CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

88-058/S-001;S-002;S-003; S-004;S-005;S-006;S-007;S-008; S-009;S-011;S-012;S-013;S-014; S-015;S-016;S-017;S-018;S-019; S-020;S-021;S-022;S-023;S-024

Trade Name: Vicodin Tablets

Generic Name: hydrocodone bitartrate/acetaminophen 5mg/500mg

Sponsor: Knoll Pharmaceutical Company

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
88-058/S-001;S-002;S-003; S-004;S-005;S-006;S-007;S-008; S-009;S-011;S-012;S-013;S-014; S-015;S-016;S-017;S-018;S-019; S-020;S-021;S-022;S-023;S-024

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Reviews / Information Included in this ANDA Review.	
Approval Letter	X
Tentative Approval Letter(s)	
Final Printed Labeling(s)	X
CSO Labeling Review(s)	
Chemistry Review(s)	X
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

**88-058/S-001;S-002;S-003;
S-004;S-005;S-006;S-007;S-008;
S-009;S-011;S-012;S-013;S-014;
S-015;S-016;S-017;S-018;S-019;
S-020;S-021;S-022;S-023;S-024**

APPROVAL LETTERS

NOV 26 1984

NDA 88-058/S-001, S-002, S-003

Knoll Pharmaceutical Company
Attention: Mr. Agamemnon C. Hanzas
30 North Jefferson Road
Whippany, New Jersey 07981

Gentlemen:

Reference is made to your supplements dated July 29, 1984 and January 30, 1984 regarding your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vicodin (hydrocodone bitartrate 5 mg and acetaminophen 500 mg) Tablets.

Reference is also made to your communication dated July 17, 1984.

The supplemental applications provide for:

S-001 - a ——— procedure
S-002 - two year expiration date for the ——— tablets.
S-003 - a major control procedure change for the dosage form.

We have completed the review of these supplemental applications and they are approved. Our letter of January 7, 1983 detailed the conditions relating to the approval of this application.

The material submitted is being retained in our files.

Sincerely yours,

/S/ 11/26/84

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

cc:
NWK-DO
HFN-230 /S/ 11-21-84
HFN-83
JLMeyer/CChang/mk/11/20/84
7095A /S/ 11/23/84

APPROVAL

NOV 26 1984

NDA 88-058/S-004, S-005

Knoll Pharmaceutical Company
Attention: Mr. Agamemnon C. Hanzas
30 North Jefferson Road
Whippany, New Jersey 07981

Gentlemen:

Reference is made to your supplements dated October 9, 1984 regarding your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vicodin (hydrocodone bitartrate 5 mg and acetaminophen 500 mg) Tablets.

Reference is also made to your communication dated October 23, 1984.

The supplemental applications provide for:

S-004 - labeling revision for the new tablet design shape.
S-005 - manufacturing revision for the new tablet shape.

We have completed the review of these supplemental applications and they are approved. Our letter of January 7, 1983 detailed the conditions relating to the approval of this application.

The material submitted is being retained in our files.

Sincerely yours,

/S/ 11/26/84

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

cc:
NWK-DO
HFN-230
HFN-83
TPoux/JLMeyer/CChang/mk/11/20/84
7095A

/S/ 11-21-84

APPROVAL

/S/ 11/23/84

ANDA 88-058/S-006, S-007

JUN 24 1986

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

Dear Mr. Ashworth:

Reference is made to your supplemental new drug applications submitted pursuant to Section 314.70 of the Regulations, dated December 16, 1985, regarding your abbreviated new drug application for Vicodin Tablets (5 mg Hydrocodone Bitartrate/500 mg Acetaminophen).

Reference is also made to your communication dated April 21, 1986.

The supplemental applications provide for (1) S-006: The packaging of Vicodin Tablets in 160cc white plastic bottles with ——— metal caps, and (2) S-007: The packaging of Vicodin Tablets in 625cc white plastic bottles with ——— metal caps.

We have completed the review of these supplemental applications and they are approved. Our letter of January 7, 1983 detailed the conditions relating to the approval of this abbreviated application.

The material submitted is being retained as part of your application.

Sincerely yours,

/s/ 6/24/86

Marvin Seiffe, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

cc:
HFN-237
CChang/W[illegible]ane/tr/6/20/
0840S
Approval Multiple Supplements

/s/ 10/23/86

/s/ 2-3-86

ANDA 88-058/S-008, S-009, S-011

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

MAY 11 1987

Dear Dr. Ashworth:

Reference is made to your supplemental new drug applications submitted pursuant to Section 314.70 of the Regulations, dated January 21, and November 10, 1986, regarding your abbreviated new drug application for VICODIN (Hydrocodone Bitartrate and Acetaminophen) Tablets, 5 mg/500 mg.

Reference is also made to your correspondence dated March 23, 1987.

The supplemental applications provide for (1) S-008; Packaging of Vicodin tablets in blister packages, (2) S-009; Expiration dating for the new package; and (3) S-011; Labeling for unit-dose packaging.

We have completed the review of these supplemental applications and they are approved. Our letter of January 7, 1983 detailed the conditions relating to the approval of this abbreviated application.

The material submitted is being retained as part of your application.

Sincerely yours.

/S/

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

/S/ 5-11-87

/S/ 5-8-87

cc:
HFN-237
YMille/CChang/MLarrane/tr/5/5/87
1492S
Approval Multiple Supplements

ANDA 88-058/S-012

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

MAY 11 1987

Dear Sir:

Reference is made to your supplemental new drug application submitted pursuant to Section 314.70 of the Regulations, dated February 17, 1987, regarding your abbreviated new drug application for VICODIN (Hydrocodone Bitartrate and Acetaminophen) Tablets, 5 mg/500 mg.

The supplemental application provides for revised unit dose strip carton of 25, unit dose carton for 4 x 25, dump dispenser and container labels (100s and 500s) and package insert labeling.

We have completed the review of this supplemental application and it is approved. Our letter of January 7, 1983 detailed the conditions relating to the approval of this abbreviated application.

However, at the time of next printing or within 90 days whichever comes first, revise the package insert labeling so it is in accord with our current labeling guideline for this product. The one exception to the guideline is the second paragraph in the DOSAGE AND ADMINISTRATION section which should be revised to read:

> The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total 24 hour dose should not exceed 8 tablets.

If you wish to include the dose for naloxone in the text of the insert it must be revised to reflect the dose currently reflected in the labeling of Narcan. When available submit draft copy for our review and comment. We are aware that further revision of the DOSAGE AND ADMINISTRATION may occur shortly and you should not prepare final printed labeling until requested to do so.

Furthermore, you must use the current phrasing for the [redacted] warning [redacted] Agents; Labeling in Drugs for Human Use; Warning Statement; Federal Register, Vol. 51, No. 234; December 5, 1986; pages 43900-43904]. The warning should be the first paragraph in the WARNINGS section.

[redacted]

The material submitted is being retained in our files.

Sincerely yours,

/s/

FOR 5-6-87

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

/s/ 5/7/87

cc:
HFN-238
KJohnson/YVille/t- 5/6/87
1501S
Approval
Pages 1-2

/s/ 5/7/87

/s/ 5/8/87

APPEARS THIS WAY
ON ORIGINAL

ANDA 88-058/S-013, S-014, S-015

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

FEB 29 1988

Dear Dr. Ashworth:

Reference is made to your supplemental new drug applications submitted pursuant to Section 314.70 of the Regulations, dated May 8, 1987, regarding your abbreviated new drug application for VICODIN (Hydrocodone Bitartrate and Acetaminophen) Tablets, 5 mg/500 mg.

Reference is also made to your correspondence dated December 4, 1987.

The supplemental applications provide for 1) S-013; Packaging of Vicodin tablets in a 128 fluid ounce plastic bottle (3000 tablets) with a [redacted] cap, (2) S-014; 4 month expiration dating for the new package, and (3) S-015; labeling for the new package.

We have completed the review of these supplemental applications and they are approved. However, we refer you to our letter dated January 29, 1988 in response to supplement 16 for comments concerning the need for further revision of the package insert labeling. Our letter of January 7, 1983 detailed the conditions relating to the approval of this abbreviated application.

The material submitted is being retained as part of your application.

Sincerely yours,

/S/ LOR 2-29-88

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

2/8/88

cc:
HFN-237
YMille/CChang/WMa.nane/trc/2/25/88
2134m page 18
Approval Multiple Suppl.

ANDA: 88-058/S-016

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

JUL 1 1988

Dear Dr. Ashworth:

Reference is made to your supplemental new drug application submitted pursuant to Section 314.70 of the Regulations, dated June 10, 1987 regarding your abbreviated new drug application for VICODIN (Hydrocodone Bitartrate and Acetaminophen) Tablets, 5 mg/500 mg.

Reference is also made to your communications dated August 5, 1987; September 17, 1987; May 13, 1987 and June 7, 1988 amending this supplement.

The supplemental application provides for revised package insert labeling to reflect a major revision of the text.

We have completed the review of this supplemental application and it is approved. Our letter of January 7, 1983 detailed the conditions relating to the approval of this abbreviated application.

We acknowledge your commitment to utilize insert #5828 until you introduce the 3000 tablet package size. At that time you will revise the HOW SUPPLIED section of the insert and notify the Agency of the change.

The material submitted is being retained in our files.

Sincerely yours,

/S/ for 7-1-88

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

cc:
HFD-238 /S/ 6/30/88
HFD-83 /S/ 6/30/88
YMille/TPoux/je/6-28-88
approval
7886A/pg 3

ANDA 88-058/S-017

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

JAN 19 1988

Dear Dr. Ashworth:

Reference is made to your supplemental new drug application submitted pursuant to Section 314.70 of the Regulations, dated August 21, 1987, regarding your abbreviated new drug application for VICODIN (Hydrocodone Bitartrate and Acetaminophen) Tablets, 5 mg/500 mg.

The supplemental application provides for the manufacture of Vicodin tablets in an expanded tablet production facility directly adjoining your current operations at the Whippany, New Jersey site.

We have completed the review of this supplemental application and it is approved. Our letter of January 7, 1983 detailed the conditions relating to the approval of this abbreviated application.

The material submitted is being retained as part of your application.

Sincerely yours,

/S/ for 1-19-88

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

cc:
HFN-237
/S/ 1/18/88
CChang/WMalone/trc/1/14/88
2089m page 14
Approval One Supplement

/S/ 1/19/88

ANDA 88-058/S-018, S-019

AUG 20 1992

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

Dear Sir:

Reference is made to your supplemental new drug applications dated February 1, 1989 submitted pursuant to Section 314.70 of the Regulations, regarding your abbreviated new drug application for Vicodin (Hydrocodone Bitartrate and Acetaminophen, 5 mg/500 mg) Tablets.

Reference is also made to your communications dated June 7, 1991 and ~~July 8~~ August 10, 1992 amending these supplements.

The supplemental applications provide for revised package insert labeling (S-018) and the use of ——————— without added ——— in the manufacturing process (S-019).

We have completed the review of these supplemental applications, and they are approved. Our letter of January 7, 1983 detailed the conditions relating to the approval of this abbreviated application.

The material submitted is being retained in our files.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 88-058/S-020

Knoll Pharmaceuticals
Attention: Robert W. Ashworth, Ph.D.
30 North Jefferson Road
Whippany, New Jersey 07981

SEP 10 1992

Dear Sir:

Reference is made to your supplemental new drug application dated August 18, 1992, submitted pursuant to Section 314.70(c) (Special Supplement-Changes Being Effected) of the Regulations, regarding your abbreviated new drug application for VICODIN(Hydrocodone Bitartrate and Acetaminophen Tablets), 5 mg/500 mg.

The supplemental application provides for revised unit-dose blisters.

We have completed the review of this supplemental application and it is approved. Our letter of January 7, 1983, detailed the conditions relating to the approval of this abbreviated application.

The material submitted is being retained in our files.

Sincerely yours,

Kenneth Johnson /PR

9-10-92

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc;
HFD-638
HFD-600
HFC-130/JAllen
KRoberts/JPhillips
hab 9/8/92
88058S.020
approval HFD-82
FINAL

Jerry Phillips 9/14/92

K Roberts 9-9-92

ANDA 88-058/S-021

Knoll Pharmaceutical Company
Attention: Robert W. Ashworth, Ph.D.
3000 Continental Drive-North
Mount Olive, NJ 07828-1234

FEB 15

Dear Sir:

This is in reference to your supplemental new drug application dated August 6, 1999, submitted under 505(j) of Federal Food, Drug and Cosmetic Act, regarding your abbreviated new drug application for Vicodin®.

The supplemental application provides for the addition of a testing facility located at 140 Hanover Avenue, Cedar Knolls, NJ to perform routine stability testing and to serve as an alternate release testing site.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/s/

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

ANDA 88-058/S-022

Knoll Pharmaceutical Company
Attention: Robert W. Ashworth, Ph.D.
3000 Continental Drive-North
Mount Olive, NJ 07828-1234

MAR 16 2000

Dear Sir:

This is in reference to your supplemental new drug application dated September 10, 1999, submitted under 505(j) of Federal Food, Drug and Cosmetic Act, regarding your abbreviated new drug application for Vicodin®.

The supplemental application provides for a site change for blister-packaging operations from [redacted] to Knoll Pharmaceutical located at 30 North Jefferson Road, Whippany, New Jersey.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/S/ 3/16/2000

for

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

ANDA 88-058/S-023

Knoll Pharmaceutical Company
Attention: Robert W. Ashworth, Ph.D.
3000 Continental Drive-North
Mount Olive, NJ 07828-1234

JUN 27 2000

Dear Sir:

This is in reference to your supplemental new drug application dated March 6, 2000, submitted under 505(j) of Federal Food, Drug and Cosmetic Act, regarding your abbreviated new drug application for Vicodin®.

The supplemental application provides for an alternate

We have completed the review of this supplemental application and it is approved. Please note, however, that you are requested to file a copy of the executed batch record for the first production lot and the final product certificate of analysis in the annual report. We acknowledge your commitment to place the first three production batches on stability.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/S/

6/27/00

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

ANDA 88-058/S-024

Knoll Pharmaceutical Company
Attention: Deborah A. Panei
3000 Continental Drive North
Mt. Olive NJ 07828

APR 2 2001

Dear Madam:

This is in reference to your supplemental new drug application dated October 12, 2000, submitted under 505(j) of Federal Food, Drug and Cosmetic Act, regarding your abbreviated new drug application for Vicodin® (hydrocodone bitartrate and acetaminophen tablets USP, 5 mg/500 mg).

This supplemental application, submitted as "Changes Being Effected in 30 days", provides for the following change:

> A new analytical monograph which combines previously used procedures for release and stability testing into a single procedure. In addition, the [redacted] test has been deleted.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

/S/ 4/2/01

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

**88-058/S-001;S-002;S-003;
S-004;S-005;S-006;S-007;
S-008; S-009;S-011;S-012;
S-013;S-014;S-015;S-016;
S-017;S-018;S-019;S-020;
S-021;S-022;S-023;S-024**

FINAL PRINTED LABELING(S)

S-018
S-019 1

5830

VICODIN® TABLETS

knoll®
BASF Group

APPROVAL

8/20/1992

DESCRIPTION:

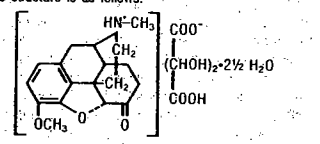
Each VICODIN® tablet contains:

Hydrocodone Bitartrate (**WARNING:** May be habit forming.)	5 mg
Acetaminophen	500 mg

Other ingredients include colloidal silicon dioxide, corn starch, croscarmellose sodium Type A, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose, povidone, and stearic acid.

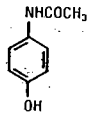
Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is: 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5).

Its structure is as follows:



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

Acetaminophen, 4'-hydroxyacetanilide, 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 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.

Radioimmunoassay 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 peripheral and central influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalmic 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:

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respirator-

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:

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 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 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 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 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 of 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 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. Chlorpromazine 0.7 to 1.0 mg/kg q6h, and paregoric 2 to 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 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 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 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 af-

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 1.0 mg/kg q6h, and paregoric 2 to 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 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 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 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 Tablets are subject to the Federal Controlled Substance Act (Schedule III).

Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, VICODIN Tablets should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when VICODIN 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 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 or two tablets every four to six hours as needed for pain. The total 24 hour dose should not exceed 8 tablets.

HOW SUPPLIED:

White, capsule shaped tablet bisected on one side and imprinted with "VICODIN" on the other side.

Bottles of 100—NDC #0044-0727-02.

Bottles of 500—NDC #0044-0727-03.

Hospital Unit Dose Package—100 tablets (4x25 tablets)—NDC #0044-0727-41.

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 CII Narcotic.

MR 1987/5809
RE-3/Vic5830/2-9-88
Revised February, 1988 5830

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

BASF Group

knoll®

APPROVED

NOV 26 1984

25 Tablets

NEW TABLET DESIGN
Same Formulation

NDC 0044-0727-91

vicodin®

See back panel for pouch opening instructions.

