ANDA: 89-736 SPONSOR: KNOLL PHARM. 1 OF 1
TRADE NAME: VICODIN ES GENERIC: HYDROCODONE
BITAR/ACETAM 7.5/750MG

ANDA: 89-736

SPONSOR: KNOLL PHARM

APPROVAL LETTER: Y

FINAL PRINTED LABEL: Y

CHEMIST REVIEW: Y

UPDATE DATE: 03/07/89

TRADE NAME: VICODIN ES

GENERIC: HYDROCODONE BITAR/ACETAM 7.5/750mg

BIO/DISSOLUTION REVIEW: Y

FEDERAL REGISTER NOTICE: Y

APRVL

LTR

ANDA 89-736

DEC 9 1988

Knoll Pharmaceutical
Attention: Robert W. Ashworth, Ph.D.
30 North Jefferson Road
Whippany, NJ 07981

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Vicodin ES (Hydrocodone Bitartrate 7.5 mg and Acetaminophen 750 mg) Tablets.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

Any significant change in the conditions outlined in this abbreviated application requires an approved supplemental application before the change may be made, except for changes made in conformance with other provisions of Section 314.70 of the New Drug Regulations.

Postmarketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80 and 314.81 of the Regulations.

This Administration should be advised of any change in the marketing status of this drug.

For Initial Campaigns: We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your immediate advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Advertising and Labeling (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

For Subsequent Campaigns: We call your attention to Section 314.81(b)(3) of the Regulations which requires that materials for any subsequent advertising or promotional campaign, at the time of their initial use, be submitted to our Division of Drug Advertising and Labeling (HFD-240) with a completed Form FD-2253.

Sincerely yours,

12/9/88

Steven Sciffe, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drug Evaluation and Research

cc:
HFN-230
HFN-237
HFN-10
HFN 83 0
YMille/MGoldman/gp/12/8/88
1414g (APPROVAL)


FPL

VICODIN ES®
TABLETS 5833

DESCRIPTION:

Each VICODIN ES® tablet contains:

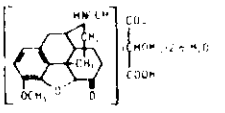
Hydrocodone Bitartrate ..... 7.5 mg

(**WARNING:** May be habit forming.)

Acetaminophen ..... m.

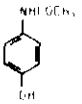
Other ingredients include colloidal silicon dioxide, c... starch, croscarmellose sodium, Type A magnesium stearate, povidone, stearic acid, and sodium metabisulfite.

Hydrocodone bitartrate is an opioid analgesic and an 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). Its structure is as follows:



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2½H_2O$ M.W. 494.50

Acetaminophen: 4-hydroxyacetanilide is a non-opiate, non-salicylate analgesic and antipyretic which occurs as a white, odorless crystalline powder possessing a slightly bitter taste. Its structure is as follows:



$C_8H_9NO_2$ M.W. 151.16

CLINICAL PHARMACOLOGY:

Hydrocodone is a semisynthetic ... codic analgesic and antitussive with multiple actions qua...tively 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.

Radioim... massay techniques have recently been developed for the analysis of hydrocodone in human plasma. After a 10 mg oral dose of hydrocodone bitartrate, a mean peak serum drug level of 23.6 ng/mL and an elimination half-life of 3.8 hours were found.

The analgesic action of acetaminophen involves both peripheral and central 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. Acetaminophen is rapidly and almost completely absorbed from the gastrointestinal tract, producing maximum serum concentrations within 30 minutes to one hour. The plasma half-life in adults and children ranges from 0.90 hours to 3.25 hours with an average of approximately 2 hours. The drug distributes uniformly in most body fluids and is approximately 25% protein bound. Acetaminophen is conjugated in the liver with less than 3% of the dose excreted unchanged in 24 hours. The primary metabolic pathway is conjugation to sulfate and glucuronide by-products. A minor oxidative pathway forms cysteine and mercapturic acid. These compounds are subsequently excreted by the kidneys into the urine.

INDICATIONS AND USAGE

For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS:

Hypersensitivity to acetaminophen or hydrocodone.

WARNINGS:

VICODIN ES Tablets contain sodium metabisulfite a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than non-asthmatic people.

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:

Special Risk Patients: As with any narcotic analgesic agent, VICODIN ES 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.

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

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

Drug Interactions: Patients receiving other narcotic analgesics, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with VICODIN ES Tablets may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

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

The concurrent use of anticholinergics with hydrocodone may produce paralytic ileus.

