

May 8, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane
Room 4-62
Rockville, MD 20857

CITIZEN PETITION

The undersigned submits this Petition, pursuant to Section 505(j)(2)(c) of the Federal Food, Drug, and Cosmetic Act (the Act) and 21 C.F.R. Sections 314.93(b) and 10.30 of the Food and Drug Administration's regulations, to request the Commissioner of Food and Drugs to make a determination that a certain opioid analgesic elixir drug product is suitable for filing under an abbreviated new drug application (ANDA).

A. Action Requested

Petitioner requests that the Commissioner of Food and Drugs make a determination that an abbreviated new drug application (ANDA) is suitable for elixirs containing 10 mg hydrocodone bitartrate/325 mg acetaminophen per 10 mL.

B. Statement of Grounds

The Drug Price Competition and Patent Term Restoration Act of 1984 ("the Waxman-Hatch Act") extends eligibility for the submission of ANDA's to certain drug products identical to those approved via new drug applications, as identified in the *List of Approved Drug Products with Therapeutic Equivalence Evaluations* ("the Orange Book") published by the Food and Drug Administration. Where the proposed drug product differs from the "listed drug" in one or more respects, a person may petition the Agency, under section 505(j)(2)(c) of the Act, for a determination that the proposed drug is suitable to be submitted as an ANDA.

The listed drug product that forms the basis for this petition Norco™, 10 mg/325 mg, (ANDA 40-148, manufactured by Watson Labs). See Orange Book, page 3-5, at Exhibit A. To the best of petitioner's knowledge, applicable U.S. patents with respect to the drug substances, hydrocodone bitartrate and acetaminophen, have expired.

DDP-1291

CPI

The proposed drug product differs from the listed drug products only in regard to dosage form (elixir instead of tablet). Otherwise, the proposed drug product is identical with respect to active ingredients, strength, route of administration, and conditions of use.

The availability of an elixir dosage form of hydrocodone bitartrate and acetaminophen would provide a valuable dosage alternative, particularly for those patients who have trouble swallowing tablets, the geriatric population and other situations where a liquid dosage would be preferred.

The proposed product's dosage form is the same as several other types of approved opioid analgesic drugs which are available in liquid form. For instance, Capital and Codeine (acetaminophen and codeine), NDA 85883 (*Orange Book* at 3-2); Dilaudid (hydromorphone hydrochloride), NDA 19891 (*Orange Book* at 3-182); and Lortab Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir), ANDA 81051 (*Orange Book* at 3-4) attached as Exhibit B.

In view of the availability of other approved opioid analgesics as elixirs and an appropriate patient base for such a form (e.g., geriatric patients), the healthcare community would benefit from the availability of an elixir dosage form of hydrocodone bitartrate and acetaminophen 10 mg/325 mg per 10 mL. The proposed product contains the same active ingredients, at the same strength and route of administration, and would be labeled with the same conditions of use as the listed 10 mg/325 mg, [See Exhibits C (Side-By-Side comparison of Norco insert and proposed insert) and D (Side-By-Side comparison of Norco labeling and proposed labeling)] and packaged in an appropriate container-closure system (See Exhibit E).

Based on the foregoing, Petitioner believes that an elixir dosage form of hydrocodone bitartrate and acetaminophen 10 mg/325 mg per 10 mL warrants a finding of ANDA suitability and that the commissioner should grant permission for the filing of an ANDA for a hydrocodone bitartrate and acetaminophen elixir in the strengths of 10 mg/325 mg per 10 mL.

C. Environmental Impact

A categorical exclusion is claimed as the granting of this Petition will result in an ANDA for a drug product that is consistent with the parameters for exclusion established in 21 C.F.R. 25.24(c)(1).

D. Economic Impact

Information under this section will be submitted if requested by the Commissioner following review of this Petition.

E. Certification

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

PHARMACEUTICAL ASSOCIATES, INC.