Each tablet co
hydrocodon mg.
(Warning be habit forming.)
acetam
Usual do package insert.
Store c temperature
(59°-8 5°-30°
Cautio ederal law prohibits
dispens with
iption.

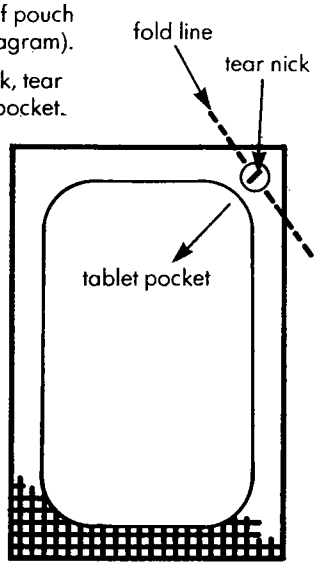
C III

5721

KNOLL PHARMACEUTICAL COMPANY
30 NORTH JEF PANY, NEW JERSEY 07981

Directions for opening enclosed child-resistant foil pouches:

1. Fold back corner of pouch at tear nick (see diagram).
2. Starting at tear nick, tear foil toward tablet pocket.



100 TABLETS NDC 0044-0727-41

vicodin®

Each tablet contains: hydrocodone bitartrate 5 mg. **(Warning:** May be habit forming.**)** acetaminophen 500 mg.

Usual adult dose: See package insert.

Storage: 59°-86°F. 15°-30°C.

Caution: Federal law prohibits dispensing without prescription.

KNOLL PHARMACEUTICAL COMPANY
30 NORTH JEFFERSON ROAD, WHIPPANY, NEW JERSEY 07981

100 TABLETS NDC 0044-0727-41

vicodin®

Each tablet contains: hydrocodone bitartrate 5 mg. **(Warning:** May be habit forming.**)** acetaminophen 500 mg.

Usual adult dose: See package insert.

Storage: 59°-86°F. 15°-30°C.

Caution: Federal law prohibits dispensing without prescription.

KNOLL PHARMACEUTICAL COMPANY
30 NORTH JEFFERSON ROAD, WHIPPANY, NEW JERSEY 07981

5719

Usual adult dose: See package insert.
Storage: 59°-86°F, 15°-30°C.
Caution: Keep out of reach of children.
This package is not child resistant.

KNOLL PHARMACEUTICAL COMPANY
30 NORTH JEFFERSON ROAD, WHIPPANY, NEW JERSEY 07981

100 TABLETS NDC 0044-0727-41

NEW TABLET DESIGN
Same Formulation

vicodin®

Each tablet contains: hydrocodone bitartrate 5 mg.
(Warning: May be habit forming.) acetaminophen 500 mg.
Usual adult dose: See package insert.
Storage: 59°-86°F. 15°-30°C.
Caution: Federal law prohibits dispensing without prescription.

knoll® **KNOLL PHARMACEUTICAL COMPANY**
30 NORTH JEFFERSON ROAD, WHIPPANY, NEW JERSEY 07981

5719

APPROVED
NOV 26 1984

vicodin®

100 TABLETS NDC 0044-0727-41

vicodin®

Each tablet contains: hydrocodone bitartrate 5 mg. **(Warning:** May be habit forming.) acetaminophen 500 mg.
Usual adult dose: See package insert.
Storage: 59°-86°F. 15°-30°C.
Caution: Federal law prohibits dispensing without prescription.

knoll® **KNOLL PHARMACEUTICAL COMPANY**
30 NORTH JEFFERSON ROAD, WHIPPANY, NEW JERSEY 07981

Usual adult dose: See package insert.
Storage: 59°-86°F, 15°-30°C.
Caution: Keep out of reach of children.
This package is not child resistant.

KNOLL PHARMACEUTICAL COMPANY
30 NORTH JEFFERSON ROAD, WHIPPANY, NEW JERSEY 07981

NEW TABLET DESIGN
Same Formulation

vicodin® C III

Usual adult dose: See package insert.
Storage: 59°-86°F, 15°-30°C.
Caution: Keep out of reach of children.
This package is not child resistant.

KNOLL PHARMACEUTICAL COMPANY
30 NORTH JEFFERSON ROAD, WHIPPANY, NEW JERSEY 07981

APPROVED

NOV 26 1984

KNOLL PHARMACEUTICAL COMPANY
WHIPPANY, N. J.

100 TABLETS **NEW TABLET DESIGN** **NDC** 0044-0727-02
Same Formulation

vicodin® C III

Each tablet contains:
hydrocodone bitartrate 5 mg.
(Warning: May be habit forming.)
acetaminophen 500 mg.
5718

Usual adult dose: See package insert.
Caution: Federal law prohibits dispensing without prescription.
Storage: 59°-86°F, 15°-30°C.
Dispense in tight, light-resistant container as defined in USP.

knoll **KNOLL PHARMACEUTICAL COMPANY**
30 NORTH JEFFERSON ROAD, WHIPPANY, NEW JERSEY 07981

[redacted]

NOV 26 19[illegible]

100 TABLETS **NEW TABLET DESIGN** **NDC** 0044-0727-02
Same Formulation

vicodin® C III

Each tablet contains:
hydrocodone bitartrate 5 mg.
(Warning: May be habit forming.)
acetaminophen 500 mg.
5718

Usual adult dose: See package insert.
Caution: Federal law prohibits dispensing without prescription.
Storage: 59°-86°F, 15°-30°C.
Dispense in tight, light-resistant container as defined in USP.

knoll **KNOLL PHARMACEUTICAL COMPANY**
30 NORTH JEFFERSON ROAD, WHIPPANY, NEW JERSEY 07981

[redacted]

NOV [illegible]

100 TABLETS **NEW TABLET DESIGN** **NDC** 0044-0727-02
Same Formulation

vicodin® C III

Each tablet contains:
hydrocodone bitartrate 5 mg.
(Warning: May be habit forming.)
acetaminophen 500 mg.
5718

Usual adult dose: See package insert.
Caution: Federal law prohibits dispensing without prescription.
Storage: 59°-86°F, 15°-30°C.
Dispense in tight, light-resistant container as defined in USP.

knoll **KNOLL PHARMACEUTICAL COMPANY**
30 NORTH JEFFERSON ROAD, WHIPPANY, NEW JERSEY 07981

[redacted]

NOV 26 [illegible]

vicodin® tablets C III

Hydrocodone bitartrate 5 mg (**Warning:** May be habit forming) and acetaminophen 500 mg

DIRECTIONS:

1. **START WITH UNIT #25 AND WORK SEQUENTIALLY BACKWARDS TO #1.**
2. **FOR DISPENSING: TEAR OFF BLISTER AT PERFORATIONS. TO REMOVE TABLET PRESS BLISTER SIDE OF UNIT**

APPROVED
MAY 11 1987

5783B

Knoll	1	Knoll	2	Knoll	3	Knoll	4	Knoll	5
Knoll	6	Knoll	7	Knoll	8	Knoll	9	Knoll	10
Knoll	11	Knoll	12	Knoll	13	Knoll	14	Knoll	15
Knoll	16	Knoll	17	Knoll	18	Knoll	19	Knoll	20
Knoll	21	Knoll	22	Knoll	23	Knoll	24	Knoll	25

vicodin® tablets CIII

Hydrocodone bitartrate 5 mg (**Warning:** May be habit forming) and acetaminophen 500 mg

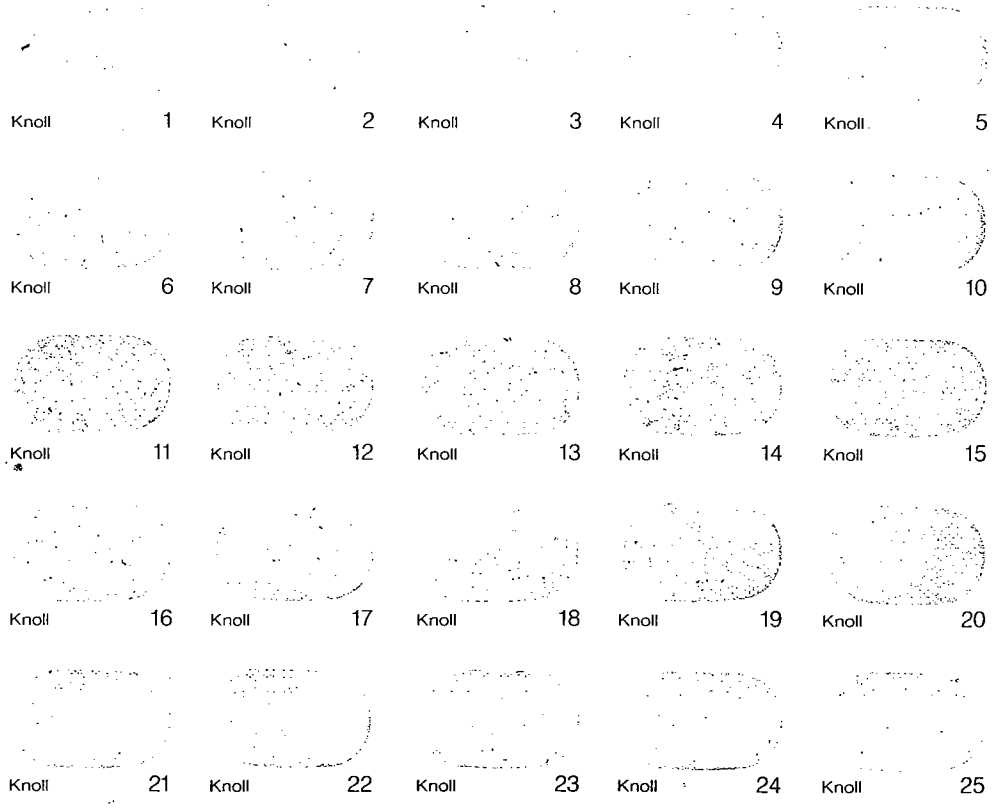
DIRECTIONS:

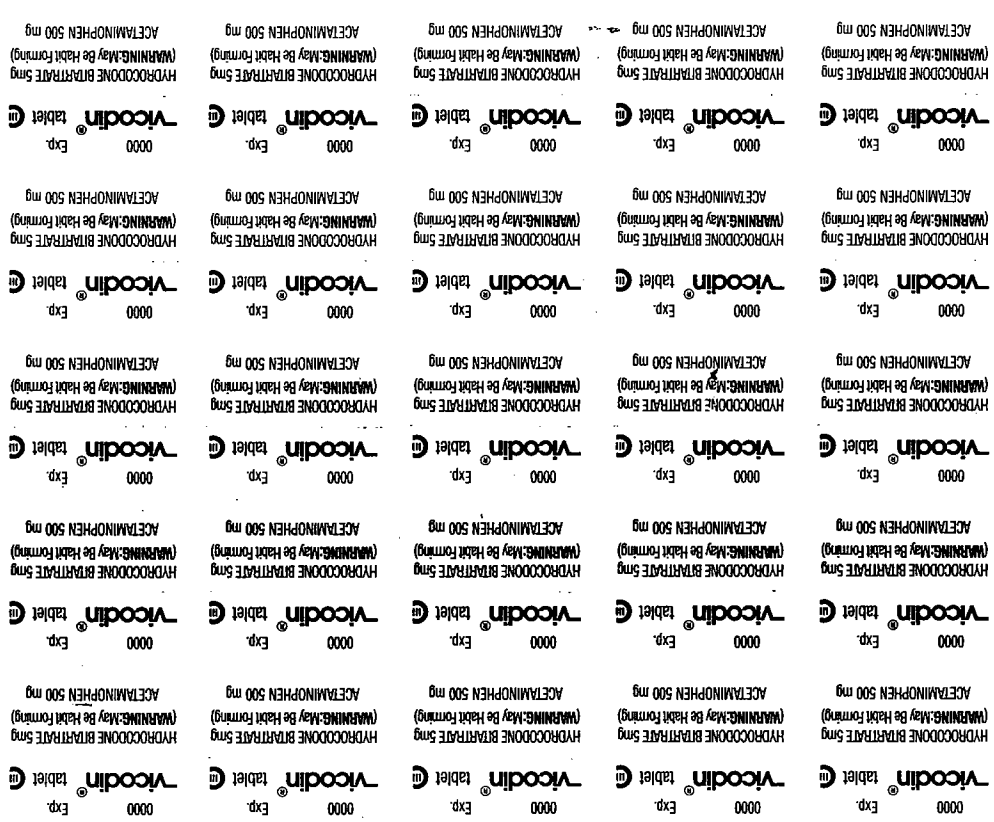
1. **START WITH UNIT #25 AND WORK SEQUENTIALLY BACKWARDS TO #1.**
2. **FOR DISPENSING: TEAR OFF BLISTER AT PERFORATIONS. TO REMOVE TABLET PRESS BLISTER SIDE OF UNIT**

APPROVED

MAY 11 1987

5783B





25 Tablets

NDC 0044-0727-01

vicodin® CIII

Each tablet contains:

hydrocodone bitartrate	5 mg
(Warning: May be habit forming.)	
acetaminophen	500 mg

Usual adult dose: See package insert.
Caution: Federal law prohibits dispensing without prescription.
Storage: 59°-86°F, (15°-30°C).

This package is not child-resistant.

Knoll Pharmaceuticals
A Unit of BASF K&F Corporation
30 North Jefferson Road
Whippany, N.J. 07981

BASF Group

5783A

100 Tablets

100 Tablets
(4-25 Tablet Blister Cards)

NDC 0044-0727-41

vicodin®

C III

vicodin®

knoll®

BASF Group

Each tablet contains:

hydrocodone bitartrate (**Warning:** May be habit forming.)	5 mg
acetaminophen	500 mg

Usual adult dose: See package insert.
Caution: Federal law prohibits dispensing without prescription.
Storage: 59°-86°F, (15°-30°C).

This package is not child-resistant.

knoll®

Knoll Pharmaceuticals
A Unit of BASF K&F Corporation
Whippany, New Jersey 07981

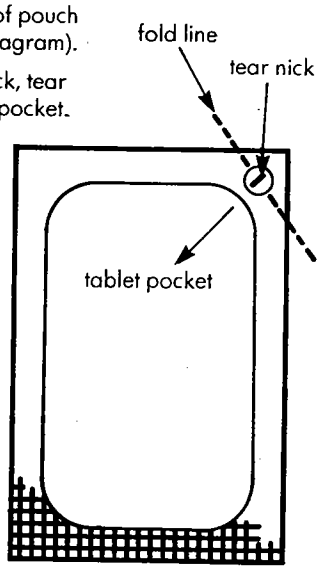
BASF Group

5784

H414

Directions for opening enclosed child-resistant foil pouches:

1. Fold back corner of pouch at tear nick (see diagram).
2. Starting at tear nick, tear foil toward tablet pocket.



APPROVED

11 87

25 Tablets

NDC 0044-0727-91

vicodin®

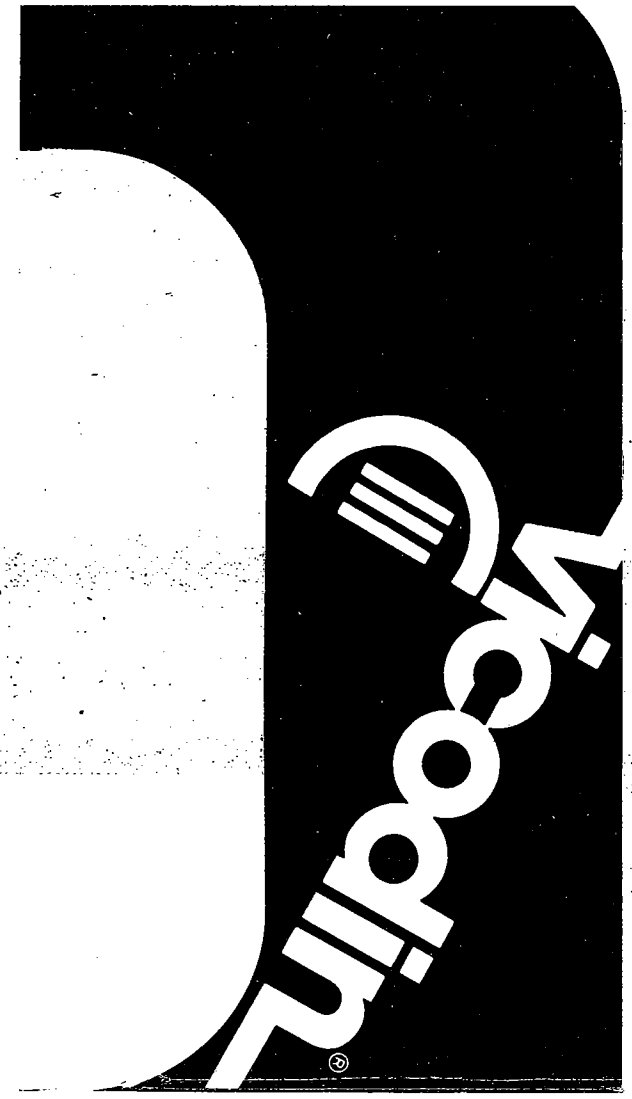
See back panel for pouch opening instructions.