Usage in Pregnancy:

Teratogenic Effects: Pregnancy Category C. Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the human dose. There are no adequate and well-controlled studies in pregnant women. VICODIN ES Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic 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 respiration 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. Chlorpromazine 0.7 to 1 mg/kg q6h and paregoric 2 or 4 drops/kg q4h have been used to treat withdrawal symptoms in infants. The duration of therapy is 4 to 28 days, with the dosage decreased as tolerated.

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

Nursing Mothers: It is not known whether this drug 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 VICODIN ES Tablets, 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 children have not been established.

ADVERSE REACTIONS:

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

Other adverse reactions include:

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

Gastrointestinal System: The antiemetic phenothiazines are useful in suppressing the nausea and vomiting which may occur (see above); however, some phenothiazine derivatives seem to be antianalgesic and to increase the amount of narcotic required to produce pain relief, while other phenothiazines reduce the amount of narcotic required to produce a given level of analgesia. Prolonged administration of VICODIN ES Tablets may produce constipation.

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

Respiratory Depression: Hydrocodone bitartrate 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. If significant respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride. Apply other supportive measures when indicated.

DRUG ABUSE AND DEPENDENCE:

VICODIN ES Tablets are subject to the Federal Controlled Substance Act (Schedule C-II).

Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, VICODIN ES Tablets should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when VICODIN ES Tablets are used for a short time for the treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE:

Acetaminophen:

Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose. Despite this, the measures outlined below should be initiated in any adult or child suspected of having ingested an acetaminophen overdose.

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.

Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. Patients' estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.

The antidote, N-acetylcysteine, should be administered as

OVER

early as possible, preferably within 16 hours of the overdose ingestion for optimal results, but in any case within 24 hours. Following recovery, there are no residual structural or functional hepatic abnormalities.

Hydrocodone:

Signs and Symptoms: 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.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including hydrocodone. Therefore, an appropriate dose of naloxone hydrochloride (see package insert) should be administered, preferably by the intravenous route, and simultaneously with efforts at respiratory resuscitation. Since the duration of action of hydrocodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

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 24 hour dose should not exceed 5 tablets.

HOW SUPPLIED:

White, oval shaped, faceted edged tablet debossed on one side and imprinted with "VICODIN ES" on the other side.

Bottles of 100—NDC #0044-0728-02

Hospital Unit Dose Package—100 tablets (4x25 tablets)—NDC #0044-0728-41

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

Dispense in a tight, light-resistant container as defined in the USP.

A Schedule Narcotic

MR 1987/5811
PI: 3/VicES5832/3 21-88
Revised March 1988 5832

Knoll Pharmaceuticals
A Unit of BASF K&F Corporation
30 North Jefferson Road
Whippany, New Jersey 07981

knoll®

Vicodin ES
Each tablet contains:
Warning: May
acetam
Usual adult dose:
Caution: Fede
out pr
Storage: Sto
in the US

CHEM
REV

1. CHEMIST'S REVIEW NO.

2. ANDA # 89-736

3. NAME AND ADDRESS OF APPLICANT

Knoll Pharmaceuticals
30 North Jefferson Road
Whippany, NJ 07981

6. NAME OF DRUG

Vicodin ES

7. NONPROPRIETARY NAME

Hydrocodone Bitartrate and Acetaminophen

10. PHARMACOLOGICAL CATEGORY

Analgesic and Antitussive

11. HOW DISPENSED

Rx

13. DOSAGE FORM

Tablets

14. POTENCY

(7.5 mg/750 mg)

15. CHEMICAL NAME AND STRUCTURE

See USP

17. COMMENTS

1. Bioavailability testing is not required for Vicodin ES-only comparative dissolution.

18. CONCLUSIONS AND RECOMMENDATIONS

Approvable

19. REVIEWER:

M. Goldman

DATE COMPLETED:

M Goldman
1/15/95

20. COMPONENTS AND COMPOSITION

	Amt/tablet
Hydrocodone Bitartrate, USP	[redacted]
Acetamino,hen[redacted]	
Colloidal Silicon Dioxide, NF	
Magnesium Stearate, NF	
[redacted]	
[redacted]	
starch	
croscarmellose sodium	
povidone	
stearic acid	
sodium metabisulfite	

21. FACILITIES AND PERSONNEL

Satisfactory

22. SYNTHESIS

A) Hydrocodone Bitartrate

1. [redacted]

2. [redacted]

B) Acetaminophen

[redacted]

23. RAW MATERIAL CONTROLS

A. NEW DRUG SUBSTANCE OK

B. OTHER INGREDIENTS OK

24. OTHER FIRM(s)

Repackager of unit dose (see below)

25. MANUFACTURING AND PROCESSING

Knoll Pharmaceuticals, 30 North Jefferson Road, Whippany, New Jersey will perform the manufacturing, processing and control operations.
Bottles of 100 packaged by Knoll.

