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CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

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August 23, 2001

OVERNIGHT COURIER 8/23/01

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

CITIZEN PETITION

The undersigned, on behalf of a client, submits this petition in quadruplicate under 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 Elixir, 7.5 mg / 325 mg per 15 mL.

A. Action Requested

The petitioner requests that the Commissioner of Food and Drugs make a determination that a Hydrocodone Bitartrate and Acetaminophen Elixir, 7.5 mg / 325 mg per 15 mL combination drug product is suitable for submission as an ANDA. The reference-listed drug, product upon which this petition is based, is LORTAB® Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir, 7.5 mg / 500 mg per 15 mL), manufactured by Mikart, Inc. Therefore, this petition seeks a change in the strength of one of the active ingredients (Acetaminophen) from that of the reference-listed drug product from 500 mg per 15 mL to 325 mg per 15 mL. Because this request involves a change in strength, there should be no need to evaluate this petition in regard to the Pediatric Final Rule.

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 500 mg per 15 mL, which is found in the listed drug, LORTAB® Elixir, manufactured by Mikart, Inc., to 325 mg per 15 mL. The listing of LORTAB® Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir, 7.5 mg / 500 mg per 15 mL) is on page 3-4 of the 21st Edition of the Approved Drug Products with Therapeutic Equivalents Evaluation (commonly referred to as "The Orange Book") (Attachment A).

01P-0374

CP1

The recommended maximum daily dosage for Hydrocodone Bitartrate according to the labeling of the reference listed drug product is 45 mg per day. The approved labeling indicates that the usual dosage is "one tablespoonful every four to six hours as needed for pain. The total daily dose should not exceed 6 tablespoonfuls." (See the approved package insert for LORTAB® Elixir, found in Attachment B.) The dosage for the proposed product is "one tablespoonful every four to six hours as needed for pain. The total daily dose should not exceed 6 tablespoonfuls." This dosage is consistent with the dosage listed in the approved LORTAB® Elixir package insert. In addition, Acetaminophen 325 mg is approved for sale in other combination products, and is sold lawfully as a stand-alone product (e.g., Tylenol®). A 325 mg dose of Acetaminophen is, therefore, both safe and effective based on either already approved FDA products or as outlined in the Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use: Tentative Final Monograph: Notice of Proposed Rule-making, (53 FR 46204, 46236) published November 16, 1988, which states that oral doses of Acetaminophen for adults may range from 325 mg to 1000 mg, not to exceed 4000 mg in a 24-hour period. (Attachment C)

As additional support for the proposed strength change for a product to include 325 mg of Acetaminophen and 7.5 mg Hydrocodone Bitartrate, we point to the fact that the FDA has approved an ANDA for a tablet product containing the exact strengths of the components proposed in the petition. (Attachment D)

In summary, the proposed strength change of the non-narcotic component from that of the reference-listed drug will not affect the product's 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. Therefore, the Agency should conclude that clinical investigations are not necessary to demonstrate the proposed product's safety or effectiveness.

The proposed labeling for Hydrocodone Bitartrate and Acetaminophen Elixir, 7.5 mg / 325 mg per 15 mL is included as Attachment E. Labeling for the proposed product will be consistent with the approved labeling for other Hydrocodone Bitartrate and Acetaminophen Elixir combination products.

For the aforementioned reasons, the undersigned requests that the Commissioner grant this petition and authorize submission of an ANDA for a liquid form of Hydrocodone Bitartrate and Acetaminophen Elixir, 7.5 mg / 325 mg per 15 mL.

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), 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
pk

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cc: G. Davis (Office of Generic Drugs)
L. Lachman

MFP1235

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT A

ACETAMINOPHEN; HYDROCODONE BITARTRATE

ELIXIR; ORAL

HYDROCODONE BITARTRATE AND ACETAMINOPHEN

AA	+ MIKART	500MG/15ML;7.5MG/15ML	N81051 001	AUG 28, 1992
		500MG/15ML;5MG/15ML	N81226 001	OCT 27, 1992
	+	500MG/15ML;5MG/15ML	N89557 001	APR 29, 1992
AA	PHARM ASSOC	500MG/15ML;7.5MG/15ML	N40182 001	MAR 13, 1998