Each tablet contains:
hydrocodone bitartrate 5 mg
(**Warning:** May be habit forming.)
acetaminophen 500 mg
Usual adult dose: See package insert.
Store at controlled room temperature
(59°-86°F, 15°-30°C).
Caution: Federal law prohibits
dispensing without prescription.

5765

knoll®

Knoll Pharmaceuticals
A Unit of BASF K&F Corporation
Whippany, New Jersey 07981



100 TABLETS NDC 0044-0727-41

vicodin®

Each tablet contains: hydrocodone bitartrate 5 mg. **(Warning:** May be habit forming.) acetaminophen 500 mg.

Usual adult dose: See package insert.

Storage: 59°-86°F (15°-30°C).

Caution: Federal law prohibits dispensing without prescription.

Knoll Pharmaceuticals
A Unit of BASF K&F Corporation
Whippany, New Jersey 07981

APPROVED
MAY 11 1987

Vicodin®

Each tablet contains:
hydrocodone bitartrate 5 mg.
(Warning: May be habit forming.)
acetaminophen 500 mg.
Usual adult dose: See package insert.
Storage: 59°-86°F (15°-30°C).
Caution: Federal law prohibits dispensing without prescription.

5767

Knoll Pharmaceuticals
A Unit of BASF K&F Corporation
Whippany, New Jersey 07981

NDC 0044-0727-03 500 Tablets

Vicodin®

Each tablet contains:
5 mg hydrocodone bitartrate
(**Warning:** May be habit forming.)
500 mg acetaminophen

Usual adult dose: See package insert.

Caution: Federal law prohibits dispensing without prescription.

Storage: 59°-86°F (15°-30°C).
Dispense in tight, light-resistant container as defined in USP.

C-III

5778

MAY 11 19

Knoll Pharmaceuticals
A Unit of BASF K&F Corporation
Whippany, New Jersey 07981

NDC 0044-0727-02 100 Tablets

vicodin®

Each tablet contains:
5 mg hydrocodone bitartrate
(Warning: May be habit forming.)
500 mg acetaminophen

Usual dosage: See package insert.

Caution: Federal law prohibits dispensing without prescription.

Storage: 59°-86°F (15°-30°C).
Dispense in tight, light-resistant container as defined in USP.

5777

Knoll Pharmaceuticals
A Unit of BASF K&F Corporation
Whippany, New Jersey 07981

MAY 11 1987

3000 Tablets

NDC 0044-0727-06

vicodin® III

Each tablet contains:

Hydrocodone bitartrate (**Warning:** May be habit forming)	5 mg
Acetaminophen	500 mg

Usual adult dosage: See package insert.

Caution: Federal law prohibits dispensing without a prescription.

Storage: Store at controlled room temperature 15°-30°C (59°-86°F).
Dispense in a tight, light-resistant container as defined in the USP.

5801

Knoll Pharmaceuticals
A Unit of BASF K&F Corporation
Whippany, New Jersey 07981

BASF Group

3000 Tablets

NDC 0044-0727-06

vicodin® III

Each tablet contains:

Hydrocodone bitartrate (**Warning:** May be habit forming)	5 mg
Acetaminophen	500 mg

Usual adult dosage: See package insert.

Caution: Federal law prohibits dispensing without a prescription.

Storage: Store at controlled room temperature 15°-30°C (59°-86°F).
Dispense in a tight, light-resistant container as defined in the USP.

5801

Knoll Pharmaceuticals
A Unit of BASF K&F Corporation
Whippany, New Jersey 07981

BASF Group

APPROVED
FEB 29 1988

3000 Tablets

NDC 0044-0727-06

vicodin® III

Each tablet contains:

Hydrocodone bitartrate (**Warning:** May be habit forming)	5 mg
Acetaminophen	500 mg

Usual adult dosage: See package insert.

Caution: Federal law prohibits dispensing without a prescription.

Storage: Store at controlled room temperature 15°-30°C (59°-86°F).
Dispense in a tight, light-resistant container as defined in the USP.

5801

Knoll Pharmaceuticals
A Unit of BASF K&F Corporation
Whippany, New Jersey 07981

BASF Group

APPROVED
FEB 29 1988

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

88-058/S-001;S-002;S-003; S-004;S-005;S-006;S-007;S-008; S-009;S-011;S-012;S-013;S-014; S-015;S-016;S-017;S-018;S-019; S-020;S-021;S-022;S-023;S-024

CHEMISTRY REVIEW(S)

CHEMIST's REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT	Statement Date: DESI 7289	NDA NUMBER: 88-058/S-001,S-002

NAME AND ADDRESS OF APPLICANT

Knoll Pharmaceutical Company - Whippany, NJ 07981

ORIGINAL
AMENDMENT
SUPPLEMENT
RESUBMISSION
CORRESPONDENCE
REPORT
OTHER

PURPOSE OF AMENDMENT/SUPPLEMENT

Control revision & exp. date

DATE(s) of SUBMISSION:
as per letter

PHARMACOLOGICAL CATEGORY	NAME OF DRUG	HOW DISPENSED
analgesic & antitussive	Hydrocodone Bitartrate & APAP	RX XX OTC
DOSAGE FORM(S)	POTENCY(IES)	RELATED IND/NDA/DMF
tablet	5 mg & 500 mg	88-058
STERILIZATION	SAMPLES	

LABELING

1. Satisfactory per KJ
2. "New formula" sticker not needed per Mr. Knapp's memo

BIOLOGIC AVAILABILITY

NA

ESTABLISHMENT INSPECTION

not on alert list

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

PACKAGING

Satisfactory, amber glass

STABILITY

Protocol: Satisfactory

REMARKS AND CONCLUSION: Review W/F

Note: (a)
(b) DMF

C. Chang /S/ 3-30-84

CHEMIST's REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT	Statement Date: DESI 7289	NDA NUMBER: 88-058/S-001,S-002

NAME AND ADDRESS OF APPLICANT

Knoll Pharmaceutical Company - Whippany, NJ 07981

ORIGINAL
AMENDMENT
SUPPLEMENT
RESUBMISSION
CORRESPONDENCE
REPORT
OTHER

PURPOSE OF AMENDMENT/SUPPLEMENT

Control revision & exp. date

DATE(s) of SUBMISSION

as per letter

PHARMACOLOGICAL CATEGORY	NAME OF DRUG	HOW DISPENSED
analgesic & antitussive	Hydrocodone Bitartrate & APAP	RX XX OTC
DOSAGE FORM(S)	POTENCY(IES)	RELATED IND/NDA/DMF
tablet	5 mg & 500 mg	88-058
STERILIZATION	SAMPLES	

LABELING

1. Satisfactory per KJ
2. "New formula" sticker not needed per Mr. Knapp's memo

BIOLOGIC AVAILABILITY

NA

ESTABLISHMENT INSPECTION

not on alert list

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

PACKAGING

Satisfactory, amber glass

STABILITY

Protocol: Satisfactory

REMARKS AND CONCLUSION: Review W/F

Note: (a)
(b) DMF

C. Chang 12-29-83

ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

SUPPLEMENT DATE:

NDA NUMBER: 88-058/S-001, S-002, S-003

DESI 7289

NAME AND ADDRESS OF APPLICANT

[illegible]11 Pharmaceutical Company
Whippany, NJ 07981

ORIGINAL
AMENDMENT
SUPPLEMENT
RESUBMISSION
CORRESPONDENCE
REPORT
OTHER

PURPOSE OF AMENDMENT

Control revision

DATE(S) OF SUBMISSION(S)

As per letter

PHARMACOLOGICAL CATEGORY	NAME OF DRUG	HOW DISPENSED
Analgesic & antitussive	Hydrocodone Bitartrate & APAP	RX X OTC
DOSAGE FORM(S)	POTENCY(IES)	RELATED IND/NDA/DMF
Tablet	5 mg & 500 mg	88-058
STERILIZATION	SAMPLES	

LABELING

1. Satisfactory per K. Johnson.
2. "New formula" sticker not needed per Mr. Knapp's memo.

BIOLOGIC AVAILABILITY

N/A

ESTABLISHMENT INSPECTION

Not on "Alert" list

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

PACKAGING

Satisfactory, amber glass.

STABILITY

Protocol: Satisfactory.

REMARKS AND CONCLUSIONS: Review W/F

Note: (a)
(b) DMF

C. Chang /S/ - 7-2-84

ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

DESI 7289

88-058/S-001, S-002

NAME AND ADDRESS OF APPLICANT

Knoll Pharmaceutical Company - Whippany, NJ 07981

ORIGINAL
AMENDMENT
SUPPLEMENT
RESUBMISSION
CORRESPONDENCE
REPORT
OTHER

PURPOSE OF AMENDMENT/SUPPLEMENT

Control revision & exp. date

DATE(s) of SUBMISSIC

PHARMACOLOGICAL CATEGORY	NAME OF DRUG	RX-OTC DISPENSED
analgesic & antitussive	**Hydrocodone & Bitartrate & APAP**	as per letter RX ____ OTC ____ XX
DOSAGE FORM(S)	POTENCY(IES)	RELATED IND/NDA/DMF
tablet	**5 mg & 500 mg**	
STERILIZATION	SAMPLES	
		88-058

LABELING

1. Satisfactory per KJ

BIOLOGICAL EVALUATION

New formula - sticker not needed per Mr. Knapp's memo

ESTABLISHMENT INSPECTION

NA

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

not be certified

PACKAGING

Satisfactory, amber glass

STABILITY

Protocol:

Exp. Date: **Satisfactory**

REMARKS AND CONCLUSION:

Charles Change

Note: (a)

(b) DMF #

/S/ 6-6-83

CHEMIST'S REVIEW FOR
ABBREVIATED NEW DRUG APPLICATION
OR SUPPLEMENT

STATEMENT DATE:

DESI 7289

NDA NUMBER:

85-058/S-001, S-002
S-003, S-004, S-005

NAME AND ADDRESS OF APPLICANT

Knoll Pharmaceutical Company
Lippany, NJ 07981

ORIGINAL
AMENDMENT
SUPPLEMENT
RESUBMISSION
CORRESPONDENCE
REPORT
OTHER

PURPOSE OF AMENDMENT

Manuf. & Labeling revisions (S-004, S-005)

Control revision & ~~~ procedures (S-001, S-002, S-003)

DATE(S) OF SUBMIS:

PHARMACOLOGICAL CATEGORY	NAME OF DRUG	HOW DISPENSED
Analgesic & antitussive	Hydrocodone Bitartrate & APAP	RX X OTC
DOSAGE FORM(S)	POTENCY(IES)	RELATED IND/NDA/DI
Tablet	5 mg & 500 mg	88-058
STERILIZATION	SAMPLES	

LABELING

1. Satisfactory per T.Poux
2. "New formula" sticker not needed per Mr. Knapp's memo.

BIOLOGIC AVAILABILITY

N/A

ESTABLISHMENT INSPECTION

Not on "Alert" list

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

PACKAGING

Satisfactory, amber glass. Black metal cap.

STABILITY

REMARKS AND
CONCLUSIONS: Note: (a)
(b) DMF #

APPROVALS

C. Chang

/S/ 11-21-84

ABBR[illegible]ATED NEW DRUG APPLICATION OR SUPPLEMENT

STATEMENT DATE:

DESI 7289

NDA NUMBER:

85-058/S-001, S-002
S-003, S-004, S-005

NAME AND ADDRESS OF APPLICANT

Knoll Pharmaceutical Company
ippany, NJ 07981

ORIGINAL
AMENDMENT
SUPPLEMENT
RESUBMISSION
CORRESPONDENCE
REPORT
OTHER

PURPOSE OF AMENDMENT

Manuf. & Labeling revisions (S-004, S-005)

Control revision & [illegible] procedures (S-001, S-002, S-003)

DATE(S) OF SUBMISS:

PHARMACOLOGICAL CATEGORY	NAME OF DRUG	HOW DISPENSED
Analgesic & antitussive	Hydrocodone Bitartrate & APAP	RX X OTC
DOSAGE FORM(S)	POTENCY(IES)	RELATED IND/NDA/DMF
Tablet	5 mg & 500 mg	88-058
STERILIZATION	SAMPLES	

LABELING

1. Satisfactory per T.Poux
2. "New formula" sticker not needed per Mr. Knapp's memo.

BIOLOGIC AVAILABILITY

N/A

ESTABLISHMENT INSPECTION

Not on "Alert" list

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

PACKAGING

Satisfactory, amber glass. Black metal cap.

STABILITY

Protocol: Satisfactory

REMARKS AND
CONC[illegible]IONS: Note: (a)
(b) DMF

APPROVALS

C. Chang [signature] 12-21-84

CHEMIST'S REVIEW NDA 88-058/S-006, S-007

3. NAME AND ADDRESS OF APPLICANT

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

6. NAME OF DRUG

Hydrocodone Bitartrate and Acetaminophen

8. SUPPLEMENT(s) PROVIDE(s) FOR:

S-006: Provides for the packaging of 100 Vicodin Tablets in 160 cc white plastic ——— bottles with a ——— metal cap.

S-007: Provides for the packaging of 500 Vicodin Tablets in 625 cc white plastic ——— bottles with a ——— metal cap.

10. PHARMACOLOGICAL CATEGORY

Analgesic and Antitussive

11. HOW DISPENSED

Rx

13. DOSAGE FORM(s)

Tablet

14. POTENCY

5 mg and 500 mg

17. COMMENTS

[redacted]

18. CONCLUSIONS AND RECOMMENDATIONS

Review w/f

19. REVIEWER:

Bill Marnane /S/

DATE COMPLETED:

2/4/96

CHEMIST'S REVIEW ANDA 88-058

3. NAME AND ADDRESS OF APPLICANT

Knoll Pharmaceutical Company
30 North Jefferson Road
Whippany, NJ 07981

6. NAME OF DRUG

Vicodin

7. NONPROPRIETARY NAME

Hydrocodone Bitartrate/Acetaminophen

8. SUPPLEMENT(s) PROVIDE(s) FOR:

S-008: Provides for the packaging of Vicodin Tablets in blister packages; S-009: Requests an expiration date for the new package; S-011: labeling for new packaging.

10. PHARMACOLOGICAL CATEGORY

Analgesic/Antitussive

11. HOW DISPENSED

Rx

13. DOSAGE FORM(s)

Tablet

14. POTENCY

5 mg/500 mg

15. CHEMICAL NAME AND STRUCTURE

See USP

17. COMMENTS

See History in our November 4, 1986 correspondence.

18. CONCLUSIONS AND RECOMMENDATIONS

Approval

19. REVIEWER:

Bill Marnane

DATE COMPLETED:

5/1/87

27. PACKAGING AND LABELING

[redacted]

eet

29. STABILITY

3. NAME AND ADDRESS OF APPLICANT

Knoll Pharmaceutical Company
Attention: Robert W. Ashworth
30 North Jefferson Road
Whippany, N.J. 07981

6. NAME OF DRUG

Vicodin

7. NONPROPRIETARY NAME

Hydrocodone Bitartrate/Acetaminophen

8. SUPPLEMENT(s) PROVIDE(s) FOR:

S-008: Provides for the packaging of Vicodin Tablets in blister packages.

S-009: Requests an expiration date for the new package form.

9. AMENDMENTS AND OTHER DATES:

Firm

Supplements: 006, 007, 12/16/85 providing for packaging Vicodin in bottles (160 and 625cc)
Supplements: 008, 009, 1/21/86 provided for new blister package and 2 year expiration date.
Report 07 requesting 3 year expiration-OK.
9/15/86 amendment for S-008 and S-009

FDA

2/5/86-Replied to supplements: 006, 007 (Not Approvable)
3/17/86-Replied to supplements: 008, 009 (Not Approvable)
10/28/86-Replied to supplements: 008, 009 (Not Approvable)

10. PHARMACOLOGICAL CATEGORY

Analgesic and Antitussive

11. HOW DISPENSED

Rx

13. DOSAGE FORM(s)

Tablet

14. POTENCY

5 mg and 500 mg

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approvable

19. REVIEWER:

Bill Marnane

DATE COMPLETED:

11/3/86

Redacted 1

pages of trade secret and/or confidential commercial information

CHEMIST'S REVIEW NDA 88-058/S-008, S-009

3. NAME AND ADDRESS OF APPLICANT

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

6. NAME OF DRUG

Vicodin

7. NONPROPRIETARY NAME

Hydrocodone Bitartrate/Acetaminophen

8. SUPPLEMENT(s) PROVIDE(s) FOR:

S-008: Provides for the packaging of Vicodin Tablets in blister packages.

S-009: Requests an expiration date for the new package form.

9. AMENDMENTS AND OTHER DATES:

Firm

Supplements: 006, 007, 12/16/85 providing for packaging Vicodin in [redacted] bottles (160 and 625cc)
Supplements: 008, 009, 1/21/86 provided for new blister package and 2 year expiration date.
Report 07 requesting 3 year expiration-OK.