[redacted]

26. CONTAINER

150cc Amber Glass Bottle, 45/400 Metal Cap with pulp and vinyl seal, coil

[redacted]

27. PACKAGING AND LABELING

100 tablet bottles
Hospital Unit Dose Package

28. LABORATORY CONTROLS (IN-PROCESS AND FINISHED DOSAGE FORM)

OK

29. STABILITY

Request 24 months expiration for bottles and 18 months for blister

30. CONTROL NUMBERS

Satisfactory

32. LABELING

Satisfactory

34. RECALLS

Not on Alert List.

BIO/DIS

REV

6/30/87

Hydrocodone Bitartrate/Acetaminophen
Tablet, 7.5 mg/750 mg
ANDA #89-136
Reviewer: Sikta Pradhan
Wang [redacted]

Knoll Pharmaceuticals, Inc.
Whippany, NJ
Submission Date:
May 13, 1987

Review of a Request for Waiver

Knoll Pharmaceuticals, Inc. has Acetaminophen/Hydrocodone Bitartrate, 500 mg/5 mg tablets currently in the market. The firm intended to market the higher strength of the drug, Acetaminophen/Hydrocodone Bitartrate, 750 mg/7.5 mg and consequently filed a petition under section 505(J)(2)(C) to get Agency's permission for an ANDA application. The petition was denied on November 7, 1985.

Knoll Pharmaceuticals, Inc. filed another petition for reconsideration on November 15, 1985. The request for reconsideration was granted on March 13, 1987.

In this ANDA application, the firm has submitted the composition and dissolution testing data of Acetaminophen/Hydrocodone Bitartrate, 750 mg/7.5 mg tablets and requested for waiver of in-vivo bioequivalence study requirements for the test drug under 21 CFR 320.22 (d)(4) Regulation.

I. The formulation of the test product is listed below:

Material	Amt/tablet
Hydrocodone Bitartrate, USP	7.5 mg
Acetaminophen DC-90 (direct compression-90%)	833.3 mg
[redacted]	[redacted]

Acetaminophen DC-90 (equivalent to 750.0 mg acetaminophen)

acetaminophen
[redacted]

II. Dissolution Testing:

Conditions:

Apparatus:	USP XXI, Paddle
Speed:	50 RPM
Medium:	0.001 N HCl
No. of Tablets:	12
Sampling Times:	15, 30, 45 minutes.
Reference Drugs:	Two Different Batches of Test Product
Assay Method:	HPLC

Results: The result (attached) showed that more than 90% of Acetaminophen and Hydrocodone Bitartrate of the test product was dissolved in 30 minutes.

Comments:

1. The dissolution testing conducted by Knoll Pharmaceuticals, Inc. on the test product is acceptable. However, the firm should be advised to use 900 ml of 0.9% saline rather than 500 ml of it in the future.

2. According to the Therapeutic Equivalence Classification, Acetaminophen/Hydrocodone Bitartrate tablet is rated as "AA". Therefore, no in-vivo bioequivalence study is required on the test product.

Recommendations:

1. The dissolution testing conducted by Knoll Pharmaceuticals, Inc. on its Acetaminophen/Hydrocodone Bitartrate, 750 mg/7.5 mg tablet (Vicodin ES, oval shape) tablets, Lot #PD-D2-3 is acceptable. Therefore, the waiver of in-vivo bioequivalence study requirements for Acetaminophen/Hydrocodone Bitartrate, 750 mg/7.5 mg tablets Lot #PD-D2-3 of the test product is granted. THE TEST PRODUCT SHOULD BE CODED AA IN THE THERAPEUTIC EQUIVALENCE LIST.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of .9% saline of 37°C using USP XXI Apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

> Not less than 75% of the labeled amount of acetaminophen and hydrocodone in the dosage form is dissolved in 30 and 45 minutes, respectively.

