per tablet. The listing of NORCO® (Hydrocodone Bitartrate and Acetaminophen Tablet, 10 mg / 325 mg) is on Page 3-5 of the 21st Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations (commonly referred to as "The Orange Book"). Please see Attachment A.

According to the labeling of the reference-listed drug product, the usual dosage is "one tablet every four to six hours, as needed for pain. The total daily dose should not exceed 6 tablets". The approved package insert for NORCO® Tablets, is included in Attachment C. The dosage for the proposed product is " one tablet every four to six hours as needed for pain. The total daily dose should not exceed 6 tablets." This dosage is consistent with the dosage listed in the approved NORCO® package insert. Acetaminophen 300 mg has been approved by the FDA as a safe and effective dose of that component in other combination products, such as Acetaminophen and Codeine Phosphate. Please see Attachment B.

In summary, the proposed strength change of the non-narcotic component from that of the reference-listed drug will not affect the products safety or efficacy. The indication remains unchanged, and the proposed dosing is consistent with dosing recommendations in the labeling of the approved reference-listed drug product's labeling and is supported by other FDA approved doses of 300 mg of the

Acetaminophen component in other approved products. Therefore, the Agency should conclude that clinical investigations are not necessary to demonstrate the proposed products safety or effectiveness.

The proposed labeling for Hydrocodone Bitartrate and Acetaminophen Tablets USP 10 mg / 300 mg is included as Attachment D. Labeling for the proposed product is consistent with the approved labeling for the reference-listed Hydrocodone Bitartrate and Acetaminophen Tablet combination product upon which this petition is based.

For the aforementioned reasons, the undersigned requests that the Commissioner grant this petition and authorize submission of an ANDA for Hydrocodone Bitartrate and Acetaminophen Tablets, 10 mg / 300 mg.

C. Environmental Impact

According to 21 C.F.R. § 25.31(a), this petition qualifies for a categorical exemption from the requirement to submit an environmental assessment.

D. Economic impact Statement

According to 21 C.F.R. § 10.30(b), the petitioner will, upon request by the Commissioner, submit economic impact information.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

Robert W. Pollock
Vice President
Lachman Consultant Services, Inc
1600 Stewart Avenue, Westbury, NY 11590

RWP/pk

Attachments:

A. Page 3-5, Approved Drug Products with Therapeutic Equivalence Evaluations, 21st Edition
B. Page 3-3, Approved Drug Products with Therapeutic Equivalence Evaluations, 21st Edition
C. NORCO® (Hydrocodone Bitartrate and Acetaminbphen) Tablets, 10 mg / 325 mg Insert Labeling
D. Draft Insert Labeling for Proposed Drug Product

cc: G. Davis (OGD)
L. Lachman (LCS)

MFP1269

ATTACHMENT A

APPROVED DRUG PRODUCTS

with
THERAPEUTIC EQUIVALENCE EVALUATIONS

The products in this list have been approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This volume is current through December 3 1, 2000.

21 ST EDITION

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF INFORMATION TECHNOLOGY
DIVISION OF DATA MANAGEMENT AND SERVICES

2001

ACETAMINOPHEN; HYDROCODONE BITARTRATE

TABLET; ORAL

		HYDROCODONE BITARTRATE AND ACETAMINOPHEN		
AA	+ MIKART	500MG;7.5MG	NE9699 001	AUG 25, 1989
AA	+	650MG;7.5MG	N89689 001	JUN 29, 1988
AA	+	650MG;10MG	N81223 001	MAY 29. 1992
AA	PEACHTREE	500MG;10MG	N40210 001	AUG 13, 1397
AA	UCB	650MG;7.5MG	N40134 001	NOV 21, 1996
AA	VINTAGE PHARMS	325MG;10MG	N40355 001	MAY 31, 2000
AA		500MG;2.5MG	N40144 002	APR 25, 1997
AA		500MG;5MG	N89831 001	SEP 07, 1989
AA		500MG;5MG	NS9971 001	DEC 02. 1988
AA		500MG;7.5MG	N40144 001	FEB 22, 1996
AA		500MG;10MG	N40356 001	MAY 31, 2000
AA		650MG;7.5MG	N40155 001	APR 14, 1997
AA		650MG;10MG	N40143 001	FEB 22, 1996
AA		660MG;10MG	N40358 001	MAY 31, 2000
AA		750MG;7.5MG	N40157 001	APR 12, 1996
AA	+ WATSON LABS	325MG;7.5MG	N40248 001	APR 28, 2000
AA		325MG;10MG	N40248 002	APR 28, 2000
AA		500MG;2.5MG	N40123 003	MAR 04, 1996
AA		500MG;2.5MG	N81079 001	AUG 30, 1991
AA		500MG;5MG	N40122 001	MAR 04, 1996
AA		500MG;5MG	N89883 001	DEC 01, 1988
AA		500MG;7.5MG	N40123 004	MAR 04, 1996