FDA

2/5/86-Replied to supplements: 006, 007 (Not Approvable)
3/17/86-Replied to supplements: 008, 009 (Not Approvable)

10. PHARMACOLOGICAL CATEGORY

Analgesic and Antitussive

11. HOW DISPENSED

Rx

13. DOSAGE FORM(s)

Tablet

14. POTENCY

5 mg and 500 mg

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approvable

19. REVIEWER:

Bill Marnan

DATE COMPLETED:

3/17/86

cmc

Redacted _____1____

pages of trade secret and/or confidential commercial information

3. NAME AND ADDRESS OF APPLICANT

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

6. NAME OF DRUG

Vicodin

7. NONPROPRIETARY NAME

Hydrocodone Bitartrate and Acetaminophen

8. SUPPLEMENT(s) PROVIDE(s) FOR:

S-013: New 128 oz. (3000 tablet) package
S-014: 24 month expiration date for S-013
S-015: Labelig for S-013

10. PHARMACOLOGICAL CATEGORY

Analgesic/Antitussive

11. HOW DISPENSED

Rx

13. DOSAGE FORM(s)

Tablets

14. POTENCY

5 mg/500 mg

18. CONCLUSIONS AND RECOMMENDATIONS

Review w/f

19. REVIEWER:

William Marnane

/S/

DATE COMPLETED:

8/10/82

APPEARS THIS WAY
ON ORIGINAL

3. NAME AND ADDRESS OF APPLICANT

Knoll Pharmaceutical Company
30 North Jefferson Road
Whippany, NJ 07981

6. NAME OF DRUG

Vicodin

7. NONPROPRIETARY NAME

Hydrocodone Bitartrate and Acetaminophen

8. SUPPLEMENT(s) PROVIDE(s) FOR:

S-017: Manufacture of Vicodin tablets in an

10. PHARMACOLOGICAL CATEGORY

Analgesic/Antitussive

11. HOW DISPENSED

Rx

13. DOSAGE FORM(s)

Tablet

14. POTENCY

5 mg/500 mg

17. COMMENTS

EER is acceptable

18. CONCLUSIONS AND RECOMMENDATIONS

Approval

19. REVIEWER:

Bill Marnane

2089m

DATE COMPLETED:

11/15/88

APPEARS THIS WAY
ON ORIGINAL

CHEMISTRY REVIEW FOR ANDA OR SUPPLEMENT

rev #1

ANDA 88-058/S-018, S-019

NAME AND ADDRESS OF APPLICANT:
Knoll Pharmaceuticals
30 North Jefferson Road
Whippany, NJ 07981

PURPOSE OF AMENDMENT/SUPPLEMENT
Revision of package insert - deleting [redacted] (S-018)
Firm will use only [redacted] in manuf. of subject product. (S-019)

DATE(S) OF SUBMISSION(S)
2/1/89
10/20/89

PHARMACOLOGICAL CATEGORY	TRADE NAME	
analgesic/antitussive	Vicodin	
DOSAGE FORM	**POTENCY**	**RX OR OTC**
Tablet	5 mg hydrocodone bitartrate/ 500 mg acetaminophen	Rx

SAMPLES

RELATED IND/NDA/DMF
DMF - [redacted] (September 1989 update)
DMF - [redacted] (equipment description for plant located in [redacted])

LABELING
Insert revision - satisfactory - Review dated 1/4/90 Y. Mille (S-018)

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS
Change: Component [redacted] does not contain [redacted]

PACKAGING
Containers as described in package insert: Plastic bottles - 100's, 500's hospital unit dose package - 100 (4 X 25 tablets).

STABILITY
Lot #H48-150 tested for assay and dissolution. Stored at:

1. RT, tested at 0, 3, 6, 9, 12, months.
2. 37°C/75% RH, tested at 1, 3, months
3. 45°C, tested at 2 months.

Data are satisfactory, however insufficient. Product should also be tested for appearance, friability, hardness, color and moisture . DAta must be submitted for studies on both bottle sizes (100's, 500's) and unit dose blister packaged samples. 24 month expiry date is requested for product packaged in bottle, and 18 month expiry date for product packed in unit dose blisters (same as approved product). Firm commits to put the first three commerical lots into stability program.

REMARKS AND CONCLUSION

S-019 is Not Approvable at this time.

1. Stability data are insufficient.

   a) Additional test should be performed at each test station.

   b) All 3 package sizes(100's, 500's, blister packs) should be put on studies.

2. DMF — is deficient.

/S/ 1/19/90

Shirley S. Brown 1/11/90
R/D Init. by RMPatel 1/12/90
jth: 1/18/90 0485j

1/22/90

APPEARS THIS WAY
ON ORIGINAL

Review FT 1/18/90

Review #2

ANDA

88-058/S-018, S-019

NAME AND ADDRESS OF APPLICANT:

Knoll Pharmaceuticals
30 North Jefferson Road
Whippany, NJ 07981

PURPOSE OF SUPPLEMENT

S-018 Revision of package insert, deleting ——— warning
S-019 Manufacture of drug product using only ———

DATES OF SUBMISSIONS

2-1-89	original submission
10-20-89	amendment
2-1-90	correspondence
2-8-90	amendment
9-17-90	amendment

PHARMACOLOGICAL CATEGORY	TRADE NAME	NONPROPRIETARY NAME
analgesic/ antitussive	Vicodin	hydrocodone bitartrate/ acetaminophen

DOSAGE FORM	POTENCY	RX OR OTC
tablet	5mg/ 500mg	Rx

RELATED DMFs

6999 - equipment description for plant located in ——— manufacturing

3142 - updated 9/6/90 remains deficient

LABELING

Satisfactory as of 10-20-89

ESTABLISHMENT INSPECTION

pending. EER dated 1-12-90

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

Change: Applicant's use of [redacted] manufactured without [redacted]

PACKAGING

Containers as described in package insert: plastic bottles - 100s, 500s and hospital unit dose blisters-100 (4 X 25)

STABILITY

10-20-89

Lot #H48-150 (container size is not described) - tests: assay and dissolution. Stored at:

1. RT, tested at 0, 3, 6, 9, 12 months
2. 37°C/75% RH, tested at 1, 3 months
3. 45°C, tested at 2 months

2-8-90

Lot #H48-150 (100s) - tests: assay and dissolution. Stored at:

1. RT, tested at 0, 3, 6, 9, 12, 18 months
2. 37°C/75% RH, tested at 1, 3 months
3. 45°C, tested at 2 months

Lot #10762738 (unit dose blisters) - tests: description, disintegration, hardness, friability, assay and dissolution. Storage condition - RT.

Test stations are 0 and 6 months.

Lot #10760099 (500s) - tests: description, disintegration, hardness, friability, assay and dissolution. Storage condition - RT.

Test stations are 0 and 6 months.

Lot #10760109 (100s) - tests: description, disintegration, hardness, friability, assay and dissolution. Storage condition - RT.

Test stations are 0 and 6 months.

Lot #10760359 (unit dose blisters) - tests: description, hardness, friability, assay and dissolution.
Storage conditions - RT.
Test stations are 0 and 6 months.

Lot #10762718 (100s) - tests: description, disintegration, hardness, friability, assay and dissolution.
Storage condition - RT.
Test stations are 0 and 6 months.

Lot #10762728 (500s) - tests: description, disintegraton, hardness, friability, assay and dissoluton.
Storage condition - RT.
Test stations are 0 and 6 months.

REMARKS AND CONCLUSION

(1) Stability data are not sufficient to support an expiry date of 24 months in the bottled product and 18 months for the unit dose blister.

(2) DMF —— remains deficient.

(3) EER is pending. Request dated 1-12-90.

SUPPLEMENTS ARE NOT APPROVABLE AT THIS TIME.

Reviewer
Shirley S. Brown

Date Completed
3/26/91
3-8-91

cc: ANDA #88-058/S-019
Review Chemist's name: Shirley S. Brown
Supervisor's name: Bob Permisohn (acting)
cls/03/25/91/b:88-058.REV

ORIGINAL

MAY 20 1992

Chemistry Review #3

ANDA

88-058/S-018, S-019

NAME AND ADDRESS OF APPLICANT:

Knoll Pharmaceuticals
30 North Jefferson Road
Whippany, NJ 07981

PURPOSE OF SUPPLEMENT

S-018 Revision of package insert, deleting [redacted] warning
S-019 Manufacture of drug product using only [redacted]

DATES OF SUBMISSIONS

2-1-89	original submission
10-20-89	amendment
2-1-90	correspondence
2-8-90	amendment
9-17-90	amendment
*6-7-91	amendment

PHARMACOLOGICAL CATEGORY	TRADE NAME	NONPROPRIETARY NAME
analgesic/ antitussive	Vicodin	hydrocodone bitartrate/ acetaminophen

DOSAGE FORM	POTENCY	RX OR OTC
tablet	5mg/ 500mg	Rx

RELATED DMFs

6999 - equipment description for plant located in [redacted] manufacturing

3142 - manufacture of [redacted]
Satisfactory. Review dated 6/20/91 by OGD.

LABELING

Satisfactory as of 10-20-89 (K. Shah)

ESTABLISHMENT INSPECTION

Pending. EER dated 1-12-90, Re-Request 4/2/92.

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

Change: Applicant will use [redacted] which is manufactured without adding [redacted]

Satisfactory

PACKAGING

No change. Containers as described in package insert: plastic bottles - 100s, 500s and hospital unit dose blisters-100 (4 X 25)

Satisfactory

STABILITY

Lot #H48-150 (160cc plastic bottle, **100s**) - tests: assay and dissolution. Stored at:

1. RT, tested at 0, 3, 6, 9, 12 18, **24**, 36 months
2. 37°C/75% RH, tested at 1, 3 months
3. 45°C, tested at 2 months

Lot #10762738 (**unit dose blisters**) - tests: description, disintegration, hardness, friability, assay and dissolution.
Storage condition - RT.
Test stations are 0, 6, 12, **18** and 24 months.

Lot #10760099 (500s) - tests: description, disintegration, hardness, friability, assay and dissolution.
Storage condition - RT.
Test stations are 0 and 6 months.

Lot #10760109 (100s) - tests: description, disintegration, hardness, friability, assay and dissolution.
Storage condition - RT.
Test stations are 0 and 6 months.

Lot #10760359 (**unit dose blisters**) - tests: description, hardness, friability, assay and dissolution.
Storage conditions - RT.
Test stations are 0, 6, 12, **18** and 24 months.

Lot #10762718 (**100s**) - tests: description, disintegration, hardness, friability, assay and dissolution.
Storage condition - RT.
Test stations are 0, 6, 12, 18 and **24** months.

Lot #10762728 (**500s**) - tests: description, disintegration, hardness, friability, assay and dissolution.
Storage condition - RT.
Test stations are 0, 6, 12, 18 and **24** months.

Satisfactory

REMARKS AND CONCLUSION

(1) Stability data are sufficient to support an expiry date of 24 months for the bottled product and 24 months for the unit dose blister as requested by applicant.

(2) DMF ___ is acceptable.

(3) EER is pending. Request dated 1-12-90 and 4/02/92.

SUPPLEMENTS ARE APPROVABLE PENDING RECEIPT OF ACCEPTABLE EER.

7/8/92 EER - acceptable 8/5/92
psBrown 8/10/92

Reviewer
Shirley S. Brown

Date Completed
5/18/92
2/25/92

M. Smela 8/10/92
Acknowledges withdrawal of i ——— n toxicity (FAX attached) from DMF ...

Hardcopy of withdrawal rec'd by submission dated 8/10/92
MJS 8/19/92

cc: ANDA #88-058/S-019
Review Chemist's name: Shirley S. Brown
Supervisor's: MSmela/03/04/92
M Smela 5/20/92

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 88-058/S-021

3. NAME AND ADDRESS OF APPLICANT
Knoll Pharmaceutical Company
Attention: Robert W. Ashworth, Ph.D.
3000 Continental Drive-North
Mount Olive, NJ 07828-1234

6. PROPRIETARY NAME
Vicodin®

7. NONPROPRIETARY NAME
Hydrocodone bitartrate and acetaminophen

8. SUPPLEMENT(s) PROVIDE(s) FOR:
The addition of a testing facility located at 140 Hanover Avenue, Cedar Knolls, NJ to perform routine stability testing and to serve as an alternate release testing site.

9. AMENDMENTS AND OTHER DATES:
August 6, 1999

10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
N/A

13. DOSAGE FORM
Tablet

14. POTENCY
5 mg/500 mg

17. COMMENTS
Submitted as CBE supplement.

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable.

19. REVIEWER:
A.Langowski

DATE COMPLETED:
1/6/2000

Redacted 1

CMC

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1. CHEMISTRY REVIEW NO. 1

2. ANDA # 88-058/S-022

3. NAME AND ADDRESS OF APPLICANT
Knoll Pharmaceutical Company
Attention: Robert W. Ashworth, Ph.D.
3000 Continental Drive-North
Mount Olive, NJ 07828-1234

6. PROPRIETARY NAME
Vicodin®

7. NONPROPRIETARY NAME
Hydrocodone bitartrate and acetaminophen

8. SUPPLEMENT(s) PROVIDE(s) FOR:
Provides for a [redacted]

9. AMENDMENTS AND OTHER DATES:
September 10, 1999 - Original Submission

10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
N/A

13. DOSAGE FORM
Tablet

14. POTENCY
5 mg/500 mg

17. COMMENTS
Submitted as CBE supplement.

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable.

19. REVIEWER:
A.Langowski

DATE COMPLETED:
03/06/00

Redacted 1 CMC

pages of trade secret and/or confidential commercial information

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 88-058/S-023

3. NAME AND ADDRESS OF APPLICANT
Knoll Pharmaceutical Company
Attention: Robert W. Ashworth, Ph.D.
3000 Continental Drive-North
Mount Olive, NJ 07828-1234

6. PROPRIETARY NAME
Vicodin®

7. NONPROPRIETARY NAME
Hydrocodone bitartrate and acetaminophen

8. SUPPLEMENT(s) PROVIDE(s) FOR:
Provides for an alternate

9. AMENDMENTS AND OTHER DATE:
Submission date; March 6,

10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesic

Rx

12. RELATED IND/NDA/DMF(s)
N/A

13. DOSAGE FORM
Tablet

14. POTENCY
5 mg/500 mg

17. COMMENTS
Submitted as PAS expedite.

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable.

19. REVIEWER:
A.Langowski

DATE COMPLETED:
06/05/00

Redacted 3

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ANDA 88-058

NAME AND ADDRESS OF APPLICANT:
Knoll Pharmaceutical Company
Attention: Deborah A. Panei
3000 Continental Drive North
Mt. Olive NJ 07828

PURPOSE OF AMENDMENT/SUPPLEMENT
S-024 Provides for a new analytical monograph which combines individual tests previously used for release and stability testing into one procedure. In addition, the

DATE(S) OF SUBMISSION(S)
October 12, 2000

PHARMACOLOGICAL CATEGORY
Analgesic

NONPROPRIETARY NAME
Hydrocodone Bitartrate and ...ophen

DOSAGE FORM	POTENCY	RX OR OTC
Tablet	5 mg/500 mg	Rx

SAMPLES	RELATED IND/NDA/DMF	STERILIZATION
N/A	N/A	N/A

LABELING
N/A

BIOEQUIVALENCY STATUS
N/A

ESTABLISHMENT INSPECTION
N/A

APPEARS THIS WAY
ON ORIGINAL

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

PACKAGING
N/A

STABILITY
No data, but procedures have been incorporated into single monograph.

REMARKS AND CONCLUSION
Approve.

RECALLS

Reviewer
A.Langowski

ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt Yes x
No

If no, explain reason(s) below.

APPEARS THIS WAY
ON ORIGINAL

Redacted 3

CMC S-025 & S-026

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

**88-058/S-001;S-002;S-003;
S-004;S-005;S-006;S-007;S-008;
S-009;S-011;S-012;S-013;S-014;
S-015;S-016;S-017;S-018;S-019;
S-020;S-021;S-022;S-023;S-024**

ADMINISTRATIVE DOCUMENTS

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 88058/023**
Stamp: **07-MAR-2000** Regulatory Due:
Applicant: **KNOLL PHARM**
30 NORTH JEFFERSON RD
WHIPPANY, NJ 07981

Priority: Org Code: **600**
Action Goal: District Goal: **07-AUG-2000**
Brand Name: **VICODIN TABS**
Established Name: **ACETAMINOPHEN;HYDROCODONE BITARTRATE**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **500 MG/5 MG**

FDA Contacts:				
	M. ANDERSON	**(HFD-640)**	**301-827-5789**	**, Project Manager**
	A. LANGOWSKI	**(HFD-647)**	**301-827-5849**	**, Review Chemist**
	G. SMITH	**(HFD-647)**	**301-827-5849**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 27-JUN-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CRU** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **27-JUN-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 88058/022**
Stamp: **13-SEP-1999** Regulatory Due:
Applicant: **KNOLL PHARM**
30 NORTH JEFFERSON RD
WHIPPANY, NJ 07981

Priority: Org
Action Goal: Dist
Brand Name: **VICODIN TABS**
Established Name: **ACETAMINO**
E BITARTRA
Generic Name:
Dosage Form: **TAB (TABLET**
Strength: **500 MG/5 MG**

FDA Contacts: **A. LANGOWSKI (HFD-647) 301-827-5849 , Review Chemist**
G. SMITH (HFD-647) 301-827-5849 , Team Leader

Overall Recommendation:

ACCEPTABLE on 23-SEP-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment: **2211084**
KNOLL PHARMACEUTICALS
30 NORTH JEFFERSON RD
WHIPPANY, NJ 07981

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE** Responsibilities: **FINISHED DO**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **22-SEP-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING

Amendment to Supplement/FPL Container Labels, Package Insert Labeling

DATE OF REVIEW: January 27, 1988

ANDA #:88-058/S-015 CO. NAME: Knoll Pharmaceuticals

NAME OF DRUG: Trade: VICODIN
Generic: Hydrocodone Bitartrate and Acetaminophen Tablets, 5 mg/500 mg

DATE OF SUBMISSION: December 4, 1987

COMMENTS:

Container - Satisfactory in FPL for 3000s

Insert - Satisfactory
However, we refer you to our letter in response to Supplement 16 for comments concerning the need for further revision of the labeling.