TABLET; ORAL

ANEXSIA

AA	MALLINCKRODT	500MG;5MG	N89160 001	APR 23, 1987

ANEXSIA 10/660

AA	+ MALLINCKRODT	660MG;10MG	N40084 003	JUL 29, 1996

ANEXSIA 7.5/650

AA	MALLINCKRODT	650MG;7.5MG	N89725 001	SEP 30, 1987

CO-GESIC

AA	SCHWARZ PHARMA	500MG;5MG	N87757 001	MAY 03, 1982

HY-PHEN

AA	ASCHER	500MG;5MG	N87677 001	MAY 03, 1982

HYDROCODONE BITARTRATE AND ACETAMINOPHEN

AA	BARR	500MG;2.5MG	N40307 001	JUL 26, 2000
AA		500MG;5MG	N40308 001	JUL 26, 2000
AA		500MG;7.5MG	N40307 002	JUL 26, 2000
AA		500MG;10MG	N40309 001	JUL 26, 2000
AA		650MG;7.5MG	N40307 003	JUL 26, 2000
AA		650MG;10MG	N40307 004	JUL 26, 2000
AA		750MG;7.5MG	N40308 002	JUL 26, 2000
AA	ENDO PHARMS	500MG;5MG	N40281 001	SEP 30, 1998
AA		500MG;7.5MG	N40280 001	SEP 30, 1998

ACETAMINOPHEN; HYDROCODONE BITARTRATE

TABLET; ORAL

HYDROCODONE BITARTRATE AND ACETAMINOPHEN

AA	ENDO PHARMS	650MG;7.5MG	N40280 002	SEP 30, 1998
AA		650MG;10MG	N40280 003	SEP 30, 1998
AA		750MG;7.5MG	N40281 002	SEP 30, 1998
		400MG;5MG	N40288 001	NOV 27, 1998
		400MG;7.5MG	N40288 002	NOV 27, 1998
		400MG;10MG	N40288 003	NOV 27, 1998
AA	EON	500MG;5MG	N40149 001	JAN 27, 1997
AA		750MG;7.5MG	N40149 002	JAN 27, 1997
AA	HALSEY	500MG;5MG	N40236 001	SEP 25, 1997
AA		650MG;7.5MG	N40240 002	NOV 26, 1997
AA		650MG;10MG	N40240 001	NOV 26, 1997
AA		750MG;7.5MG	N40236 002	SEP 25, 1997
AA	MALLINCKRODT	325MG;5MG	N40409 001	OCT 20, 2000
AA		325MG;7.5MG	N40405 001	SEP 08, 2000
AA		325MG;10MG	N40400 001	JUL 26, 2000
AA		500MG;5MG	N40084 002	JUN 01, 1995
AA		500MG;7.5MG	N40201 001	FEB 27, 1998
AA		500MG;10MG	N40201 002	FEB 27, 1998
AA		750MG;7.5MG	N40084 001	JUN 01, 1995
AA	+ MIKART	500MG;2.5MG	N89698 001	AUG 25, 1989
AA		500MG;5MG	N89271 001	JUL 16, 1986
AA		500MG;5MG	N89697 001	JAN 28, 1992

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT B

50474909

LORTAB® Elixir

C III

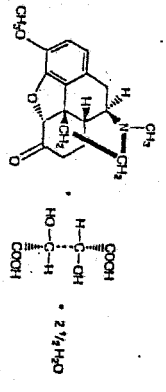
HYDROCODONE* BITARTRATE AND ACETAMINOPHEN ELIXIR
7.5 mg/500 mg per 15 mL
***Warning: May be habit forming**

540A09 Rev. 3/97

DESCRIPTION:

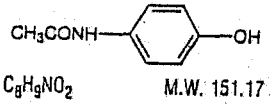
Hydrocodone bitartrate and acetaminophen is supplied in liquid form for oral administration.

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



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$
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

Lortab Elixir contains:

	Per 5 mL	Per 15 mL
Hydrocodone Bitartrate	2.5 mg	7.5 mg
(Warning: May be habit forming)		
Acetaminophen	167 mg	500 mg
Alcohol	7%	7%

In addition, the liquid contains the following inactive ingredients: citric acid anhydrous, ethyl maltol, glycerin, methylparaben, propylene glycol, propylparaben, purified water, saccharin sodium, sorbitol solution, sucrose, with D&C Yellow #10 and FD&C Yellow #6 as coloring and natural and artificial flavoring.

CLINICAL PHARMACOLOGY:

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

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

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

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

See OVERDOSAGE for toxicity information.