By: Kaye B. McDonald
Kaye B. McDonald
201 Delaware Street
Greenville, SC 29605
(864) 277-7282 Ext. 230

Enclosures:

- A. *Orange Book*, page 3-5.
- B. *Orange Book*, pages 3-2, 3-4, and 3-182.
- C. Side-By-Side comparison of Norco™ package insert (May 1998) and proposed insert.
- D. Side-By-Side comparison of Norco™ and labeling and proposed labeling for hydrocodone bitartrate and acetaminophen 10 mg/325 mg per 10 mL.
- E. Description of container and closure system for hydrocodone bitartrate and acetaminophen 10 mg/325 mg per 10 mL.

Exhibit A

ACETAMINOPHEN; HYDROCODONE BITARTRATE

<u>TABLET; ORAL</u>		
<u>HYDROCODONE BITARTRATE AND ACETAMINOPHEN</u>		
<u>AA</u>	VINTAGE PHARMS	<u>650MG; 10MG</u>
<u>AA</u>		<u>750MG; 7.5MG</u>
<u>AA</u>	WATSON LABS	<u>500MG; 2.5MG</u>
<u>AA</u>		<u>500MG; 2.5MG</u>
<u>AA</u>		<u>500MG; 5MG</u>
<u>AA</u>		<u>500MG; 5MG</u>
<u>AA</u>		<u>500MG; 7.5MG</u>
<u>AA</u>		<u>500MG; 7.5MG</u>
<u>AA</u>		<u>500MG; 10MG</u> ✓
<u>AA</u>		<u>650MG; 7.5MG</u>
<u>AA</u>		<u>650MG; 7.5MG</u>
<u>AA</u>		<u>650MG; 10MG</u> ✓
<u>AA</u>		<u>650MG; 10MG</u>
<u>AA</u>		<u>750MG; 7.5MG</u>
<u>AA</u>		<u>750MG; 7.5MG</u>
<u>AA</u>	ZENITH GOLDLINE	<u>500MG; 5MG</u>
<u>LORTAB</u>		
<u>AA</u>	MALLINCKRODT	<u>500MG; 5MG</u>
<u>AA</u>	+ UCB	<u>500MG; 10MG</u>
		325MG; 5MG
	NORCO	
	+ WATSON LABS	325MG; 10MG ✓
<u>VICODIN</u>		
<u>AA</u>	+ KNOLL PHARM	<u>500MG; 5MG</u>

ACETAMINOPHEN; HYDROCODONE BITARTRATE

<u>TABLET; ORAL</u>			
<u>VICODIN ES</u>			
<u>AA</u>	+ KNOLL PHARM	<u>750MG; 7.5MG</u>	N89736 001 DEC 09, 1988
<u>VICODIN HP</u>			
<u>AA</u>	KNOLL PHARM	<u>660MG; 10MG</u>	N40117 001 SEP 23, 1996
<u>ACETAMINOPHEN; OXYCODONE</u>			
<u>CAPSULE; ORAL</u>			
<u>OXYCODONE AND ACETAMINOPHEN</u>			
<u>AA</u>	HALSEY	<u>500MG; 5MG</u>	N40219 001 JAN 22, 1998
<u>ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE</u>			
<u>CAPSULE; ORAL</u>			
<u>OXYCODONE AND ACETAMINOPHEN</u>			
<u>AA</u>	AMIDE PHARM	<u>500MG; 5MG</u>	N40199 001 DEC 30, 1998
<u>AA</u>	MALLINCKRODT	<u>500MG; 5MG</u>	N40257 001 AUG 04, 1998
<u>AA</u>	VINTAGE PHARMS	<u>500MG; 5MG</u>	N40106 001 JUL 30, 1996
<u>AA</u>	WATSON LABS	<u>500MG; 5MG</u> ✓	N40234 001 OCT 30, 1997
<u>ROXILOX</u>			
<u>AA</u>	ROXANE	<u>500MG; 5MG</u>	N40061 001 JUL 03, 1995
<u>TYLOX</u>			
<u>AA</u>	+ JOHNSON RW	<u>500MG; 5MG</u>	N88790 001 DEC 12, 1984
<u>SOLUTION; ORAL</u>			
<u>ROXICET</u>			
	ROXANE	325MG/5ML; 5MG/5ML	N89351 001 DEC 03, 1986
<u>TABLET; ORAL</u>			
<u>OXYCET</u>			
<u>AA</u>	MALLINCKRODT	<u>325MG; 5MG</u>	N87463 001 DEC 07, 1983
<u>OXYCODONE AND ACETAMINOPHEN</u>			
<u>AA</u>	DURAMED	<u>325MG; 5MG</u>	N40272 001 JUN 30, 1998