ACETAMINOPHEN; HYDROCODONE BITARTRATE

TABLET; ORAL

		HYDROCODONE BITARTRATE AND ACETAMINOPHEN		
AA	WATSON LABS	500MG;7.5MG	N81080 001	AUG 30, 1991
AA		500MG;10MG	N40148 002	FEB 14, 1997
AA		650MG;7.5MG	N40094 001	SEP 29, 1995
AA		650MG;7.5MG	N40123 001	MAR 04, 1996
AA		650MG;10MG	N40094 002	SEP 29. 1995:
AA		650MG;10MG	N40123 002	MAR 04, 1996
AA		660MG;10MG	N40094 003;	AUG 08, 2000
AA		750MG;7.5MG	N40122 002:.	MAR 04, 1996
AA		750MG;7.5MG	N81083 '0.01:'	AUG 30, 1991
AA	ZENITH GOLDLINE	500MG;5MG	N89696 001	APR 21, X988
	LORTAB			
AA	MALLINCKRODT	500MG;5MG	N87722 001,	JUL 09, 1982.
AA	+ UCB	325MG;5MG	N40099 001	JUN 25. 1997
AA	+	500MG;10MG	N40100 0 0 1 .	JAN 26, 1996
	NORCO			
AA	+ WATSON LABS	325MG;10MG	N40148 001	FEE 14, 1997
	VICODIN			
AA	+ KNOLL PHARM	500MG;5MG	N88058 001	JAN 07, 1983
	VICODIN ES			
AA	+ KNOLL PHARM	750MG;7.5MG	N89736 00'1	DEC 09, 1988
	VICODIN HP			
AA	KNOLL PHARM	660MG;10MG	N40117 001	SEP 23, 1996

ATTACHMENT B

APPROVED DRUG PRODUCTS
with
THERAPEUTIC EQUIVALENCE EVALUATIONS

The products in this list have been approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This volume is current through December 31, 2000.

21ST EDITION

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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2001

ACETAMINOPHEN; CODEINE PHOSPHATE

TABLET; ORAL

ACETAMINOPHEN AND CODEINE PHOSPHATE

AA	DURAMED	**300MG;15MG**	**N40223 001**	NOV 18, 1997
AA		**300MG;30MG**	**N40223** 002	NOV 18, 1997
AA		**300MG;60MG**	**N40223** 003	NOV **18, 1997**
AA	GENEVA PHARMS	**300MG;30MG**	**381250 001**	JUL 16, 1992
AA		**300MG;60MG**	**N81249 001**	JUL 16, 1992
AA	MIKART	**300MG;30MG**	**N89238 001**	FEB 25, 1986
+		650MG;30MG	MAN89231 001	MAR 07, 1986
+		650MG;60MG	N89363 001	SEP 09, 1991
AA	MUTUAL PHARM	**300MG;15MG**	**N89671 001**	FEB 10, 1988
AA		**300MG;30MG**	FEB**N89672**1988	
AA		**300MG;60MG**	**PJ89673 001**	FEB 17, 1988
AA	PHARMERAL	**300MG;30MG**	**N87762 001**	DEC 10, 1982
AA	PUREPAC PHARM	**300MG;30MG**	N86681 **001**	
AA		**300MG;60MG**	N86683 **001**	
AA	TEVA	**300MG;15MG**	N88027 **001**	MAR 06, 1985
AA		**300MG;30MG**	MAR**N88028**1985	
AA		**300MG;60MG**	MAR**N88029**1985	
AA	VINTAGE PHARMS	**300MG;15MG**	**N89990 001**	SEP 30, 1988
AA		**300MG;30MG**	SEP**N89905**1988	
AA		**300MG;60MG**	SEP**N89928**1988	
AA	WATSON LABS	**300MG;15MG**	SEP**N89997**1988	
AA		**300MG;30MG**	DEC**N89998**1994	
AA		**300MG;60MG**	DEC**N89999**1994	DEC 28, 1994
AA	ZENITH GOLDLINE	**300MG;60MG**	**N87083 001**	