Sikta Pradhan 6/25/87

Sikta Pradhan, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED BY RMHATRE
FT INITIALED BY RMHATRE

Concur: Shrikant V. Dighe, Ph.D. Date: 6/29/87
Director,
Division of Bioequivalence

SPradhan/ngo[redacted]/6/10/87

cc: ANDA 89-736, original, HFN-230(2), HFN-258 (Pradhan, Mhatre), HFN-200 (Hare), HFN-22 (C. Hooton), drug file

[redacted] Results

Time [redacted]

Reference Product Acetaminophen/Hydrocodone bitartrate Vicodin Tablet 750 mg/7.5 mg

Lot # H47-33

	Mean % Dissolved	Range	(CV)	Mean % Dissolved	Range	(CV)
Mean			( )			( )
15				76.5	59.7 - 86.4	9.3
			( )			( )
30				82.2	71.5 - 89.5	6.6
			( )			( )
45				82.9	73.4 - 88.3	4.7

Lot # _____ Lot # _____

15				[redacted]	76.0 - 94.8	6.4
				[redacted]	[redacted]	3.5
			( )			( )
45	[redacted]		( )	92.6	84.8 - [redacted]	(3.2)
			( )			( )
			( )			( )
			( )			( )

7/02/87

Hydrocodone Bitartrate/Acetaminophen
Tablet, 7.5 mg/750 mg
ANDA #89-736
Reviewer: Sikta Pradhan
Wang [redacted]

Knoll Pharmaceuticals, Inc.
Whippany, NJ
Submission Date:
May 13, 1987

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I. The formulation of the test product is listed below:

Material	Amt/tablet
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Acetaminophen DC-90 (direct compressi[redacted]-90%)	833.3 mg
[redacted]	[redacted]
Acetaminophen DC-90 (equivalent to 750.0 mg acetaminophen)	
acetaminophen	
[redacted]	

II. Dissolution Testing:

Conditions:

Apparatus:	USP XXI, Paddle
Speed:	50 RPM
Medium:	0.002 N HCl
No. of Tablets:	12
Sampling Times:	15, 30, 45 minutes.
Reference Drugs:	Two Different Batches of Test Product
Assay Method:	HPLC

Results: The result (attached) showed that more than 90% of Acetaminophen and Hydrocodone Bitartrate of the test product was dissolved in 30 minutes.

Comments:

1. The dissolution testing conducted by Knoll Pharmaceuticals, Inc. on the test product is acceptable. However, the firm should be advised to use 900 ml of 0.9% saline rather than 500 ml of it in the future.

2. According to the Therapeutic Equivalence Classification, Acetaminophen/Hydrocodone Bitartrate tablet is rated as "AA". Therefore, no in-vivo bioequivalence study is required on the test product.

Recommendations:

1. The dissolution testing conducted by Knoll Pharmaceuticals, Inc. on its *Acetaminophen/Hydrocodone* Bitartrate, 750 mg/7.5 mg tablet (Vicodin ES, oval shape) tablets, Lot #PD-02-3 is acceptable. Therefore, the waiver of in-vivo bioequivalence study requirements for Acetaminophen/Hydrocodone Bitartrate, 750 mg/7.5 mg tablets Lot #PD-02-3 of the test product is granted. THE TEST PRODUCT SHOULD BE CODED AA IN THE THERAPEUTIC EQUIVALENCE LIST.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of .9% saline of 37°C using USP XXI Apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

> Not less than 75% of the labeled anount of acetaminophen and hydrocodone in the dosage form is dissolved in 30 and 45 minutes, respectively.

Sikta Pradhan 6/25/87

Sikta Pradhan, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED BY RMHATRE
FT INITIALED BY RMHATRE

Concur: Charles M Dighe Jr Date: 6/29/87
Shrikant V. Dighe, Ph.D.
Director,
Division of Bioequivalence

SPradhan/ngo/[redacted]/6/10/87

cc: ANDA 89-736, original, HFN-230(2), HFN-258 (Pradhan, Mhatre), HFN-200 (Hare), HFN-22 (C. Hooton), drug file

Results Acetaminophen/Hydrocodone Bitartrate (Vicodin ES)