Exhibit B

PRESCRIPTION DRUG PRODUCT LIST

3-2

ACETAMINOPHEN; BUTALBITAL; CAFFEINE

CAPSULE; ORAL
ANOQUAN
AB ROBERTS AND HAUCK 325MG; 50MG; 40MG N87628 001
 OCT 01, 1986
BUTALBITAL, ACETAMINOPHEN AND CAFFEINE
AB WEST WARD 500MG; 50MG; 40MG N40261 001
 OCT 28, 1998
BUTALBITAL, ACETAMINOPHEN, CAFFEINE
AB GRAHAM DM 325MG; 50MG; 40MG N88758 001
 MAR 27, 1985
ESGIC-PLUS
AB + MIKART 500MG; 50MG; 40MG N40085 001
 MAR 28, 1996
FEMCET
AB MALLINCKRODT 325MG; 50MG; 40MG N89102 001
 JUN 19, 1985
TRIAD
AB MALLINCKRODT 325MG; 50MG; 40MG N89023 001
 JUN 19, 1985
 TABLET; ORAL
BUTALBITAL, ACETAMINOPHEN AND CAFFEINE
AB MALLINCKRODT 325MG; 50MG; 40MG N87804 001
 JAN 24, 1985
AB MIKART 325MG; 50MG; 40MG N89175 001
 JAN 21, 1987
AB + 500MG; 50MG; 40MG N89451 001
 MAY 23, 1988
AB WATSON LABS 500MG; 50MG; 40MG N40267 001
 JUL 30, 1998
AB WEST WARD 325MG; 50MG; 40MG N89718 001
 JUN 12, 1995
BUTALBITAL, APAP, AND CAFFEINE
AB HALSEY 325MG; 50MG; 40MG N89536 001
 FEB 16, 1988
FIORICET
AB + NOVARTIS 325MG; 50MG; 40MG N88616 001
 NOV 09, 1984

ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE

CAPSULE; ORAL
 FIORICET W/ CODEINE
 + NOVARTIS 325MG; 50MG; 40MG; 30MG N20232 001
 JUL 30, 1992

ACETAMINOPHEN; CAFFEINE; DIHYDROCODEINE BITARTRATE

CAPSULE; ORAL
ACETAMINOPHEN, CAFFEINE, AND DIHYDROCODEINE BITARTRATE
AA MIKART 356.4MG; 30MG; 16MG N40109 001
 AUG 26, 1997
DHC PLUS
AA + PURDUE FREDERICK 356.4MG; 30MG; 16MG N88584 001
 MAR 04, 1986

ACETAMINOPHEN; CODEINE PHOSPHATE

CAPSULE; ORAL
 PHENAPHEN W/ CODEINE NO. 2
 + ROBINS AH 325MG; 15MG N84444 001
 PHENAPHEN W/ CODEINE NO. 3
 + ROBINS AH 325MG; 30MG N84445 001
 PHENAPHEN W/ CODEINE NO. 4
 + ROBINS AH 325MG; 60MG N84446 001