ACETAMINOPHEN; CODEINE PHOSPHATE

TABLET; ORAL

	ACETAMINOPHEN AND CODEINE PHOSPHATE #2		
AA	SUPERPHARM	**300MG;15MG**	**M89183 001** OCT **18, 1985**
	ACETAMINOPHEN W/ CODEINE NO. 3		
AA	ROXANE	**300MG;30MG**	**W84656 001**
	ACETAMINOPHEN W/ CODEINE PHOSPHATE #3		
AA	ZENITH GOLDLINE	**300MG;30MG**	**N85868 001**
	CAPITAL WITH CODEINE		
+	CARNRICK	325MG;30MG	**N83643 001**
	TYLENOL Wi CODEINE NO. 1		
+	JOHNSON RW	300MG;7.5MG	**N85055** 001
	TYLENOL W/ CODEINE NO. 2		
AA +	JOHNSON RW	**300MG;15MG**	**N85055 002**
	TYLENOL W/ CODEINE NO. 3		
AA +	JOHNSON RW	**300MG;30MG**	**N85055 003**
	TYLENOL W/ CODEINE NO. 4		
AA +	JOHNSON RW	**300MG;60MG**	**185055 004**

ACETAMINOPHEN; HYDROCODONE BITARTRATE

CAPSULE; ORAL

	ACETAMINOPHEN AND HYDROCODONE BITARTRATE		
AA	CENT PHARMS	**500MG;5MG**	**N88898 001** MAR 27, 1985
AA	**ALLAY**		
	ZENITH GOLDLINE	**500MG;5MG**	189907 001 JAN 13, 1989
	HYDROCET		
AA	MALLINCKRODT	**500MG;5MG**	189006 001 AUG 09, 1985
	HYDROCODONE BITARTRATE AND ACETAMINOPHEN		
AA	MALLINCKRODT	**500MG;5MG**	**N88956 001** JUL 19, 1985
AA	MIKART	**500MG;5MG**	**N81067 001** **NOV** 30, **1989**
AA		**500MG;5MG**	**N81068 001** NOV 30, 1989
AA		**500MG; 5MG**	**N81069 001** NOV 30, I.989
AA		**500MG;5MG**	**N81070 001** NOV 30, 1989
AA		**500MG;5MG**	**N89008** 001 FEB 21, 1986
	LORCET-HD		
AA +	MALLINCK**500MG;**	**5MG**	N87336 **001** JUL 08, 1982

ATTACHMENT C

6

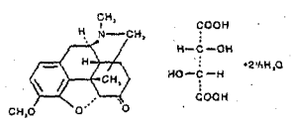
NORCO®
(Hydrocodone Bitartrate and Acetaminophen Tablets, USP)

Rx only

DESCRIPTION

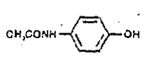
NORCO® (Hydrocodone bitartrate and acetaminophen) is supplied in tablet form for oral administration.

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



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2½\ H_2O$ 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	Acetaminoohen
NORCO® 7.5/325	7.5 mg	325 mg
NORCO" 101325	10 mg	325 mg

In addition, each tablet contains the foliowing 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 0-demethylation, N-demethylation and 6-ketoreduction to the corresponding 6-α- and 6-ß-hydroxymetabolites. See OVERDOSAGE for toxicity information.

Acetaminoohen: Acetaminophen is rapidly absorbed from the gastrointestinal tract a distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, may be increased by liver damage and following overdosage. Eliminatior acetaminophen is principally by liver metabolism [conjugation) and subsequent r excretion of metabolites. Approximately 85% of an oral dose appears in the urine wi 24 hours of administration, most as the glucuronide conjugate, with small amount 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 exhibi hypersensitivity to hydrocodone or acetaminophen.

WARNINGS

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

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

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosi *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 o 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 ail 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, antianxiety 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: Acetaminophsn 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: Teratooenic 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.

Nonteratoaenic 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).

Dermatoiogical: 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 analgesiceffect. 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.

Acetaminoohen: 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 potentially lethai polydrug overdose, and consultation with a regional poison cont center is recommended.

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

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

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associatec 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 patien 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 acetaminaphen 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 debassed with "NORCO 729" on the other side. Each tablet contains 7.5 mg hydrocodane bitartrate and 325 mg-acetaminophen. They are supplied as fallows:

Bottles of 30	NDC 52544-729-30
Bottles of.1 00	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°C to 30°C (59°F to 86°F).