Time	Test Product 750 mg/7.5 mg Tablet Lot # ED-D2-3 Mint shape (oval)			Reference Product (Vicodin ES) Tablet Lot # ED-D2-3P Oval shape (Supplied)		
	Mean % Dissolved	Range	(CV)	Mean % Dissolved	Range	(CV)
min			( )			( )
15	58.8	[redacted]	( )	90.0	[redacted]	( )
			( )			( )
30	97.3	[redacted]	( )	97.0	[redacted]	( )
			( )			( )
45	96.2	[redacted]	( )	96.3	[redacted]	( )
			( )			( )
			( )			( )
			( )			( )

Acetaminophen

	Lot #			Lot #		
			( )			( )
	83.5	[redacted]	( )	92.0	[redacted]	( )
			( )			( )
30	95.0	[redacted]	( )	94.0	[redacted]	( )
			( )			( )
45	92.4	[redacted]	( )	91.3	[redacted]	( )
			( )			( )
			( )			( )
			( )			( )

Hydrocodone Bitartrate

Results

Time

Lot #

Time	Mean % Dissolved	Range	(CV)	Mean % Dissolved	Range	(CV)
min						
15				76.5	[redacted]	9.3
30				52.2	[redacted]	5.6
45				52.5	[redacted]	4.7

Acetaminophen

Reference Product Vicodin Tablet 750 mg/5 mg

Lot # H47-33

Lot #

Lot #

15				[redacted]		8.4
30						
45				[redacted]		( )
				72.6		(5.2)
						( )
						( )

Hydrocodone
7.5 mg/325 mg

FR

NOTICE

[DESI 7289]

CODEINE, WITH ACETAMINOPHEN, ASPIRIN, AND CAFFEINE FOR ORAL USE

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated a report received from the National Academy of Sciences—National Research Council, Drug Efficacy Study Group, on trigesic with codeine tablets (NDA 7-289) containing codeine, acetaminophen, aspirin, and caffeine; E. R. Squibb & Sons, Division Olin Mathieson Chemical Corp., 745 Fifth Avenue, New York, N.Y. 10022.

Such drugs are regarded as new drugs (21 U.S.C. 321(p)). Supplemental new drug applications are required to revise the labeling in and to update previously approved applications providing for such drugs. A new drug application is required from any person marketing such drug without approval.

A. *Effectiveness classification.* 1. The Food and Drug Administration has considered the Academy's report, as well as other available evidence, and concludes that combination drugs containing codeine with acetaminophen, aspirin, and caffeine are effective for the relief of mild to moderate pain.

B. *Conditions for approval and marketing.* The Food and Drug Administration is prepared to approve abbreviated new drug applications and abbreviated supplements to previously approved new drug applications under conditions described herein.

1. *Drug.* Preparations containing codeine, acetaminophen, aspirin, and caffeine in tablet form suitable for oral administration.

2. *Labeling conditions.* a. The label bears the statement, "Caution: Federal law prohibits dispensing without prescription."

b. The drug is labeled to comply with all requirements of the Act and regulations, and the labeling bears adequate information for safe and effective use of the drug. The indication for use is: For the relief of mild to moderate pain.

3. *Marketing status.* Marketing of such drugs may be continued under the conditions described in the notice entitled "Policy Statement for Marketing New Drugs Subject to Drug Efficacy Study, published in the FEDERAL REGISTER July 14, 1972 (37 FR 13773), as follows:

a. For holders of "deemed approved" new drug applications (i.e., an application which became effective on the basis of safety prior to October 10, 1962), the submission of a supplement for revised labeling and an abbreviated supplement for updating information as described in paragraph (a)(1)(ii) and (iii) of the notice of July 14, 1970.

b. For any person who does not hold an approved or effective new drug application, the submission of an abbreviated new drug application as described in paragraph (a)(3)(i) of that notice.

c. For any distributor of the drug, the use of labeling in accord with this announcement for any such drug shipped within the jurisdiction of the Act as described in paragraph (b) of that notice.

A copy of the Academy's report has been furnished to the firm referred to above. Communications forwarded in response to this announcement should be identified with the reference number DESI 7289, directed to the attention of the appropriate office listed below, and addressed to the Food and Drug Administration, 5500 Fishers Lane, Rockville, MD 20852.

Supplements (identify with NDA number): Office of Scientific Evaluation (BD-100), Bureau of Drugs.

Requests for the Academy's report: Drug Efficacy Study Information Control (BD-66), Bureau of Drugs.

All other communications regarding this announcement: Drug Efficacy Study Implementation Project Office (BD-60), Bureau of Drugs.