SOLUTION; ORAL

ACETAMINOPHEN AND CODEINE PHOSPHATE
AA ALPHARMA 120MG/5ML; 12MG/5ML N85861 001
AA HI TECH PHARMA 120MG/5ML; 12MG/5ML N40119 001
 APR 26, 1996
AA MIKART 120MG/5ML; 12MG/5ML N89450 001
 OCT 27, 1992
AA MORTON GROVE 120MG/5ML; 12MG/5ML N87006 001
AA MOVA 120MG/5ML; 12MG/5ML N40098 001
 SEP 20, 1996
AA PHARM ASSOC 120MG/5ML; 12MG/5ML N87508 001
ACETAMINOPHEN W/ CODEINE
AA ROXANE 120MG/5ML; 12MG/5ML N86366 001
AA + JOHNSON RW 120MG/5ML; 12MG/5ML N85057 001

SUSPENSION; ORAL

ACETAMINOPHEN AND CODEINE PHOSPHATE
AA CARNRICK 120MG/5ML; 12MG/5ML N86024 001
AA CAPITAL AND CODEINE
AA ALPHARMA 120MG/5ML; 12MG/5ML N85883 001

TABLET; ORAL

ACETAMINOPHEN AND CODEINE PHOSPHATE
AA DURAMED 300MG; 15MG N40223 001
 NOV 18, 1997
AA 300MG; 30MG N40223 002
 NOV 18, 1997

PRESCRIPTION DRUG PRODUCT LIST

3-4

ACETAMINOPHEN; HYDROCODONE BITARTRATE

ACETAMINOPHEN; HYDROCODONE BITARTRATE

<u>ELIXIR; ORAL</u>		
<u>AA</u>	<u>HYDROCODONE BITARTRATE AND ACETAMINOPHEN</u> + MIKART	<u>500MG/15ML; 7.5MG/15ML</u>
		✓ N81051 001 AUG 28, 1992
		N81226 001 OCT 27, 1992
		N89557 001 APR 29, 1992
<u>AA</u>	PHARM ASSOC	<u>500MG/15ML; 7.5MG/15ML</u> MAR 13, 1998
<u>TABLET; ORAL</u>		
<u>AA</u>	<u>ANEXSIA</u> MALLINCKRODT	<u>500MG; 5MG</u> N89160 001 APR 23, 1987
<u>AA</u>	<u>ANEXSIA 10/660</u> + MALLINCKRODT	<u>660MG; 10MG</u> N40084 003 JUL 29, 1996
<u>AA</u>	<u>ANEXSIA 7.5/650</u> MALLINCKRODT	<u>650MG; 7.5MG</u> N89725 001 SEP 30, 1987
<u>AA</u>	<u>CO-GESIC</u> SCHWARZ PHARMA	<u>500MG; 5MG</u> N87757 001 MAY 03, 1982
<u>AA</u>	<u>HY-PHEN</u> ASCHER	<u>500MG; 5MG</u> N87677 001 MAY 03, 1982
<u>AA</u>	<u>HYDROCODONE BITARTRATE AND ACETAMINOPHEN</u> ENDO PHARMS	<u>500MG; 5MG</u> N40281 001 SEP 30, 1998
<u>AA</u>		<u>500MG; 7.5MG</u> N40280 001 SEP 30, 1998
<u>AA</u>		<u>650MG; 7.5MG</u> N40280 002 SEP 30, 1998
<u>AA</u>		<u>650MG; 10MG</u> N40280 003 SEP 30, 1998
<u>AA</u>		<u>750MG; 7.5MG</u> N40281 002 SEP 30, 1998
		N40288 001 NOV 27, 1998
		N40288 002 NOV 27, 1998
		N40288 003 NOV 27, 1998
<u>AA</u>	EON	<u>500MG; 5MG</u> N40149 001 JAN 27, 1997