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

See OVERDOSAGE for toxicity information.

INDICATIONS AND USAGE:

Lortab Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir) is indicated for the relief of moderate to moderately severe pain.

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

WARNINGS:

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

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

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

PRECAUTIONS:

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

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when Lortab Elixir 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 narcotics, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with hydrocodone bitartrate and acetaminophen elixir may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

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

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

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

Pregnancy:

Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Lortab Elixir 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 the pediatric population 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 Lortab Elixir 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, pruritis.

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

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

DRUG ABUSE AND DEPENDENCE:

Controlled Substance: Lortab Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir) 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 dependance is unlikely to develop when hydrocodone bitartrate and acetaminophen elixir 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 endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

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

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

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

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

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION:

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

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

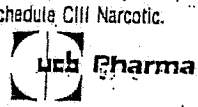
HOW SUPPLIED:

Lortab® Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir) is a yellow-colored tropical fruit punch flavored liquid containing hydrocodone bitartrate 7.5 mg (Warning: May be habit forming) and acetaminophen 500 mg per 15 mL, with 7% alcohol. It is supplied in containers of 1 pint (473 mL) NDC 50474-909-16.

Storage: Store at controlled room temperature, 15°-30°C (59°-86°F). Dispense in a tight, light-resistant container with a child-resistant closure.

CAUTION: Federal law prohibits dispensing without prescription.

A Schedule CIII Narcotic.



Manufactured For:
UCB PHARMA, INC.
Smyrna, GA 30080

Manufactured By:
MIKART, INC.
Atlanta, GA 30318

Revised 3/97
Code 540A00
P/N 2H12020G

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT C

Federal Register

Wednesday
November 16, 1988

Part IV

Department of Health and Human Services

Food and Drug Administration

21 CFR Parts 310, 343, and 369
Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph; Notice of Proposed Rulemaking

Panel should be followed and that no deviations from this schedule should be allowed. The reply comment expressed concern that the 975-mg dose of aspirin might be used beyond the daily maximum of four doses and present a toxicity problem.

The agency disagrees with the comment's request for an aspirin dosage regimen of 15 gr (975 mg) aspirin every 4 hours, not to exceed four doses per day. The agency concurs with the Panel's statement that this dosage regimen would not provide any significant improvement in analgesic or antipyretic effectiveness (42 FR 35361). Furthermore, although the total daily dosage of this regimen does not exceed the maximum aspirin daily dosage of 4 g (60 gr), the agency is concerned that a four-hour dosage interval for a 975 mg dose may result in consumers ignoring the daily maximum limit of four doses with continued use possibly leading to salicylate toxicity. (See also comment 63 below.)

Reference

(1) Comment No. C00060, Docket No. 77N-0094, Dockets Management Branch.

63. Two comments objected to the Panel's recommendation that following an initial dose of 1,000 mg acetaminophen (two dosage units of 500 mg each), subsequent doses should be restricted to 500 mg every 3 hours or 1,000 mg every 6 hours. Stating that this recommendation was based upon the dosage recommended for aspirin, the comments contended that, given the linear pharmacokinetics of acetaminophen, it is irrational to base acetaminophen's dosage and frequency of administration on the nonlinear pharmacokinetics of aspirin. One comment urged that the dosage for acetaminophen be 1,000 mg every 4 to 6 hours, not to exceed 4 g in 24 hours.

The agency is not adopting the comment's recommendation of an acetaminophen dosage regimen of 1,000 mg every 4 hours for the same reason it is not adopting the regimen of 975 mg aspirin every 4 hours. (See comment 62 above.)

The agency believes at this time that it is reasonable for acetaminophen and aspirin to have the same dosage and frequency of administration because, based upon the data submitted to the Panel, the safe and effective OTC dosage ranges for acetaminophen and aspirin are the same—325 mg to 650 mg every 4 hours, not to exceed 4 g in 24 hours. Also, aspirin and acetaminophen are indicated for the same OTC uses, have been extensively promoted as comparable OTC analgesics (with different side effects), and are widely and interchangeably used by consumers.