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

WATSON PHARMA

Watson Pharma, Inc.
a subsidiary of
Watson Laboratories, Inc., Corona CA 92880

13897
Revised: May '2000

ATTACHMENT D

C III

HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP

(10 **mg/300** mg)

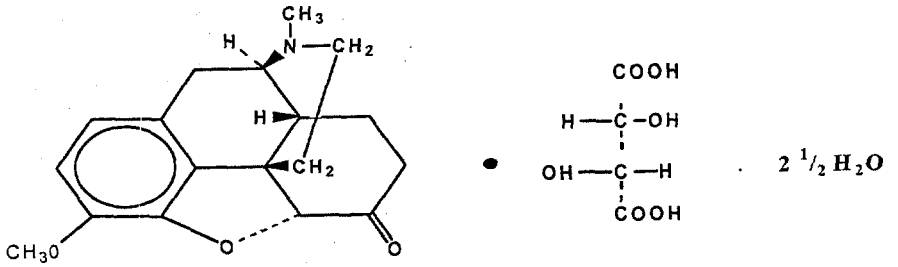
R_x Only

Code 000000
Rev. 09/01

DESCRIPTION

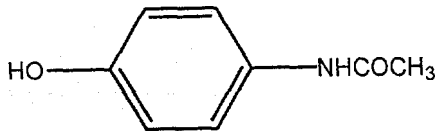
Hydrocodone Bitartrate and Acetaminophen Tablets is supplied in tablet form for oral administration.

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



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

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



$C_8H_9NO_2$ MW = 151.17

Hydrocodone Bitartrate and Acetaminophen Tablets, for oral administration is available in the following strength:

Hydrocodone Bitartrate*.....	10 mg
(*Warning: May be habit forming)	
Acetaminophen.....	300 mg

Inactive Ingredients:

In accordance with good pharmaceutical practice and the provisions of USP 24 <1091> this section of the labeling will indicate the therapeutically inactive ingredients contained in this dosage form once established.

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 0-demethylation, N-demethylation and 6-ketoreduction to the corresponding 6-a- and 6-β-hydroxymetabolites. See **OVERDOSAGE** for toxicity information.

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

INDICATIONS AND USAGE

Hydrocodone Bitartrate and Acetaminophen Tablets is indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

Hydrocodone Bitartrate and Acetaminophen Tablets should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.

WARNINGS

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

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

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

Nonteratoaenic 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 non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

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

Gastrointestinal System: Prolonged administration of Hydrocodone Bitartrate and Acetaminophen Tablets may produce constipation.

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

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

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis. Potential effects of high dosage are listed in the **OVERDOSAGE** section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Hydrocodone Bitartrate and Acetaminophen Tablets is classified as a Schedule III controlled substance.

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

Acetaminonhen: 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 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 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:

Hydrocodone Bitartrate and Acetaminophen Tablets, USP 10 mg/300 mg

Dosage Form: Tablets

Shape, Color, and Scoring: To be determined.

Packaging: To be determined.

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

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

A Schedule CIII Narcotic.

Manufactured by:
Manufacturer

Code 000000
Rev. 09/01

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Form 10 No. 0215

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Company LACHMAN CONSULTANT SERVICE INC

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4a Express Package Service — *Packages up to 150 lbs.* Delivery commitment may be later in some areas.

- [X] FedEx Priority Overnight — Next business morning
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- [ ] FedEx Express Saver — Third business day
- [ ] **NEW** FedEx Extra Hours — Later drop-off with next business afternoon delivery for select locations

4b Express Freight Service — *Packages over 150 lbs.* Delivery commitment may be later in some areas.

- [ ] FedEx 1Day Freight* — Next business day
- [ ] FedEx 2Day Freight — Second business day
- [ ] FedEx 3Day Freight — Third business day

* Call for Confirmation.

5 Packaging * Declared value limit $500

- [ ] FedEx Envelope*
- [X] FedEx Pak* — Includes FedEx Small Pak, FedEx Large Pak, and FedEx Sturdy Pak
- [ ] Other Pkg. — Includes FedEx Box, FedEx Tube, and customer pkg.

6 Special Handling Include FedEx address in Section 3.

- [ ] **SATURDAY Delivery** — Available only for FedEx Priority Overnight and FedEx 2Day to select ZIP codes
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Does this shipment contain dangerous goods? One box must be checked.

- [ ] No
- [ ] Yes — As per attached Shipper's Declaration
- [ ] Dry Ice — Dry Ice, 9, UN 1845 ____ x ____ kg
- [ ] Cargo Aircraft Only

Dangerous Goods (incl. Dry Ice) cannot be shipped in FedEx packaging or with FedEx Extra Hours service.

7 Payment *Bill to:* Enter FedEx Acct. No. or Credit Card No. below.

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- [ ] Recipient
- [ ] Third Party
- [ ] Credit Card
- [ ] Cash/Check
- [ ] Obtain Recip. Acct. No.

Total Packages	Total Weight	Total Charges
1	2	Credit Card Auth.

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By signing you authorize us to deliver this shipment without obtaining a signature and agree to indemnify and hold us harmless from any resulting claims.

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