<u>TABLET; ORAL</u>			
<u>AA</u>	<u>HYDROCODONE BITARTRATE AND ACETAMINOPHEN</u> EON	<u>750MG; 7.5MG</u>	N40149 002 JAN 27, 1997
<u>AA</u>	HALSEY	<u>500MG; 5MG</u>	N40236 001 SEP 25, 1997
<u>AA</u>		<u>650MG; 7.5MG</u>	N40240 002 NOV 26, 1997
<u>AA</u>		<u>650MG; 10MG</u>	N40240 001 NOV 26, 1997
<u>AA</u>		<u>750MG; 7.5MG</u>	N40236 002 SEP 25, 1997
<u>AA</u>	MALLINCKRODT	<u>500MG; 5MG</u>	N40084 002 JUN 01, 1995
<u>AA</u>		<u>500MG; 7.5MG</u>	N40201 001 FEB 27, 1998
<u>AA</u>		<u>500MG; 10MG</u>	N40201 002 FEB 27, 1998
<u>AA</u>		<u>750MG; 7.5MG</u>	N40084 001 JUN 01, 1995
<u>AA</u>	+ MIKART	<u>500MG; 2.5MG</u>	N89698 001 AUG 25, 1989
<u>AA</u>		<u>500MG; 5MG</u>	N89271 001 JUL 16, 1986
<u>AA</u>		<u>500MG; 5MG</u>	N89697 001 JAN 28, 1992
<u>AA</u>		<u>500MG; 7.5MG</u>	N89699 001 AUG 25, 1989
<u>AA</u>		<u>650MG; 7.5MG</u>	N89689 001 JUN 29, 1988
<u>AA</u>		<u>650MG; 10MG</u>	N81223 001 MAY 29, 1992
<u>AA</u>	PEACHTREE	<u>500MG; 10MG</u>	N40210 001 AUG 13, 1997
<u>AA</u>	UCB	<u>650MG; 7.5MG</u>	N40134 001 NOV 21, 1996
<u>AA</u>	VINTAGE PHARMS	<u>500MG; 2.5MG</u>	N40144 002 APR 25, 1997
		<u>500MG; 5MG</u>	N89831 001 SEP 07, 1988
		<u>500MG; 5MG</u>	N89971 001 DEC 02, 1988
		<u>500MG; 7.5MG</u>	N40144 001 FEB 22, 1996
		<u>650MG; 7.5MG</u>	N40155 001 APR 14, 1997

PRESCRIPTION DRUG PRODUCT LIST

3-182

HYDROCORTISONE SODIUM SUCCINATE

INJECTABLE; INJECTION
SOLU-CORTEF

AP + PHARMACIA AND UPJOHN EQ 500MG BASE/VIAL N09866 003
AP + EQ 1GM BASE/VIAL N09866 004

HYDROCORTISONE VALERATE

CREAM; TOPICAL
HYDROCORTISONE VALERATE

AB COPLEY PHARM 0.2% N74489 001
AUG 12, 1998
AB TARO 0.2% N75042 001
AUG 25, 1998
AB + WESTCORT WESTWOOD SQUIBB 0.2% N17950 001