RECOMMENDATIONS:

1. Inform the firm of above comments.

2. From a labeling viewpoint this supplement is approvable.

/S/
Yana Mille

cc:
HFN-238 /S/ 1/28/88
YMille/trc/1/28/88 /S/
2105m page 13
Review of Prof. Labeling

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING

SUPPLEMENT
DRAFT: Container Label

DATE OF REVIEW: June 19, 1987

ANDA/NDA#: 88-058/S-015 NAME OF FIRM: Knoll

NAME OF DRUG: Trade: VICODIN
Generic: Hydrocodone Bitartrate and Acetaminophen Tablets, 5 mg/500 mg

DATE OF SUBMISSION: May 8, 1987

COMMENTS:

Container: Satisfactory in draft for 3000s

RECOMMENDATIONS:

1. Inform the firm of above comments.

2. Request the firm prepare and submit final printed container labels.

3. The 3000 tablet package size will be available upon special request only. However, it is the policy of this Division that all marketed containers should be noted in the HOW SUPPLIED section of labeling. Therefore, we ask that the firm add this information to the insert.

/S/
Yana Mille

cc:
HFN-238
YMille/KJohnson/bc/6/22/87
RPL
1800m/pg6

/S/ 6/26/87

/S/ 6/26/87

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING

Amendment; Supplememt/FPL

DATE OF REVIEW: March 27, 1987

NDA#: 88-058/S-011, S-012 NAME OF FIRM: Knoll Pharmaceuticals

NAME OF DRUG: Trade: VICODIN
Generic: Hydrocodone Bitartrate and Acetaminophen Tablets 5 mg/500 mg

DATE OF SUBMISSION: February 17, 1987

COMMENTS:

Unit Dose

A. Blister Cards-Not Submitted
We are awaiting your response to our letter dated February 10, 1987.

B. Individual Unit Dose Packets for Dump Dispenser and Strip Cartons - Not Submitted
Submit twelve final printed copies of the unit-dose packets currently in use.

Carton - Satisfactory for:
A. Strip Carton of 25
B. Unit Dose Carton 4 x 25
C. Dump Dispenser

Container - Satisfactory for 100s and 500s

Insert - Satisfactory
However, at the time of next printing or within 90 days whichever comes first, revise the package insert labeling so it is in accord with our current labeling guideline for this product. The one exception to the guideline is the second paragraph in the DOSAGE AND ADMINISTRATION section which should be revised to read:

> The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total 24 hour dose should not exceed 8 tablets.

If you wish to include the dose for naloxone in the text of the insert it must be revised to reflect the dose currently reflected in the labeling of Narcan. When available submit draft copy for our review and comment. We are aware that further revision of the DOSAGE AND ADMINISTRATION may occur shortly and you should not prepare final printed labeling until requested to do so.

Furthermore, you must use the current phrasing for the ——— warning ——— Agents; Labeling in Drugs for Human Use; Warning Statement; Federal Register, Vol. 51, No. 234; December 5, 1986; pages 43900-43904]. The warning should be the first paragraph in the WARNINGS section.

[redacted]

RECOMMENDATIONS:

1. Inform the firm of above comments.

/S/ 4/7/87
Yana Mille

cc:
HFN-238
KJohnson/YMil /S/ 4/4/87
1417S
Review of P... Labeling
Pages 5-6

/S/ 4/7/87

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING

Amendment; Supplement; FPL; Unit Dose Blister Cards
and Carton for the Blister Cards

DATE OF REVIEW: April 20, 1987

ANDA/NDA#: 88-058/S-011 NAME OF FIRM: Knoll Pharmaceuticals

NAME OF DRUG: Trade: VICODIN
Generic: Hydrocodone Bitartrate and Acetaminophen Tablets
5mg/500mg

DATE OF SUBMISSION: March 23, 1987

COMMENTS:

1. Unit Dose Blister Card - Satisfactory

2. Unit Dose Carton for 4x25 Blister Cards. — Satisfactory

RECOMMENDATIONS:

1. Inform the firm of above comments.

2. Chemist:

Substitute number 1 above for item A under Unit-Dose in our review dated March 27, 1987. Add number 2 above as letter D. under carton in our review dated March 27, 1987.

/S/ 4/30/87

Yana Mille /S/

HFN-238
KJohnson/YMille/shd/4-30-87
3400A/pg
RPL/DRAFT

/S/ 4/30/87

APPEARS THIS WAY
ON ORIGINAL

File in ANDA

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

April 2, 1992

From Office of Generic Drugs HFD- 630/634

Requestor's Name DAVE Doleski / Shirley Brown Phone 295-8310

Subject ESTABLISHMENT EVALUATION REQUEST

To Division of Manufacturing & Product Quality (HFD-320)

Sterile Product _____ Non Sterile Product ✓

Application and Supplement No. 88-058/S-018, S-019

Brand Name *(if any)* Vicoden Tablets

Establishment Name, Dosage Form and Strength Hydrocodone Bitartrate 5mg and Acetaminophen 500 mg Profile Class Code: TCM

Priority Classification: _____ *(See SMG BD-4820.3)*

Applicant's Name: Knoll Pharmaceuticals

Address: 30 North Jefferson Road, Whippany, NJ 07981

Facilities to be Evaluated: (*Name, full Address, DMF No., and responsibility*) **For HFD 320 Use** Status & Date of Inspection:

1: [redacted]

2 [redacted]

Other Information or Special Requests: _____

****

For HFD-320 Use Only: Date Received: _____

CGMP Compliance Status of Facilities Evaluated: _____

CSO: _____ Date Completed: _____

Distribution: Original and First Copy: HFD-320
Remaining Copies: Requesting Office Use

FORM FDA 3274 (3/90)

DATE: May 15, 1992

FROM: Shirley S. Brown

TO: Michael Smela

SUBJECT: EER Facilities to be Evaluated

ANDA 88-058/S-019
Vicodin Tablets (hydrocodone bitartrate and acetaminophen)
Knoll Pharmaceuticals

The [redacted] operates [redacted] active ingredient,

1. [redacted]

2. [redacted]

APPEARS THIS WAY
ON ORIGINAL

Knoll Pharmaceuticals

TELEFAX

BASF Group

Date: July 8, 1992 Pages: 2 Time: _____

To: Valerie Vashio/CSO-Office of Generic Drugs

Fax No.: 301-295- 8180

From: Claudia Skarbek

Copy to: _____

Information for file Vashio CSO 7/8/92

Re: Vicodin Tablets (ANDA88-058)
S-018 and S-019

Dear Valerie:

As discussed this morning, please let me know later today if the attached letter will suffice for approval of the subject supplements.

Thank you,

Claudia Skarbek

Claudia Skarbek
Regulatory Associate

CS:dsb
attach.

DEPARTMENT OF HEALTH & HUMAN SERVICES 3381 Public Health Service

Memorandum

8 July 92

From Division of Generic Drugs HFD- 634

Requestor's Name V Vashio Phone 295 8370

Subject ESTABLISHMENT EVALUATION REQUEST

To Division of Manufacturing & Product Quality (HFD-320)

Sterile Product _____ Non Sterile Product ✓

Application and Supplement No. 88-058 / ~~S-018~~, S-019

Brand Name *(if any)* VICODIN TABLETS

Establishment Name, Dosage Form and Strength Hydrocodone Bitartrate 5mg and ACETAMINOphen 500mg Profile Class Code: TCM

Priority Classification: _____ *(See SMG BD-4820.3)*

Applicant's Name: KNOLL PHARMACEUTICALS

Address: 30 NORTH Jefferson Road, Whippany, NJ 07981

Facilities to be Evaluated: (*Name, full Address, DMF No., and responsibility*)

For HFD 320 Use
Status & Date of Inspection:

1. [redacted] 2/26/91
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]

Other Information or Special Requests: Please reprocess, see attachment for DMF [redacted]

****

For HFD-320 Use Only: Date Received: 7/9/92

CGMP Compliance Status of Facilities Evaluated: Acceptable

CSO: Melissa Pascua Date Completed: 8/5/92

Distribution: Original and First Copy: HFD-320
Remaining Copies: Requesting Office Use

FORM FDA 3274 (3/90)

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE: 11 Aug 92

NDA NUMBER: 88-058

IND NUMBER: S-018, S-019

TELECON/MEETING

INITIATED BY: ☐ APPLICANT/SPONSOR ☒ FDA

MADE: ☐ BY TELEPHONE ☐ IN PERSON

PRODUCT NAME: Vicodin Tablets

FIRM NAME: Knoll

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Claudia Skarbek

TELEPHONE NO.: 201 887 8300

Phone call was made to Knoll to request the hard copy document of the July 8, 1992 fax.

Mr. Skarbek agreed and would submit correspondence to the file

APPEARS THIS WAY ON ORIGINAL

SIGNATURE: Washington CSO

DIVISION: OGD

FORM FD 2587 (11/77)

ORIGINAL IND/NDA

U. S. GOVERNMENT PRINTING OFFICE-1984-432-976/7126

6.1 Brown, S. 228 6

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

2812 S. Brown

Memorandum

Date April 2, 1992

From Office of Generic Drugs

HFD- 630/634

Requestor's Name DAVE Doleski / Shirley Brown

Phone 295-8310

Subject ESTABLISHMENT EVALUATION REQUEST

To Division of Manufacturing & Product Quality (HFD-320)

Sterile Product _____ Non Sterile Product ✓

Application and Supplement No. [redacted] /S-018, [redacted]

Brand Name *(if any)* Vicoden Tablets

Establishment Name, Dosage Form and Strength Hydrocodone Bitartrate 5mg and Acetaminophen 500 mg

Profile Class Code: TCM

Priority Classification: _____ *(See SMG BD-4820.3)*

Applicant's Name: Knoll Pharmaceuticals

Address: 30 North Jefferson Road, Whippany, NJ 07981

Facilities to be Evaluated: *(Name, full Address, DMF No., and responsibility)*

For HFD 320 Use
Status & Date of Inspection:

[illegible] 2U UN 6/3/92

[illegible] UKU NC 2/26/91

Other Information or Special Requests: _____

****

For HFD-320 Use Only:

Date Received: APR 20 1992

CGMP Compliance Status of Facilities Evaluated: #1 unacceptable, #2 acceptable

CSO: Melissa Garcia

Date Completed: 6/19/92

Distribution: Original and First Copy: HFD-320
Remaining Copies: Requesting Office Use

* See attached memo &

FORM FDA 3274 (3/90)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PHS - MID-ATLANTIC REGION
FOOD AND DRUG ADMINISTRATION

DATE: 6/4/92

FROM: Matthew H. Lewis, District Director
Newark District

SUBJ: ANDA #88-058 (S-018,19)

TO: Compliance Evaluation Staff, HFD-320
FAX: FTS 295-8202

INFO: MPQAS, HFC-120, FTS 443-4625
Richard Davis, RFDD/HFR-MA1
Diana Kolaitis, DCB, NWK-DO
Elaine C. Messa, DIB, NWK-DO

PRODUCT: Hydrocodone Bitartrate 5mg and Acetaminophen 500mg

APPLICANT: Knoll Pharmaceutical
30 North Jefferson Road
Whippany, NJ 07981

ESTAB: [redacted] **CFN:** [redacted]

ESTAB TYPE: [redacted]

DISTRICT RECOMMENDATION: Withholding Approval

DATE CONCURRENCE REQUESTED FROM CDER: 5/7/92

DATE NDA/ANDA AUDITED: 6/3/92

COMMENTS: Based upon inspectional findings, Newark District recommends the following:

Withholding approval of pending application because [redacted] does not manufacture [redacted]

Matthew H. Lewis, D.D.
Newark District

MHL:kb

6,1 Brown, S. 228

DEPARTMENT OF HEALTH & HUMAN SERVICES 2811 Public Health Service S. Brown

Memorandum

April 2, 1992

From Office of Generic Drugs HFD- 630/634

Requestor's Name DAVE Doleski/Shirley Brown Phone 295-8310

Subject ESTABLISHMENT EVALUATION REQUEST

To Division of Manufacturing & Product Quality (HFD-320)

Sterile Product _____ Non Sterile Product ✓

Application and Supplement No [redacted] S-019

Brand Name *(if any)* Vicoden Tablets

Establishment Name, Dosage Form and Strength Hydrocodone Bitartrate 5mg and Acetaminophen 500 mg Profile Class Code: TCM

Priority Classification: _____ *(See SMG BD-4820.3)*

Applicant's Name: Knoll Pharmaceuticals

Address: 30 North Jefferson Road, Whippany, NJ 07981

Facilities to be Evaluated: (*Name, full Address, DMF No., and responsibility*)

For HFD 320 Use
Status & Date of Inspection:

UAI 6/3/92

AC 2/26/91

Other Information or Special Requests: _____

****

For HFD-320 Use Only:

Date Received: APR 20 1992

CGMP Compliance Status of Facilities Evaluated: #1 Unacceptable #2 Acceptable

CSO: Melissa Garcia Date Completed: 6/19/92

Distribution: Original and First Copy: HFD-320
Remaining Copies: Requesting Office Use

* See attached memo *

FORM FDA 3274 (3/90)

DEPARTMENT OF HEALTH & HUMAN SERVICES

PN

Memorandum

DATE: 1-12-90

TO : Division of Manufacturing & Product Quality (HFN-320)

FROM: Division of Generic Drugs HFN 234

Requester's Name R. M. Patel, Ph.D Phone 443-1396

ESTABLISHMENT EVALUATION REQUEST

Sterile Product No Non Sterile Product Yes

Application and Supplement No. 88-058 /S018 and S019

Brand Name *(if any)* Vicodin Tablets

Establishment Name, Dosage Form and Strength Hydrocodone Bitartrate 5mg and Acetaminophen 500mg

Profile Class Code: TCM

Priority Classification: — *(See SMG BD-4820.3)*

Applicant's Name: Knoll Pharmaceuticals

Address: 30 North Jefferson Road, Whippany, NJ 07981

Facilities to be Evaluated: *(Name, full Address, DMF No., and responsibility)*

For HFN-320 Use
Status & Date of Inspection:

1. [redacted]
2. [redacted]
3. [redacted] OAI 4/25/89
4. [redacted] OAI 3/27/89

Other Information or Special Requests: Cause Inspection to determine whether only the ownership changed from [redacted] and/or the transfer of manufacturing processes.

For HFN-320 Use Only: Date Received 1-19-90

CGMP Compliance Status of Facilities Evaluated:

CSO: Date Completed

Distribution: Original and First Copy: HFN-320
Remaining Copies: Requesting Office Use

FORM FDA 3274 (6/86)

O⇒N+320 DR⇒N

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

**88-058/S-001;S-002;S-003;
S-004;S-005;S-006;S-007;S-008;
S-009;S-011;S-012;S-013;S-014;
S-015;S-016;S-017;S-018;S-019;
S-020;S-021;S-022;S-023;S-024**

CORRESPONDENCE

10/23/01
1 pr
&
10/8/01
1 pr

Redacted 2

pages of trade secret and/or confidential commercial information

5/1/01 e
10/23/00
lwks

Redacted 3

pages of trade secret and/or confidential commercial information

Redacted 2

pages of trade secret and/or confidential commercial information

Knoll Pharmaceutical Company

knoll®

BASF Pharma

March 6, 2000

NDA NO. 88-058 REF NO. SCC-023

NDA SUPPL FOR [redacted]

Douglas L. Sporn
Director, Office of Generic Drugs
HFD 600, Bldg MPN2
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852-1833

SUPPLEMENT – EXPEDITED REVIEW REQUESTED

Subject: ANDA 88-058
Vicodin® (hydrocodone bitartrate and acetaminophen tablets, USP) 5mg/500mg

Dear Mr. Sporn:

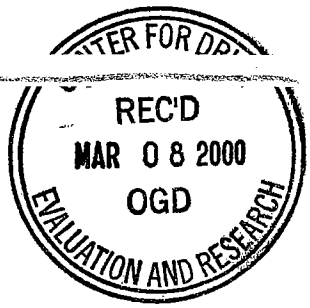
Rhodia supplies Knoll with [redacted]

Knoll has been informed that effective April 1, 2000 [redacted] will then [redacted] was inspected by FDA on March 10-11, 1999 as part of a pre-approval inspection. No Form 483 was issued.