All identical, related, or similar products, not the subject of an approved new drug application, are covered by the new drug application policy announced and are subject to this notice. See 21 CFR 130.40 (37 FR 25185, October 21, 1972). Any person who wishes to determine whether a specific product is covered by this notice should write to the Food and Drug Administration, Bureau of Drugs, Office of Compliance (BD-200), 5600 Fishers Lane, Rockville, MD 20852.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 502, 505, 52 Stat. 1050-53, as amended, 21 U.S.C. 352, 355) and the Administrative Procedure Act (5 U.S.C. 554) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: December 26, 1972.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.73-2462 Filed 2-1-73;8:45 am]

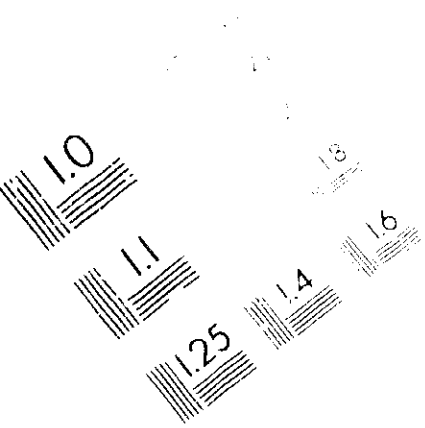
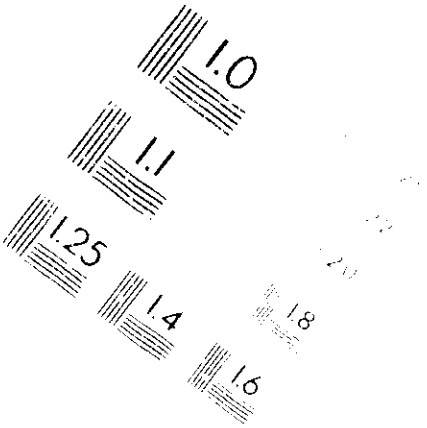
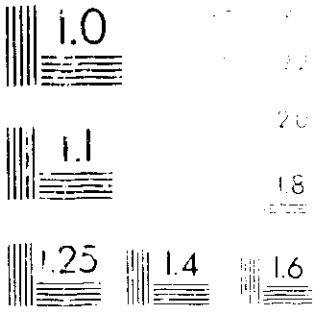
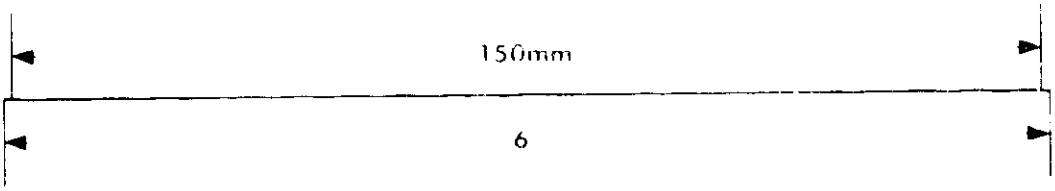
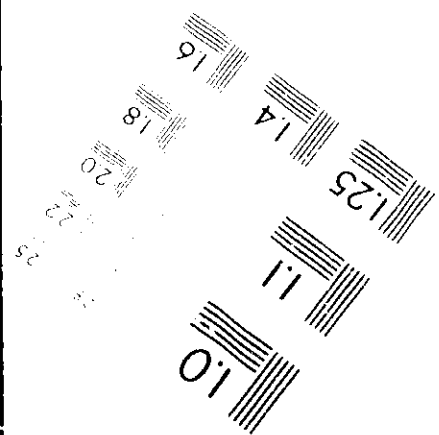


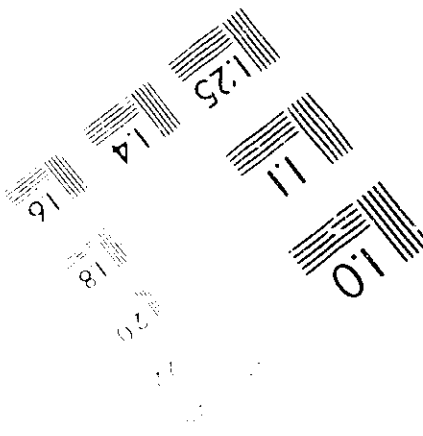
IMAGE EVALUATION TEST TARGET (MT-3)











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