OINTMENT; TOPICAL

HYDROCORTISONE VALERATE

AB TARO 0.2% N75043 001
AUG 25, 1998
AB + WESTCORT WESTWOOD SQUIBB 0.2% N18726 001
AUG 08, 1983

HYDROFLUMETHIAZIDE

TABLET; ORAL

DIUCARDIN

AB WYETH AYERST 50MG N83383 001

HYDROFLUMETHIAZIDE

AB PAR PHARM 50MG N88850 001
MAY 31, 1985

SALURON

AB + ROBERTS LABS 50MG N11949 001

HYDROFLUMETHIAZIDE; RESERPINE

TABLET; ORAL

RESERPINE AND HYDROFLUMETHIAZIDE

BP PAR PHARM 50MG;0.125MG N88907 001
SEP 20, 1985

SALUTENSIN

BP + ROBERTS LABS 50MG;0.125MG N12359 003

SALUTENSIN-DEMI

ROBERTS LABS 25MG;0.125MG N12359 004

HYDROMORPHONE HYDROCHLORIDE

INJECTABLE; INJECTION

DILAUDID-HP

AP + KNOLL PHARM 10MG/ML N19034 001
250MG/VIAL JAN 11, 1984
N19034 002
AUG 04, 1994

HYDROMORPHONE HCL

AP ABBOTT 10MG/ML N74598 001
JUN 19, 1997
AP STERIS 10MG/ML N74317 001
AUG 23, 1995

SOLUTION; ORAL

DILAUDID

AA + KNOLL PHARM 5MG/5ML N19891 001
DEC 07, 1992

HYDROMORPHONE HCL

AA ROXANE 5MG/5ML N74653 001
JUL 29, 1998

TABLET; ORAL

DILAUDID

AB + KNOLL PHARM 8MG N19892 001
DEC 07, 1992

HYDROMORPHONE HCL

AB ROXANE 8MG N74597 001
JUL 29, 1998

HYDROXOCOBALAMIN

INJECTABLE; INJECTION

HYDROXOCOBALAMIN

+ STERIS 1MG/ML N85998 001

HYDROXYAMPHETAMINE HYDROBROMIDE

SOLUTION/DROPS; OPHTHALMIC

PAREDRINE

+ PHARMICS 1% N00004 004

Exhibit C

ANDA Product

Listed Drug

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR, USP

NORCO® TABLETS



DESCRIPTION

Hydrocodone Bitartrate And Acetaminophen Elixir, for oral administration, contains hydrocodone bitartrate and acetaminophen in the following strengths per 10 mL:

Hydrocodone Bitartrate, USP 10 mg
Acetaminophen, USP 325 mg

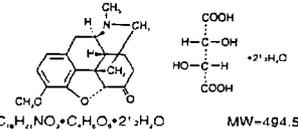
In addition, the elixir contains the following inactive ingredients: Alcohol, 7%, Methylparaben, Sodium Saccharin, Sucrose, Propylene Glycol, Glycerin, Sorbitol Solution, Mixed Fruit Flavor, and FD&C Blue No. 1.

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

DESCRIPTION

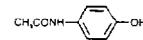
NORCO® (Hydrocodone bitartrate and acetaminophen) is supplied in tablet form for oral administration.

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



$C_{24}H_{31}NO_5 \cdot C_4H_4O_6 \cdot 2H_2O$ MW=494.50

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



$C_8H_9NO_2$ MW=151.17

Each NORCO® tablet contains:

Hydrocodone Bitartrate 10 mg
[WARNING: May be habit forming]
Acetaminophen 325 mg

In addition, each tablet contains the following inactive ingredients: croscarmellose sodium, crospovidone, D&C yellow #10 aluminum lake, magnesium stearate, microcrystalline cellulose, pregelatinized starch, povidone and stearic acid.

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.

CLINICAL PHARMACOLOGY

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The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating sensors. 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.

= Brand Name / Generic Name

= Change due to Dosage form

ANDA Product

Listed Drug

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 3- α - and 6- β -hydroxymetabolites.

See OVERDOSAGE for toxicity information.

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

See overdose for toxicity information.

INDICATIONS AND USAGE

Hydrocodone 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, acetaminophen, or any other component of this product.

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 opioids 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, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries.

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See OVERDOSAGE for toxicity information.

INDICATIONS AND USAGE

NORCO Tablets are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

NORCO 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.

= Brand Name /
Generic Name

ANDA Product

Listed Drug

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

PRECAUTIONS

General: Special Risk Patients: As with any opioid 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 opioids, 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 opioids, 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 opioids, antihistamines, antipsychotics, anti-anxiety 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

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

PRECAUTIONS

General: Special Risk Patients: As with any narcotic analgesic agent, NORCO® 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 NORCO® Tablets are used postoperatively and in patients with pulmonary disease. Information for Patients: NORCO® Tablets, 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.