The formulation of [redacted] remains unchanged. The [redacted] and release testing will continue to be [redacted] as well. Stability data has been [redacted] and indicates no significant differences between the [redacted] at 36 months.

In anticipation of this [redacted], Knoll has [redacted] of Vicodin tablets through May, 2000. Effective June 1, Knoll will begin to use [redacted] In order not to interrupt its supply to the market, Knoll is requesting an Expedited Review of this supplement.

The following information is provided to support the [redacted]



- Letter from [redacted] effective April 1, 2000
- Letter of authorization to cross-reference [redacted] DMF [redacted] dated November 22, 1999.
- Knoll Technical Support Report demonstrating comparability of [redacted]

Knoll commits to placing the first three production batches of Vicodin tablets [redacted] on stability.

If there are questions concerning this submission, I can be reached at 973/426-6012.

Sincerely,

Robert W. Ashworth, Ph.D.
Director, Regualtory Affairs

RWA:dsb

anda88-058.doc

APPEARS THIS WAY
ON ORIGINAL

Knoll Pharmaceutical Company

EER requested 9/21/99 jm

knoll®

FEDERAL EXPRESS

BASF Pharma

NDA NO. _____ REF NO. SEB022

NDA SUPPL FOR Facility Rev / S1

9/21/99

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
SEP 13 1999
CDR

September 10, 1999

Douglas L. Sporn, Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852-1833

Subject: **ANDA 88-058**
Vicodin® (hydrocodone bitartrate and acetaminophen tablets, USP) 5 mg/ 500 mg
SUPAC Supplement: Packaging Site Change - Changes Being Effected

Dear Mr. Sporn:

Pursuant to 21 CFR 314.70(a) and the Agency's letter to industry dated February 18, 1997, clarifying issues pertaining to the interpretation of the Scale-up and Post-Approval Changes Guidance for Immediate-Release Products (SUPAC-IR), which was published on November 30, 1995, Knoll Pharmaceutical Company hereby submits this supplemental application to provide for a

Vicodin tablets are currently manufactured, packaged, and tested by Knoll at the Whippany, New Jersey site. Blister packaging of this product was done by a at its facility located at . Knoll is planning to move the blister packaging of Vicodin tablets to its site at 30 North Jefferson Road, Whippany, New Jersey; this site underwent a satisfactory cGMP inspection on November 10, 1998. The container/closure system and equipment remain the same.

The enclosed report supports the site change using currently approved packaging materials at labeled storage conditions. As noted in the Overview, the first production batch, and annual batches thereafter, will be placed on the long-term stability program.

Sincerely,

Lidia D. Mostowy for

Robert W. Ashworth, Ph. D.
Director, Regulatory Affairs

CENTER FOR ... 1999

3000 Continental Drive-North, New Jersey 07828-1234 (973) 426-0000 Fax (973) 426-1000

Knoll Pharmaceutical Company

knoll®

BASF Pharma

EER requested 8/12/99 M Anderson

VIA FEDERAL EXPRESS

August 6, 1999

Douglas L. Sporn
Director, Office of Generic Drugs
HFD-600, Bldg. MPN2
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852-1833

Grantley /S/ 8/12/99

NDA NO. _____ REF. NO: 5 cB 021
NDA SUPPL NO: Facility Add/SE

PAC-ATLS CBE SUPPLEMENT

Subject: ANDA 88-058
Vicodin® (hydrocodone bitartrate and acetaminophen tablets, USP) 5 mg/ 500 mg
Additional Analytical Laboratory Testing Site

Dear Mr. Sporn:

Knoll Pharmaceutical Company, Whippany, NJ has expanded our Quality Control laboratories to include an additional Knoll site in Cedar Knolls, NJ. This new laboratory was previously approved in March 1999 by your Division to conduct testing for Vicodin ES tablets (ANDA 89-736). The Cedar Knolls site is now eligible to utilize a postapproval changes - analytical testing laboratory site submission for other products since it has had a successful cGMP inspection and can now confirm that we meet the four PAC-ATLS criteria:

1. The test methods approved in the application or methods that have been implemented under 21 CFR 314.70(d) will be used.

2. All postapproval commitments made by Knoll relating to the test methods have been fulfilled.

3. The new testing facility has the capability to perform the intended testing.

4. The new testing facility has had a satisfactory current good manufacturing practice inspection within the past two years.

Effective August 9, 1999, the following tests will be performed in Cedar Knolls for Vicodin Tablets:

3000 Continental Drive-North, New Jersey 07828-1234 (973) 426-0000 Fax (973) 426-1000

The new Knoll Pharmaceutical Company laboratory is located at 140 Hanover Avenue, Cedar Knolls, New Jersey, 07927.

Our intention is to conduct routine stability testing for Vicodin Tablets at the new Cedar Knolls site. The stability and release methods are the same; therefore, the site will also serve as a backup to the QC release lab in Whippany, if necessary.

Data demonstrating that the new site can perform the analytical tests transferred from the Whippany facility is contained in Appendix 1. The data generated at the receiving laboratory in Cedar Knolls, using the same samples, compared favorably to the data generated at the transferring laboratory in Whippany. A submission for Vicodin HP Tablets, ANDA 40-117, will be made separately.

If you have any questions regarding this submission, please do not hesitate to contact Lidia Mostovy at 973-426-6019 or me at 973-426-6012.

Sincerely,

Lidia D. Mostovy for

Robert W. Ashworth, Ph.D.
Director, Regulatory Affairs

Enclosure

APPEARS THIS WAY
ON ORIGINAL

Knoll Pharmaceuticals

OK as SCBE 9/4/92

1PK unit dose blister sorts/packs K 9.4.92

knoll

F Phillips 9/8/92

August 18, 1992 NDA NO. _____ REF. NO. 51-000 **BASF** Group

NDA SUPPL FOR Label Revision

FPL

CENTER FOR DRUG REC'D AUG 2 1 1992 HFD-150 EVALUATION AND RESEARCH

Roger L. Williams, M.D.
Division of Generic Drugs
Room 17-B20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: **Vicodin Tablets ANDA #88-058**
Special Supplement - Changes Being Effected
Revised Unit Dose Pouch

Dear Dr. Williams:

Reference is made to Knoll Pharmaceuticals' approved NDA #88-058 for Vicodin (5mg hydrocodone bitartrate/500mg acetaminophen) _____ Tablets. Specific reference is made to your letter dated 5/29/92 in which you requested that we revise our unit dose pouch to include the dosage form "Tablet".

Pursuant to your request, we are supplementing the subject ANDA, in duplicate, with final printed labeling.

Enclosed you will find twelve copies (8-archival copy, 4-review copy) of the final printed unit dose pouch revised to include the dosage form "Tablet". This change went into effect with the packaging of Vicodin Tablets Unit Dose _____ Control #10760532, which began on 8/10/92. The approximate date of distribution for this lot is 9/10/92.

Please include this information in the agency's file for Vicodin tablets ANDA #88-058.

Sincerely,

Claudia Sharbek/for

Robert W. Ashworth, Ph.D.
Director, Regulatory Affairs

RWA/CS/dsb
M~152

ORIGINAL

RECEIVED AUG 2 6 1992 GENERIC DRUGS

A Unit of BASF K&F Corporation
30 North Jefferson Road, Whippany, New Jersey 07981 (201) 887-8300 Telex 136466 Telefax (201) 887-8131

8 pkgs 88 mailed

ORIGINAL
SLI-020
88-058
LABEL REVISION

FPL

vicodin®
TABLET
hydrocodone bitartrate 5 mg
(WARNING: May be habit forming.)
acetaminophen 500 mg.
LOT 10760532
EXP. DATE 6/95
KNOLL PHARMACEUTICALS
CIII

APPROVED
SEP 10 1992

vicodin®
TABLET
hydrocodone bitartrate 5 mg
(WARNING: May be habit forming.)
acetaminophen 500 mg.
LOT 10760532
EXP. DATE 6/95
KNOLL PHARMACEUTICALS
CIII

APPROVED
SEP 10 1992

vicodin®
TABLET
hydrocodone bitartrate 5 mg
(WARNING: May be habit forming.)
acetaminophen 500 mg.
LOT 10760532
EXP. DATE 6/95
KNOLL PHARMACEUTICALS
CIII

APPROVED
SEP 10 1992

vicodin®
TABLET
hydrocodone bitartrate 5 mg
(WARNING: May be habit forming.)
acetaminophen 500 mg.
LOT 10760532
EXP. DATE 6/95
KNOLL PHARMACEUTICALS
CIII

APPROVED
SEP 10 1992

6.1

Knoll Pharmaceuticals

knoll

NEW CORRES

BASF Group

August 10, 1992

Division of Generic Drugs
Room 17-B20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RECEIVED
AUG 14 1992
GENERIC DRUGS

N 5018/S-018/S-019

Subject: **Vicodin Tablets ANDA #88-058**
Supplement S-018, S-019

Dear Staff Member:

Reference is made to the subject supplement for Vicodin Tablets dated February 1, 1989, and amended on 10/20/89, 2/8/90, 9/17/90 and 6/7/91. Additional reference is made to a 6/30/92 telephone conversation with Ms. Valerie Vashio, Consumer Safety Officer, at which additional information from [redacted] was requested. On 7/8/92 the requested information was telefaxed to the Division of Generic Drugs.

In accordance with 21 CFR 314.20, Knoll Pharmaceuticals hereby amends the pending application, in duplicate, with the attached information from [redacted] telefaxed to the agency on 7/8/92.

We trust the approval of the pending supplements can proceed expeditiously.

Sincerely,

Claudia Skarbek/for

Robert W. Ashworth, Ph.D.
Director, Regulatory Affairs

RWA:dsb
M~150

A Unit of BASF K&F Corporation
30 North Jefferson Road, Whippany, New Jersey 07981 (201) 887-8300 Telex 136466 Telefax (201) 887-8131

Redacted 1 7/6/92 lbr

Page(s) of trade secret and /or confidential commercial information

APR 2 1991

ANDA 88-058/S-018, S-019

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

Dear Sir:

Reference is made to your supplemental new drug applications dated February 1, 1989 submitted pursuant to Section 314.70 of the Regulations, regarding your abbreviated new drug application for Vicodin Tablets (hydrocodone bitartrate and acetaminophen, 5 mg/500 mg).

Reference is also made to your communications dated October 20, 1989, February 8 and September 17, 1990 amending these supplements.

We acknowledge receipt of your correspondence dated February 1, 1990.

These supplemental applications provide for revised package insert no. 5830 (S-018) and use of [redacted] without added [redacted] in the manufacturing process (S-019).

These supplemental application S-019 remains deficient and therefore not approvable under Section 505 of the Act for the following reasons:

1. The reference DMF [redacted] remains deficient. [redacted] is being notified.

2. Stability data are not sufficient to support an expiry date of 24 months in the bottled product and 18 months for the unit dose blister packaged product.

   Three months accelerated stability data (100s, 500s and unit dose blisters stored at 40°C/75% RH and tested at 0, 1, 2, 3 months) will support a tentative 24 month expiry date. Simultaneously, data should be collected for the same size packages stored at room conditions.

The file is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw these supplemental applications. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this

letter will be considered a major amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving these supplemental applications, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 4/1/91

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

cc: ANDA #88-058/S-018, S-019
DUP/Division File
HFD-600 Reading File
HFD-638/YMille
HFD-634/RPatel/SBRown/03/11/91 PDB 3/26/91
HFD-634/VVAshio/03/19/91
R/D initialed by SSherken
cls/03/25/91/b:88-058 LTR
F/T by cls/03/25/91
Supplemental Not Approvable
Kenneth P. Purdie for R. M. Pratt
March 27, 1991

APPEARS THIS WAY
ON ORIGINAL

ORIG

Knoll Pharmaceuticals

knoll®

BASF Group

September 17, 1990

Division of Generic Drugs
Room 17-B20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SUPPL NEW CORRES
Refer to: S-018
S-019

Subject: **Vicodin Tablets ANDA #88-058**
Supplement S-018, S-019

Dear Staff Member:

Reference is made to the subject supplement for Vicodin Tablets dated February 1, 1989. Additional reference is made to our February 8, 1990 response to your division's January 24, 1990 "not approvable" letter.

One of the deficiencies noted in our last correspondence involved [redacted] DMF # [redacted] for [redacted] We have recently been notified by [redacted] that an update for DMF # [redacted] was submitted to the agency on September 11, 1990.

Attached is a copy of the letter from [redacted] notifying Knoll Pharmaceuticals of the recent update as well as a copy of their letter authorizing Knoll to reference DMF # [redacted]

At this time, we ask the agency to re-review DMF # [redacted] We trust that the updated DMF and the information provided in our February 8, 1990 correspondence will enable an expeditious approval of ANDA #88-058/S-018, S-019.

Sincerely,

Claudia Skarbek /for

Robert W. Ashworth, Ph.D.
Director, Regulatory Affairs

CS/amd
Attachment

RECEIVED
SEP 25 1990
GENERIC DRUGS

A Unit of BASF K&F Corporation
30 North Jefferson Road, Whippany, New Jersey 07981 (201) 887-8300 Telex 136466 Telefax (201) 887-8131

Knoll Pharmaceuticals

knoll®

BASF Group

S-018 Insert Satisfactory as of 10/20/89 submission. a few changes for the time of next printing. Y. Mille 3/19/90

February 8, 1990

Division of Generic Drugs (HFD-630)
Room 17-B20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA SUPPL AMENDMENT

S/018- Label S/019 Formulation

Subject: NDA #88-058 Vicodin Tablets (hydrocodone bitartrate 5mg/acetaminophen 500mg), S-018/S-019 Amendment in Response to Not Approvable Letter (January 24, 1990)

Dear Staff Member:

Reference is made to the above noted supplemental applications filed February 1, 1989 (amended October 20, 1989) and to the Agency's letter of January 24, 1990 which stated that these supplements were not approvable. These supplements provided for a revised package insert for product without added [redacted] Reference is also made to our letter of February 1, 1990 indicating our intention to submit an amendment.

At this time, Knoll Pharmaceuticals is further amending these supplements to provide responses to the deficiency comments noted in the Agency's letter of January 24, 1990. The deficiency comments (all of which relate to S-019) are restated below followed by Knoll's response.

1. **The referenced DMF [redacted] is deficient. [redacted] is being notified.**

   Knoll was aware (September 14, 1989) of a deficiency of DMF [redacted] in connection with supplements to another of our ANDA products. At that time, we were in contact with [redacted] (the holder of DMF [redacted] prior to its transfer to [redacted]) who prepared and submitted an update responding to the noted deficiency.

   In our S-018/019 amendment of October 20, 1989, we noted that DMF 3142 had been updated on October 13, 1989 in response to that deficiency letter from FDA.

   Since receipt of the Agency's letter of January 24, 1990 we have contacted [redacted] regarding DMF [redacted] They are unaware of any deficiency letter since their update of October 13, 1989. Present information indicates that the Agency's comment relative to S-019 is inaccurate.

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30 North Jefferson Road, Whippany, New Jersey 07981 (201) 887-8300 Telex 136466 Telefax (201) 887-8131

2. **Stability data are insufficient.**

Stability studies should also include test for appearance, friability, hardness, color, and moisture.

Stability studies should include the product packaged in (1) bottle of 100, (2) bottle of 500 and (3) hospital unit dose.

Knoll's stability program is bipartate. Part one is a combined accelerated (stress) and room temperature program which gathers data to support supplemental applications such as S-019. The program tests for description, dissolution, and assay of active drug components. The testing standard employed, AR-1489 (attached), is virtually the same as edition AR-0885 which had been submitted previously as part of approved supplements S-013/014/015 (May 8, 1987).

Part two consists of an ongoing room temperature (real time) stability program which gathers data to monitor and allow extension of expiry dating. It is into this program which the first three production lots are entered as part of our stability commitment in S-019.

The ongoing program testing standard, S-50D (attached), incorporates all requested testing with the exception of moisture determination. This test has been deemed unnecessary because the individual drug product components are tested for moisture and the finished Vicodin tablets are not hygroscopic. Appearance and color are parts of the description evaluation.

As we indicated in our amendment of October 20, 1989, Knoll does not consider the deletion of [redacted] a formulation change as much as a processing change by our [redacted] Knoll is not changing the manufacturing formula or procedures for Vicodin. Thus we believe that the accelerated (stress) and room temperature data already provided (lot #H48-150) is sufficient to show comparability with the previously approved drug product.

APPEARS THIS WAY
ON ORIGINAL

To satisfy the Agency's request for additional stability data, however, we are providing the following which show acceptable stability of Vicodin.