The agency concurs with the Panel's recommended acetaminophen dosage regimens of 500 mg every 3 hours and 1,000 mg every 6 hours because these dosages are in accord with the safe and effective dosage range for acetaminophen, i.e., 325 mg to 650 mg every four hours (not to exceed 4 g in 24 hours). Based on computer simulations (Ref. 1), pharmacokinetic parameters obtained from the literature (Refs. 2 through 5), and bioavailability data comparing a 650-mg dose with a 1,000-mg dose of acetaminophen (Ref. 6), the agency has determined that a 1,000-mg dose of acetaminophen every 6 hours yields a pharmacokinetic profile equivalent to that of a 650-mg dose of acetaminophen every 4 hours. A 500-mg dose of acetaminophen every 3 hours yields a blood level profile that also is similar to that of a 650-mg dose of acetaminophen every 4 hours. Therefore, the agency is proposing alternative dosage regimens for acetaminophen of 500 mg every 3 hours and 1,000 mg every 6 hours as part of the dosage schedule in § 343.50(d)(2) of the tentative final monograph. As discussed in comment 53 above, the agency is proposing the following dosages for acetaminophen, aspirin, and sodium salicylate: 325 to 650 mg every 4 hours, 325 to 500 mg every 3 hours, or 650 to 1,000 mg every 6 hours.

References

(1) OTC Volume 03BTFM.

(2) Albert, K.S., A.J. Sedman, and J.G. Wagner, "Pharmacokinetics of Orally Administered Acetaminophen in Man," *Journal of Pharmacokinetics and Biopharmaceutics*, 2:361–393, 1974.

(3) Cummings A.J., B.K. Martin, and G.S. Park, "Kinetic Considerations Relating to the Accrual and Elimination of Drug Metabolites," *British Journal of Pharmacology and Chemotherapy*, 29:136–149, 1967.

(4) Slattery, J.T., and G. Levy, "Acetaminophen Kinetics in Acutely Poisoned Patients," *Clinical Pharmacology and Therapeutics*, 25:184–195, 1979.

(5) Prescott, L. F., and N. Wright, "The Effects of Hepatic and Renal Damage on Paracetamol Metabolism and Excretion Following Overdosage: A Pharmacokinetic Study," *British Journal of Pharmacology*, 49:602–613, 1973.

(6) Research Division, McNeil Laboratories, Inc., "Acetaminophen Plasma Level Profile Following Tylenol Acetaminophen Extra Strength Capsules and APAP/R.S. Acetaminophen Tablets, Metabolic Study No. 54," Biochemical Research Report No. 199 (780306), unpublished report, included in OTC Volume 03BTFM.

64. One comment requested that the Panel's recommended monograph be revised to state that 377 mg magnesium salicylate is equivalent to 325 mg sodium salicylate rather than the 325-mg quantity of magnesium salicylate specified by the Panel (42 FR 35420). The comment explained that commercial sodium salicylate is substantially anhydrous (Refs. 1 and 2), but that magnesium salicylate is commercially available as the tetrahydrate, which contains the equivalent of about 74.5 percent salicylic acid. Assuming that the salicylic acid content is the active moiety of analgesic salicylates and because sodium salicylate contains 86.3 percent salicylic acid, the comment calculated that about 1.16 times more magnesium salicylate tetrahydrate, or 377 mg (325 mg x 1.16), is needed to be equivalent to 325 mg sodium salicylate.

The comment also pointed out that the Panel's recommended monograph does not state the molecular composition of magnesium salicylate and requested that it be clarified to state that 377 mg magnesium salicylate tetrahydrate is equivalent to 325 mg sodium salicylate. The comment concluded that, as stated in the Panel's monograph, one could assume that the difference in the salicylic acid content between 325-mg doses of magnesium salicylate and sodium salicylate could affect the therapeutic response, especially in a multidose regimen.

The agency agrees that 377 mg magnesium salicylate tetrahydrate is equivalent to 325 mg sodium salicylate. The Panel's recommendation of 325 to 650 mg magnesium salicylate every 4 hours for analgesic effect was based on data submitted on a product containing 325 mg of the tetrahydrate form of magnesium salicylate (Ref. 3). However, for adult dosage schedules for aspirin, acetaminophen, and sodium salicylate, the Panel recommended a minimum effective dosage of 325 mg for each of these ingredients (42 FR 35358), with which the agency concurs. Based upon a minimum effective dosage of 325 mg sodium salicylate, the minimum effective dosage of magnesium salicylate tetrahydrate that would contain an equivalent amount of salicylic acid is 377 mg. Therefore, the maximum dosage for magnesium salicylate should be 754 mg instead of 650 mg, and the dosages for magnesium salicylate are being revised accordingly in this tentative final monograph, which now also specifies that the dosages are based on the tetrahydrate form of magnesium salicylate (§ 343.50(d)(6)).