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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 to

= Brand Name /
Generic Name

ANDA Product

Listed Drug

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 opioids, 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.

carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy:

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

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

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Other adverse reactions include:

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

= Brand Name / Generic Name

ANDA Product

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 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 Elixir is classified as a Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of opioids; 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 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 opioid use, although some mild degrees of physical dependence may develop after a few days of opioid therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by shortened duration of analgesic effect, and subsequently by decreases in the intensity of the 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:

Listed Drug

Gastrointestinal System: Prolonged administration of NORCO Tablets may produce constipation.
Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

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

Dermatological: Skin rash, pruritus.

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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:

= Brand Name /
Generic Name

ANDA Product

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 overdose, apnea, circulatory collapse, cardiac arrest, and death may occur.

Acetaminophen: In acetaminophen overdose, 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 - 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdose 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 cardio-respiratory 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 (1g/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. Vassopressors 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 hypo-prothrombinemia 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 the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be

Listed Drug

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 overdose, apnea, circulatory collapse, cardiac arrest and death may occur.

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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 cardio-respiratory 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 (1g/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. Vassopressors and other supportive measures should be employed as indicated. A cuffed endotracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

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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.

administered as needed to maintain adequate respiration. A opioid 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 (15 mL) every four to six hours as needed for pain. The total 24-hour dose should not exceed 6 tablespoons.

HOW SUPPLIED

Hydrocodone Bitartrate and Acetaminophen Elixir is a blue-colored, fruit flavored liquid containing 10 mg hydrocodone bitartrate, and 325 mg acetaminophen per 10 mL, with 7% alcohol. It is supplied as follows:

10mg/325mg per 10 mL:	
16 oz. Bottles	NDC 0121-0720-16
4 oz. Bottles	NDC 0121-0720-04
15 mL Unit Dose Cups	NDC 0121-0720-15

Store at controlled room temperature 20 - 25°C (68 - 77°F).

Dispense in a tight, light-resistant container.

R_x ONLY

A Schedule III controlled substance

PHARMACEUTICAL ASSOCIATES, INC.
Greenville, SC

02/00

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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 dosage should not exceed 6 tablets.

HOW SUPPLIED

NORCO[®] is supplied as a yellow, capsule-shaped tablet containing 10 mg hydrocodone bitartrate and 325 mg acetaminophen, bisected on one side and debossed with "NORCO 539" on the other side.

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

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

Rx only

WATSON PHARMA
A Division of Watson Laboratories, Inc.
Corona, CA 91720

Revised May '51
1305

= Brand Name /
Generic 1

= Change due to
dosage form

= Controlled Room
Temperature change
to current USP 2

Exhibit D

ANDA Product

Listed Drug

FRONT OF LABEL:

NDC 0121-0720-16

HYDROCODONE BITARTRATE
AND ACETAMINOPHEN ELIXIR

CIII

10 mg/325 mg per 10 mL

Hydrocodone bitartrate, USP 10 mg
(Warning: May be habit forming)
Acetaminophen, USP 325 mg
Alcohol 7%
R, ONLY
16 fl oz (473 mL)

PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

NDC 52544-539-01
NORCOTM
hydrocodone bitartrate
and acetaminophen
tablets, USP

10 mg/325 mg

FACH TABLET CONTAINS:
hydrocodone Bitartrate, USP...10 mg
(WARNING: May be habit forming)
Acetaminophen, USP...325 mg

CAUTION: Federal law prohibits
dispensing without prescription.

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

USUAL ADULT DOSAGE:
One tablet every four to six hours,
as needed for pain.
Total daily dosage should not
exceed six tablets.
See insert for full prescribing
information.
Keep this and all medication out of
the reach of children.
Store at controlled room
temperature: 15°-30°C (59°-86°F).

100 Tablets

13058
52544-539-01
53902X97
12/99
EXP:

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert
for complete prescribing information.
Lot No.
Exp. Date

LEFT SIDE OF LABEL:

Pharmacist: Dispense in a tight, light-resistant
container as defined in the USP, with a
child-resistant closure (as required).
Store at controlled room temperature—
20° - 25° C (68° - 77° F)

= Brand Name / Generic Name

= change due to dosage form

↓ = Controlled Room Temperature
changed to Current USP 24

Delivers 15 mL
NDC 0121-0720-15

**Hydrocodone Bitartrate and
Acetaminophen Elixir**

CIII

10 mg/325 mg per 10 mL

Alcohol 7%

Usual Dosage: See Package Insert for
Complete Dosage Recommendations.