- From the accelerated (stress)/room temperature program
  - o Lot #H48-150 plastic bottles of 100
    - o 3 month accelerated data
    - o 18 month room temperature data

- From the ongoing stability program (6 months room temperature data)
  - o Plastic bottles of 100 - lot #1076-2718
    lot #1076-0109
  - o Plastic bottles of 500 - lot #1076-2728
    lot #1076-0099
  - o Unit dose blisters - lot #1076-2738
    lot #1076-0359

At the time of next printing, we will incorporate the recommended changes to our package insert and provide final printed copies to the Agency. As the package insert is satisfactory (according to the Agency's letter of January 24, 1990) we will not be making these changes at this time. The 3000 tablet bottle is not currently planned for market. It will be added to the "How Supplied" section prior to distribution.

We trust that this information will enable expeditious review and approval of supplements S-018/019.

Sincerely,

Fred E. Lungla for
Robert W. Ashworth, Ph.D.
Director, Regulatory Affairs

FEL/amd

Knoll Pharmaceuticals

knoll®

BASF Group

February 1, 1990

Donald Burlington, M.D.
Acting Director
Division of Generic Drugs (HFD-230)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA #88-058 Vicodin**
Supplements S-018, S-019
Reply to Not Approvable Letter (January 24, 1990)

Dear Dr. Burlington:

Reference is made to the above noted supplemental applications filed February 1, 1989 (amended October 20, 1989) and to the Agency's letter of January 24, 1990 which stated that these supplements were not approvable.

At this time, Knoll Pharmaceuticals is notifying the Agency of its intention to file an amendment to these applications under the provisions of 21 CFR 314.120 (a). We are currently compiling information in response to the comments made in the Agency's letter of January 24, 1990.

A desk copy of this letter is also being provided to Mr. Peter Rickman, consumer safety officer.

Sincerely,

Fred E. Lynch for
Robert W. Ashworth, Ph.D.
Director
Drug Regulatory Affairs

FEL/amd
cc: Mr. Peter Rickman, CSO (HFD-232)

Knoll Pharmaceuticals

knoll

BASF Group

October 20, 1989

Richard Terselic, Acting Director
Division of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA SUPPL AMENDMENT
SA 018-019
1 Label 1 Formulation

Subject: NDA #88-058: VICODIN Tablets
Supplements S-018, S-019, S-020
Amendment: Final Printed Labeling

S-018 Package Insert Labeling Satisfactory However see review. H. Mills 1/4/90

Dear Mr. Terselic:

Reference is made to the above-noted supplements to our VICODIN (5 mg hydrocodone bitartrate/500 mg acetaminophen) NDA #88-058 submitted February 1, 1989. At this time we are amending these supplements, in duplicate, to provide the following.

1. **Final Printed Labeling** - Twelve copies of final printed insert No. 5830 are provided as follows.

   a. 1 set mounted and bound and 7 sets mounted and unbound in the archival copy of this submission

   b. 1 set mounted and bound and 3 sets unmounted and loose in an envelope in the review copy

   As no adverse comments have been received from the Agency, the labeling changes are the same as those drafted in the February 1, 1989 submission. A copy of that draft labeling is provided for purposes of comparison to the current package insert (No. 5828).

2. **Stability** - We herewith formally request the same expiration dating as is currently approved for VICODIN (24 months in bottles and 18 months in unit dose blisters). In support of this we are updating the previously provided stability data which show acceptable stability in bottles.

   We are not providing additional data on a lot in unit dose packaging but commit to putting the first three commercial-size lots into our stability program. Our rationale is as follows.

a. **The composition of the finished drug product is unchanged.**

VICODIN will continue to be manufactured according to the formula and procedure approved in NDA #88-058. The release specification remains unchanged as well.

b. **There is no difference in the quality of with or without added**

The minor processing change (deletion of

c. **The February 1, 1989 supplement to NDA #89-736 is effectively only a labeling change.**

The warning was originally required for VICODIN because in the manufacture of , could be present in that component. It was a potential inactive ingredient to VICODIN.

removed from the processing of and therefore, as defined in 21CF 201.22, the warning is no longer necessary in the package insert.

No other change is being made to VICODIN as it is detailed in approved NDA #88-058.

For these reasons, we believe that no further stability data is required at this time. We do, however, reiterate our commitment to provide full-term stability data on three initial production-size lots and to remove from distribution any lots which show unacceptable stability.

3. **DMF Authorization** - We are providing a copy of a letter from which authorizes Knoll Pharmaceuticals to reference

DMF # [redacted] (in general and the recent update of October 13, 1989 in particular) in submissions made to the Agency.

DMF # [redacted] (which covers production of the [redacted] used to manufacture VICODIN) was updated in response to comments from the Agency.

We request that the Agency re-review DMF # [redacted] to enable approval of our supplements (S-018, 019, 020) to NDA #88-058.

We trust that this information will allow expeditious approval of the above noted supplements.

A desk copy of this amendment is being provided to Mr. Peter Rickman, consumer safety officer.

Sincerely,

for Robert W. Ashworth, Ph.D.
Director, Regulatory Affairs

RWA/kg
Enclosure

Desk copy: Mr. Peter Rickman

Knoll Pharmaceuticals

February 1, 1989

NDA NO. _____ REF. NO. 019
NDA SUPPL FOR Formulation

Draft Draws
Not Satisfactory
Revise & Re-submit
JF Mills
3/15/89

BASF Group

Marvin Seife, M.D., Director (HFD-230)
Division of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA NO. _____ REF. NO. 018
NDA SUPPL FOR Label

Subject: NDA 88-058 : Vicodin Tablets
Supplemental Application (S-018) -
Revised Insert No. 5830

DRAFT LABELING

Dear Dr. Seife:

Reference is made to Knoll Pharmaceuticals' approved NDA #88-058 for Vicodin (5mg hydrocodone bitartrate/500mg acetaminophen) ~~~~ Tablets. Specific reference is made to supplemental application S-016 approved on July 1, 1988. That supplement covered package insert No. 5828 which was revised to include (among other items) a ~~~~ warning as requested in the Agency's letter of May 11, 1987.

At this time pursuant to 21 CFR 314.70 (b)(3), we are submitting a revision to our current package insert (No. 5828). The new package insert (No. 5830) has been created to delete the above-mentioned ~~~~ warning which had been added to insert No. 5828 (S-016).

The ~~~~ warning was had been added to insert No. 5828 because ~~~~ mixture), used ~~~~ in preparation of this component of the finished drug product (Vicodin tablets). ~~~~ has since informed us that they have revised their Type II Drug Master File for Acetaminophen to cover production of ~~~~ without the use of ~~~~

For marketing and safety reasons, it is the intention of Knoll Pharmaceuticals to purchase and use only ~~~~ (i.e. no added ~~~~ in the preparation of Vicodin tablets. For this reason, the package insert has been revised (No. 5830) to delete the previously included ~~~~ warnings which no longer would be required under the provisions of 21 CFR 201.22.

In support of this supplemental application, we are providing the following:

1. Revised package insert No. 5830 - Four copies (1 archival, 3 review) of draft labeling highlighting the changes being made as noted below:

   DESCRIPTION section - Deletion of " ~~~~ as one of the inactive ingredients of Vicodin tablets

   WARNING section - Deletion of the first paragraph headed, "~~~~

A Unit of BASF K&F Corporation
30 North Jefferson Road, Whippany, New Jersey 07981 (201) 887-8300 Telex 136466 Telefax (201) 887-8131

2. Revised statement of the qualitative and quantitative composition of the drug deleting the listing of [redacted] as a component of [redacted]

3. Copy of December 15, 1988 letter from [redacted] informing Knoll Pharmaceuticals that [redacted] DMF [redacted] for Acetaminophen was updated December 6, 1988 to include a new manufacturing facility for the production of [redacted] without the use of [redacted] as a [redacted]

4. Copy of December 15, 1988 letter from [redacted] authorizing FDA to reference the December 6, 1988 update of DMF [redacted] relative to Knoll Pharmaceuticals drug application for product containing Acetaminophen (i.e. Vicodin tablets).

5. Three months accelerated and six month room temperature stability data for Product Development Vicodin batch No. H48-150 (manufactured from [redacted] added [redacted]. These data demonstrate satisfactory stability of the finished drug product. Additionally, the Agency is requested to refer to [redacted] DMF # [redacted] for data on the stability of [redacted] added [redacted]

There have been no changes to either manufacturing procedures or component and finished product testing instructions as a result of the use of [redacted] added [redacted] The amount of [redacted] present in [redacted] was so small as to have had no effect upon manufacturing or testing procedures.

On the basis of the attached and referenced stability data, it is expected that there will be no adverse effect upon the stability of the finished drug product. Nonetheless, Knoll Pharmaceuticals commits to providing full term stability data on three initial production-size lots of Vicodin manufactured from [redacted] added [redacted] and to removing from distribution any lots which show unacceptable stability.

We additionally commit to the use of insert No. 5828 [redacted] warning) with any lots of Vicodin (with added [redacted], still in stock after approval of this supplement.

We trust that this supplemental application is in order and request its approval at your earliest convenience.

Sincerely,

Fred E. Leighton

for Robert W. Ashworth, Ph.D.
Director, Regulatory Affairs

FEL/amd

Knoll Pharmaceuticals

knoll

Drug

BASF Group

June 7, 1988

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA SUPPL AMENDMENT
5/016

FPL
Package Insert Labeling
(submitted 5/13/88)
Satisfa-tory
/S/
6/27/88

Subject: VICODIN ANDA 88-058/S-016

Dear Dr. Seife:

Reference is made to your letter of June 3, 1988 which noted that the How Supplied section of the insert does not reflect the 3000 tablet package size.

The final printed package insert (#5828) submitted to the Agency on May 13, 1988 was based on changes requested in your letter of January 29, 1988 and clarified in a telephone conversation with Ms. Mille on February 16, 1988. The subsequent approval of the 3000 tablet package size on February 29, 1988 was surprising as it was based on labeling submitted on December 4, 1987 (#5810) which did not reflect the Agency's most recent requests.

Since the 3000 tablet package has not yet been introduced, we intend to use our current inventory of the insert #5828 which reflects your most up-to-date requests. Prior to introducing the 3000 tablet package we will revise the How Supplied section of insert #5828 and notify the Agency accordingly.

Sincerely,

Robert W. Ashworth

Robert W. Ashworth, Ph.D.
Director, Regulatory Affairs

RWA/kg

RECEIVED
JUN 8 1988
GENERIC DRUGS

A Unit of BASF K&F Corporation
30 North Jefferson Road, Whippany, New Jersey 07981 (201) 887-8300 Telex 136466 Telefax (201) 887-8131

ANDA 88-058/S-016

Knoll Pharmaceuticals
Attention: Robert W. Ashworth
30 North Jefferson Road
Whippany, NJ 07981

JUN 3 1988

Dear Sir:

Reference is made to your supplemental new drug application submitted pursuant to Section 314.70 of the Regulations, dated June 10, 1987, regarding your abbreviated new drug application for VICODIN (Hydrocodone Bitartrate and Acetaminophen Tablets) 5 mg/500 mg.

Reference is also made to your communications dated August 6, 1987; September 17, 1987 and May 13, 1987 amending these supplements.

The supplemental application provides for revised package insert labeling to reflect a major revision of the text.

We have reviewed the final printed insert submitted and have the following comments:

The text of the proposed insert is satisfactory, however, we note that the 3000 tablet package size (approved February 29, 1988) is not reflected in the HOW SUPPLIED section of the insert. Please comment.

We anticipate a timely response so revised insert labeling can be put into use as soon as possible.

Please let us have your response promptly.

Sincerely yours,

/S/

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

/S/ 6/2/88 /S/ 6/2/88

cc:
HFN-238
TPoux/YMille/tr:/6/2/88
2230m page 12
Review w/f

Knoll Pharmaceuticals

Orig

May 13, 1988

BASF Group

Marvin Seife, M.D., Director
Division of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockvile, MD 20857

NDA SUPPL AMENDMENT
S/A016
FPL

Subject: ANDA 88-058/S-016
VICODIN Tablets Package Insert (#5828)
Final Printed Labeling

Package Insert Labeling Not satisfactory. See letter.
5/1
10/1/88

Dear Dr. Seife:

As requested by the Administration's letter dated January 29, 1988, we have made the following revisions to our package insert labeling for VICODIN (Hydrocodone Bitartrate and Acetaminophen Tablets) 5 mg/500 mg:

A) DESCRIPTION

1) [redacted]

2) Non-opiate has been hyphenated in the last paragraph.

B) ADVERSE REACTIONS

[redacted] have been deleted under "Central Nervous System".

C) DRUG ABUSE AND DEPENDENCE

A new paragraph has been set to begin with "Physical dependence".

[redacted]

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30 North Jefferson Road, Whippany, New Jersey 07981 (201) 887-8300 Telex 136466 Telefax (201) 887-8131

wording in our present insert is consistent with the Agency's labeling guidelines for Hydrocodone Bitartrate and Acetaminophen Tablets dated August 1987.

Twelve (12) copies of the final printed package insert for VICODIN Tablets, print number 5828, are enclosed.

Sincerely,

Robert W. Ashworth

Robert W. Ashworth
Director
Regulatory Affairs

RWA/smp
enclosures

ANDA 88-058/S-016

Knoll Pharmaceuticals
Attention: Robert W. Ashworth
30 North Jefferson Road
Whippany, New Jersey 07981

JAN 29 1988

Dear Sir:

Reference is made to your supplemental new drug application submitted pursuant to Section 314.70 of the Regulations, dated June 10, 1987, regarding your abbreviated new drug application for VICODIN (Hydrocodone Bitartrate and Acetaminophen Tablets) 5 mg/500 mg.

Reference is also made to your communications dated August 5, 1987 and September 17, 1987 amending this supplement.

The supplemental application provides for revised package insert labeling to reflect a major revision of the text.

We have reviewed the draft material submitted and have the following comments:

A. DESCRIPTION
1. [redacted]

2. Final Paragraph, line 1 - non-opiate (hyphenated)

B. ADVERSE REACTIONS
Central Nervous System - Delete " [redacted] They already appear in the first paragraph in this section.

C. DRUG ABUSE AND DEPENDENCE
Divide paragraph 2 into two paragraphs. The third paragraph will begin with "Physical dependence".

D. Additional Comments

[redacted]

Revise the package insert labeling as directed above, then prepare and submit draft copy for our review and comment.

Please let us have your response promptly.

Sincerely yours,

/S/ 1-29-88

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

cc:
HFN-23 /S/ 1/28/88
TPoux/YMille/trc/1/28/88
2105m pages 14-15
Review w/f

/S/ 1/28/88

APPEARS THIS WAY
ON ORIGINAL

Knoll Pharmaceuticals

FPL
1. container labels - satisfactory
Labels - satisfactory
in package insert
2. Labeling - satisfactory
however, per version
11/18/88

knoll®

Orig

December 4, 1987

BASF Group

Marvin Seife, M.D.
Director
Division of Generic Drugs (HFN-230)
Office of Drug Standards
Center for Drugs Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA SUPPL AMENDMENT
S/013
014
015 - labelat Labeling
FPL

Subject: ANDA 88-058/S-013, S-014, S-015
VICODIN® (5mg hydrocodone bitartrate and 500mg acetaminophen)

Dear Dr. Seife:

Reference is made to the Administration's letter of September 14, 1987, regarding our supplemental new drug application to provide for a plastic bottle containing 3000 VICODIN Tablets.

We offer the following in response to your comments:

1. Enclosed please find twelve (12) final printed container labels (print #5801) for the 128 fluid ounce plastic bottle. These labels are mounted three per page for three pages, plus three labels in an envelope.

2. As requested, we have added to the VICODIN insert the package size of 3000 (print #5810). Twelve (12) copies of the final printed insert are enclosed. This VICODIN insert is identical, except for the How Supplied section - Bottle of 3000, to print number 5809 which was submitted to the Administration for approval on 11/17/87.

3. The bottle of 3000 VICODIN Tablets is intended for repackaging by large drug chains. It will be available upon special request only. A 4 month expiration date is requested for this bottle.

4. The actual size of the [redacted] bottle used in the stability studies is 128 fluid ounces.

Please include this information in the Administration's files for ANDA 88-058, VICODIN (hydrocodone bitartrate and acetaminophen) Tablets, 5mg/500mg.

Sincerely,

Jeanmarie Kline /for

Robert W. Ashworth
Director, Regulatory Affairs

DEC 8 1987

JK/ls

A Unit of BASF K&F Corporation
30 North Jefferson Road, Whippany, New Jersey 07981 (201) 887-8300 Telex 136466 Telefax (201) 887-8131

ANDA: 88-058/S-013, S-014, S-015

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

SEP 14 1987

Dear Dr. Ashworth:

Reference is made to your supplemental new drug applications submitted pursuant to Section 314.70 of the Regulations, dated May 8, 1987 regarding your abbreviated new drug application for VICODIN (Hydrocodone Bitartrate and Acetaminophen) Tablets, 5 mg/500 mg.

The supplemental applications provide for (1) S-013; Packaging of Vicodin tablets in a 128 fluid ounce plastic bottle (3000 tablets) with a ——— cap, (2) 2-014; Expiration dating for the new package, and (3) S-015; Labeling for the new package.