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT D

ACETAMINOPHEN; HYDROCODONE BITARTRATE

TABLET; ORAL

HYDROCODONE BITARTRATE AND ACETAMINOPHEN

AA	+	MIKART	500MG;7.5MG	N89699 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, 1997
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, 1988
AA			500MG;5MG	N89971 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 001	AUG 30, 1991
AA		ZENITH GOLDLINE	500MG;5MG	N89696 001	APR 21, 1988
		LORTAB			
AA		MALLINCKRODT	500MG;5MG	N87722 001	JUL 09, 1982
AA	+	UCB	325MG;5MG	N40099 001	JUN 25, 1997
AA	+		500MG;10MG	N40100 001	JAN 26, 1996
		NORCO			
AA	+	WATSON LABS	325MG;10MG	N40148 001	FEB 14, 1997
		VICODIN			
AA	+	KNOLL PHARM	500MG;5MG	N88058 001	JAN 07, 1983
		VICODIN ES			
AA	+	KNOLL PHARM	750MG;7.5MG	N89736 001	DEC 09, 1988
		VICODIN HP			
AA		KNOLL PHARM	660MG;10MG	N40117 001	SEP 23, 1996

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT E

C III

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR (7.5 mg/325 mg per 15 mL)

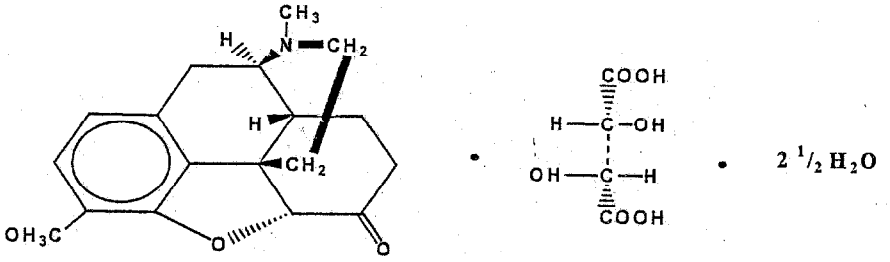
R_x Only

Code 00000
Rev. 05/01

DESCRIPTION:

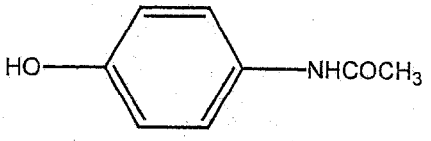
Hydrocodone bitartrate and acetaminophen is supplied in liquid form for oral administration.

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-methyl-morphinan-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 Elixir contains:

	Per 5 mL	Per 15 mL
Hydrocodone Bitartrate	2.5 mg	7.5 mg
(Warning: May be habit forming)		
Acetaminophen	108 mg	325 mg
Alcohol	7%	7%

In addition the liquid contains the following inactive ingredients: Citric Acid Anhydrous, D&C Red #33, Ethyl Maltol, FD&C Red #40, Glycerin, Methylparaben, Natural and Artificial Tropical Fruit Punch Flavoring, Propylene Glycol, Propylparaben, Purified Water, Saccharin Sodium, Sorbitol Solution, and Sucrose.

CLINICAL PHARMACOLOGY:

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

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

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

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

See **OVERDOSAGE** for toxicity information.

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

See **OVERDOSAGE** for toxicity information.

INDICATIONS AND USAGE:

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

CONTRAINDICATIONS:

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

WARNINGS:

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

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

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

PRECAUTIONS:

General: Special Risk Patients: As with any narcotic analgesic agent, Hydrocodone Bitartrate and Acetaminophen Elixir 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 Elixir 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 narcotics, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with hydrocodone bitartrate and acetaminophen elixir 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 Elixir 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 the pediatric population 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 Elixir 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, pruritis.

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

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

HOW SUPPLIED:
Hydrocodone Bitartrate and Acetaminophen Elixir is a red-colored tropical fruit punch flavored liquid containing hydrocodone bitartrate 7.5 mg (Warning: May be habit forming) and acetaminophen 325 mg per 15 mL, with 7% alcohol. It is supplied in containers of 1 pint (473 mL) NDC XXXXX-XXX-XX.

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.

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