(Lot No. and Exp. Date)

R_x ONLY

FOR INSTITUTIONAL USE ONLY
PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

.....
NDC 0121-0716-15

**HYDROCODONE BITARTRATE
AND ACETAMINOPHEN ELIXIR**

10 mg/325 mg per 10 mL

Alcohol 7%

Preservative: Methylparaben 0.15%
pH Range: 4.0 – 5.0

Usual Dosage: See Package Insert for
Complete Dosage Recommendations.

10 × 15 mL

This unit-dose package is not child-resistant.

Store at controlled room temperature,
20° - 25° C (68° - 77° F)

R_x ONLY

FOR INSTITUTIONAL USE ONLY
PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

FRONT OF LABEL:

NDC 0121-0720-04

**HYDROCODONE BITARTRATE
AND ACETAMINOPHEN ELIXIR**

CIII

10 mg /325 mg per 10 mL

Hydrocodone bitartrate, USP	10 mg
(Warning: May be habit forming)	
Acetaminophen, USP	325 mg
Alcohol 7 %	
R_x ONLY	
4 fl oz (118 mL)	

PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert
for complete prescribing information.
Lot No.
Exp. Date

LEFT SIDE OF LABEL:

Pharmacist: Dispense in a tight, light-resistant
container as defined in the USP, with a
child-resistant closure (as required).
Store at controlled room temperature
20° - 25° C (68° - 77° F)

Exhibit E

Hydrocodone bitartrate and Acetaminophen Elixir (NDC 0121-0720-) has been packaged in the following container/closure systems:

1. Bottle: 16 oz. Amber PET 28-400 container
Cap: 28-400 White Fine Ribbed P/P Closure with P/RVTLF Liner
2. Bottle: 16 oz. Amber PET 28-400 container
Cap: 28-400 White Fine Ribbed Closure with SG-90 Liner
3. Bottle: 16 oz. Brown HDPE BL-16 container
Cap: 28-400 White Fine Ribbed P/P Closure with P/RVTLF Liner
6. Bottle: 4 oz. Amber PET 24-400 container
Cap: 24-400 White Clic-Loc with P/RVTLF Liner
7. Unit Dose Cup: BP 15 HDPE Unit Dose Container made of Alathon resin.
Lidding: Paper/Polyethylene/Aluminum Foil/Heat Seal by Tekni-Plex

We intend to seek approval for all container / closure systems except the Unit Dose Cup BP 10.

Box 2944
Hartford, CT 06104-2944
CALL TOLL FREE 1-800-243-5250

PACKING LIST

PACKING LIST
NO.

005486

PHARMACEUTICAL ASSOCIATES, INC.

201 Delaware St.
GREENVILLE, SOUTH CAROLINA 29605
(864) 277-7282

DATE

5-8-00

SHIP TO

SAME AS SOLD TO UNLESS OTHERWISE INDICATED HERE

SOLD TO

Doctors Management Branch (HFA-300)
Food and Drug Administration
5600 Fishers Lane, Room 4-62
Rockville, MD 20857

OUR ORDER NO.	YOUR ORDER NO.	CARTONS-PKGS.	TOTAL WEIGHT	PPD. OR COLL	SHIPPED VIA
					UPS Next Day Air
QUANTITY ORDERED	QUANTITY BACK-ORD'D.	QUANTITY SHIPPED	DESCRIPTION		
		128	ANDA		

ORDER COMPLETE
 BALANCE TO FOLLOW

PLEASE NOTIFY US IMMEDIATELY IF ERROR IS FOUND IN SHIPMENT.

PACKED BY James Green CHECKED BY _____