We have reviewed the material submitted and have the following comments:

1. Please submit twelve (12) final printed container labels, for the 128 fluid ounce plastic bottles.

2. We note that the 3000 tablets package size will be available upon special request only. However, it is the policy of this Division that all marketed containers should be noted in the HOW SUPPLIED section of labeling. Therefore, we ask that this information be added to the insert.

3. With regard to the requested 24 month expiration date for this package size (3000 tablet). Please clarify the intended purpose of this package size. If it is for repackaging then a 4 month expiration date (the maximum amount of time allowed by the agency for repackaging without affecting the approved expiration date of a drug product) is more appropriate than the requested 24 month expiration date.

4. Please clarify the actual size of the ——— bottle used in the stability studies (page 20 of your correspondence dated May 8, 1987). Is it the 128 oz (3000 tablet) package size?

Please let us have your response promptly.

Sincerely yours,

/S/ 9/14/87

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

cc:
HFN-237 /S/ 9/11/87
HFN-83 /S/ 9/10/87
YMille/CChang/WMahane/je/9-8-87
rwf
7562A/ pg 17

Knoll Pharmaceuticals

knoll

Orig

November 17, 1987

BASF Group

Marvin Seife, M.D.
Director, Division of Generic Drugs
Center for Drugs Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA SUPPL AMENDMENT
5/016
DRAFT LABELING

Package Insert
Not Satisfactory
Revise and resubmit
- 151
1/27/88

Subject: ANDA 88-058/S-016
VICODIN Tablets Draft Package Insert (#5809)

Dear Dr. Seife:

Pursuant to the Administration's letter of September 14, 1987, we are submitting revised package insert labeling for VICODIN (hydrocodone bitartrate and acetaminophen) Tablets, 5mg/500mg. This draft labeling has been prepared in accordance with the labeling guideline for hydrocodone bitartrate and acetaminophen tablets, dated 8/87.

Four copies of the draft package insert for VICODIN Tablets, print number 5809, are enclosed for your review. This draft is submitted as the mechanical form of printed labeling for ease of review.

Please include this information in the Administration's files for ANDA 88-058, VICODIN (5mg hydrocodone bitartrate and 500mg acetaminophen) Tablets.

Sincerely,

Jeanmarie Kline /for

Robert W. Ashworth
Director, Regulatory Affairs

RWA/ls

Enclosures

A Unit of BASF K&F Corporation
30 North Jefferson Road, Whippany, New Jersey 07981 (201) 887-8300 Telex 136466 Telefax (201) 887-8131

ANDA: 88-058/S-016

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

SEP 14 1987

Dear Dr. Asworth:

Reference is made to your supplemental new drug application submitted pursuant to Section 314.70 of the Regulations, dated June 10, 1987, regarding your abbreviated new drug application for VICODIN (Hydrocodone Bitartrate and Acetaminophen) Tablets, 5 mg/500 mg.

Reference is also made to our letter dated May 11, 1987.

The supplemental application provides for revised package insert labeling to reflect 1) revision of the DOSAGE AND ADMINISTRATION section 2) the current phrasing of the ——— warning and 3) revision of the naloxone dosage information.

We have reviewed the draft material submitted and have the following comments:

1. WARNINGS

   Respiratory Depression
   Delete the final sentence.

2. PRECAUTIONS

   Usage in Pregnancy

   A. This subsection consists of two sub-subsections: Teratogenic Effects and Nonteratogenic Effects. Do not denote the sub-subsection headings in the same manner as subsection headings. We suggest:

      Usage in Pregnancy: (in bold type)
      Teratogenic Effects: Pregnancy Category C...
      Nonteratogenic Effects: Babies...

   B. — (rather than 1.0)

3. ADVERSE REACTIONS

   Respiratory Depression
   Delete sentences 4 and 5.

4. OVERDOSAGE

A. As previously stated in our letter dated May 11, 1987, if you wish to include the dose for naloxone in the text of the insert it must be revised to reflect the dose currently reflected in the labeling of Narcan. We refer you to the package insert labeling for Darvon (Eli Lilly and Company) as a model for the type of information that should be included. Note that in addition to information concerning the treatment of overdosage in adults there is also a subsection on the treatment of overdosage in children.

Alternatively, the sentence in paragraph 1 under Hydrocodone, Treatment may read:

> 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.

B. Acetaminophen

a. Revise paragraph 1 to read:

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

b. Revise paragraph 5 to read:

The antidote, N-acetylcysteine, should be administered as 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.

5. DOSAGE AND ADMINISTRATION

Paragraph 1, sentence 2 should read:

However it should be kept in mind that tolerane...

6. HOW SUPPLIED

Storage - We prefer the degrees Celcius appear before the degrees Fahrenheit.

7. The labeling guideline for this product was revised recently. Please revise your insert labeling so it is in accord with the guideline.

Revise the package insert labeling as directed above, then prepare and submit draft copy for our review and comment.

Please let us have your response promptly.

Sincerely yours,

/S/ 9/14/87

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

Enclosure: Labeling Guideline

cc:
HFN-237
YMille/CChang/WMarnane/je/9-8-87
rwf
7562A/ pg 14-16

/S/ 9/10/87

APPEARS THIS WAY
ON ORIGINAL

Knoll Pharmaceuticals

knoll®

Drug

August 21, 1987

BASF Group

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA NO. _____ REF. NO. 017
NDA SUPPLEMENT FOR Fac Add

Subject: **ANDA 88-058, VICODIN Tablets**
Supplement - EXPEDITED REVIEW REQUESTED
Manufacturing Facility Expansion

Dear Dr. Seife:

Pursuant to the provisions of 21 CFR 314.70(b)(2)(vi), we submit herewith a supplemental new drug application providing for the manufacture of VICODIN Tablets in an expanded tablet production facility directly adjoining our current operations at the Whippany, New Jersey site.

VICODIN Tablets manufactured in the newly expanded facility will be identical in every respect to those manufactured in our current facility under the subject ANDA. The tablets will be produced in the same batch size using the same procedures and equipment. In order to accomplish this, current production equipment will be relocated and requalified within the expanded facility. The specifications, test methods and packaging will remain unchanged from that provided for in the currently approved application.

We note that the information required for inclusion in this supplement was discussed with Dr. Kumkumian and representatives from your Division and the Office of Compliance on July 9, 1987. The information contained in this submission is outlined below:

- Description of manufacturing facility including site plan, floor plans and equipment descriptions and location
- Qualification procedures for utilities and equipment
- Currently approved manufacturing and controls information to facilitate review of the submission
- Stability commitment

A Unit of BASF K&F Corporation
30 North Jefferson Road, Whippany, New Jersey 07981 (201) 887-8300 Telex 136466 Telefax (201) 887-8131

- Stability protocol
- Commitment to provide (post-approval) comparative dissolution data
- GMP certification

Since the relocation of manufacturing equipment will disrupt Knoll's pharmaceutical production capability until FDA approval is received, we trust that our request for expedited review will be granted. Equipment relocation will commence in September with all qualification work being completed in time for an anticipated compliance inspection in mid to late October. Based on currently achievable inventory levels, we are hoping for a November, 1987 approval in order to insure the continuity of drug product supply to the market place.

Should you have any comments or questions regarding this submission please contact me at (201) 428-4096.

Sincerely,

Robert W. Ashworth

Robert W. Ashworth, Ph.D.
Director
Regulatory Affairs

RWA/kg

cc: Dr. Charles Kumkumian
Mr. William Marnane (desk copy)

Knoll Pharmaceuticals

knoll®

Drug

BASF Group

August 5, 1987

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA SUPPL AMENDMENT
S/014
DRAFT LABELING

Subject: ANDA 88-058, VICODIN Tablets
Supplement - EXPEDITED REVIEW REQUESTED

Dear Dr. Seife:

On June 10, 1987, we responded to the Administration's letter dated May 11, 1987 for ANDA 88-058/S-012. Since the information in the Administration letter was unclear concerning revising the Vicodin package insert at the time of next printing, we contacted the Division and spoke to Ms. Yana Mille on July 8, 1987. She clarified that the changes to the Dosage and Administration section should be made immediately and she requested that we make some additional changes to the Vicodin insert. Ms. Mille suggested we submit these changes as draft copy under 21 CFR 314.70(b).

Enclosed is a draft copy of Vicodin Insert, print number 5804. A comparison of the changes from our current Vicodin insert #5786 is included. We have also highlighted all the sections of the Vicodin package insert that were addressed in your May 11, 1987 letter to show that all changes have been incorporated.

Please retain this information in the Administration's files for ANDA 88-058, Vicodin (5mg hydrocodone bitartrate and 500mg acetaminophen) Tablets.

Sincerely,

Joanmarie Kline for

Robert W. Ashworth, Ph.D.
Director
Regulatory Affairs

JK/mrg

RECEIVED
AUG 11 1987
GENERIC DRUGS

A Unit of BASF K&F Corporation
30 North Jefferson Road, Whippany, New Jersey 07981 (201) 887-8300 Telex 136466 Telefax (201) 887-8131

Knoll Pharmaceuticals

OK10

knoll®

BASF Group

June 10, 1987

NDA NO. _____ REF. NO. 5106

NDA SUPPL FOR Label Rev

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

DRAFT LABELING

Not Satisfactory
Revise and resubmit draft
13
8/10/87

Subject: ANDA 88-058/S-~~013~~ 012

Dear Dr. Seife:

Reference is made to your letter of May 11, 1987 which requested revisions in the VICODIN package insert within 90 days. The requested revisions of the DOSAGE and ADMINISTRATION section, addition of the ——— warning and revision of the dose for naloxone are highlighted in the attached draft package inserts.

Regarding your comments relative to the composition of ———, we have confirmed that our currently listed inactive ingredients are correct. In the attached letter, Mr. Downes delineates the composition of ——— and requests that FDA contact him directly if there are any further questions.

Sincerely,

Robert W Ashworth

Robert W. Ashworth, Ph.D.
Director, Regulatory Affairs

RWA/kg

Enclosure

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JUN 16 1987
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A Unit of BASF K&F Corporation
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Knoll Pharmaceuticals

NDA NO. _____ REF. NO. 013
NDA SUPPL FOR Pkg Add.

Orig

May 8, 1987

BASF Group

NDA NO. _____ REF. NO. 014
NDA SUPPL FOR Exp Dat.
24M

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA NO. _____ REF. NO. 015
NDA SUPPL FOR Label
Draft Label Satisfactory submit FPL
DRAFT LABELING

Subject: ANDA 88-058, Vicodin® Tablets
Packaging Supplement - Plastic Bottle of 3000 Tablets

Dear Dr. Seife:

As per the requirements of 21 CFR 314.70 (b)(2)(vii), we are submitting, in both archival and review copies, a supplemental new drug application to provide for the packaging of Vicodin (5 mg hydrocodone bitartrate and 500 mg acetaminophen) Tablets in a 128 fluid ounce plastic bottle with a [redacted] cap. Approval for Vicodin Tablets in 160 cc and 625 cc plastic bottles with [redacted] caps was granted on June 24, 1986 (supplements 006 and 007) with a two-year expiration date.

This new package size of 3000 tablets will be available upon special request only, therefore, according to the provisions of 21 CFR 201.57 (K)(2) it will not be included in the "How Supplied" section of our package insert.

The information in support of this package size can be found in the following attachments:

(A) Information Regarding Packaging

1) Testing Standard, [redacted] for [redacted] 128 fluid ounce, white, [redacted] bottle.

2) Technical data regarding [redacted]

3) Testing Standard, [redacted] for [redacted] black, plastic, [redacted] cap.

4) Testing Standard, [redacted], for [redacted]

5) Packaging log for Vicodin Tablets, Bottle of 3000.

6) Draft container label for bottle of 3000.

A Unit of BASF K&F Corporation
30 North Jefferson Road, Whippany, New Jersey 07981 (201) 887-8300 Telex 136466 Telefax (201) 887-8131

(B) Stability Information

1) Stability results for Vicodin stored in [redacted] plastic bottle at 3 months (accelerated) and up to 6 months (room temperature) to support a 2 year expiration date.

2) Testing Standard, [redacted], for stability analysis of Vicodin Tablets.

3) Stability Protocol, PD-003

4) Stability Commitment

(C) DMF Authorizations

1) Letter of authorization to refer to [redacted] DMF

2) Letter of authorization to refer to [redacted] DMF [redacted]

3) Letter from [redacted] authorizing reference to DMF [redacted] for [redacted]

(D) [redacted]

1) Results of [redacted] testing on the 128 fl.oz. [redacted] bottle.

Any questions regarding this data should be forwarded to the undersigned.

Please include this information in the Administration's files for ANDA 88-058, Vicodin® (5 mg hydrocodone bitartrate and 500 mg acetaminophen) Tablets of [redacted] manufacture.

Sincerely,

Jeanmarie Kline l/for

Robert W. Ashworth, Ph.D.
Director
Regulatory Affairs

JK:lf
Enclosures

Knoll Pharmaceuticals

FPL
Unit-Dose Blister Card Satisfactory
2. Unit Dose Carton for 4 x 25 Blister Cards Satisfactory
4/20/87

Orig

BASF Group

March 23, 1987

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

5/011

FPL

Subject: ANDA 88-058/S-011, Vicodin[R] Tablets
Final Printed Labeling

Dear Dr. Seife:

As requested in the Administration's letter of February 10, 1987, enclosed please find twelve copies (4 bound, 8 unbound) of the following final printed labeling:

- VICODIN Tablet Unit Dose Carton of 100 Tablets, (4 x 25 Blister Cards), print number 5784.
- VICODIN Tablet Unit Dose Top Card for 25 Tablets, print number 5783A.
- VICODIN Tablet Unit Dose Bottom Card for 25 Tablets, print number 5783B.

The changes requested by the Administration have been incorporated into this labeling. Please include this information in your files for ANDA 88-058, VICODIN (5mg hydrocodone bitartrate and 500mg acetaminophen) Tablets of _____ manufacture.

Sincerely,

Jeanmarie Orlene/for

Robert W. Ashworth, Ph.D.
Director, Regulatory Affairs

JK/kg

Enclosure

RECEIVED
MAR 24 1987
GENERIC DRUGS

A Unit of BASF K&F Corporation
30 North Jefferson Road, Whippany, New Jersey 07981 (201) 887-8300 Telex 136466 Telefax (201) 887-8131

Knoll Pharmaceuticals

BASF Group

February 17, 1987

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Subject: ANDA 88-058/R-08, Re: Labeling Supplement
Vicodin® Tablets ([redacted] manufacture)

Dear Dr. Seife:

Please refer to your letter of February 10, 1987, regarding labeling submitted in our annual report for ANDA 88-058, Vicodin® (5 mg hydrocodone bitartrate and 500 mg acetaminophen) Tablets of [redacted] manufacture. The labeling text included in this report was originally approved under ANDA 85-667, Vicodin Tablets of [redacted] manufacture.

In 1982, Knoll requested a provision to manufacture Vicodin by a [redacted] method. On March 22, 1982, we were advised by the Administration that the [redacted] tablet was deemed a new formulation; therefore, we submitted an additional ANDA on August 12, 1982. This ANDA included approved, final printed labeling from the original ANDA # 85-667; therefore, when ANDA 88-058 was approved on January 7, 1983, this approval included the labeling submitted in this application.

The labeling for Vicodin tablets was discussed prior to submission of the new ANDA with the Division on July 14, 1982. We were told that upon approval of ANDA 88-058 we could distribute both [redacted] tablets with the existing Vicodin labeling.

As provided in 21 CFR 314.71(d), the minor changes that have been made in Vicodin labeling since initial approval have been submitted in our annual reports for ANDA 88-058. For your convenience, these changes are appended. The changes are listed chronologically by print number and include the reason for change. As requested, enclosed are twelve (12) copies of final printed labeling for each piece submitted in our annual report dated January 23, 1987.

A Unit of BASF K&F Corporation
30 North Jefferson Road, Whippany, New Jersey 07981 (201) 887-8300 Telex 136466 Telefax (201) 887-8131

It is our understanding that the changes indicated do not require prior FDA approval. Please address any questions or comments to the undersigned.

Sincerely,

Robert W. Ashworth, Ph.D.
Director
Drug Regulatory Affairs

JK:lf
Enclosures

ANDA 88-058/S-011

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

FEB 10 1987

Dear Sir:

Reference is made to your supplemental new drug application submitted pursuant to Section 314.70 of the Regulations, dated November 10, 1986, regarding your abbreviated new drug application for VICODIN (Hydrocodone Bitartrate and acetaminophen) Tablets, 5 mg/500 mg.

Reference is also made to your communication dated January 7, 1987 amending this supplement.

The supplemental application provides for unit-dose packaging (4 sheets per carton, 25 tablets per sheet).

We have reviewed the draft material submitted and have the following comments:

Unit Dose Label: Not Satisfactory

A. Inside flap

1. Based on the precedent set in the USP use the word "and" rather than " ~~—~~
Hydrocodone bitartrate... and acetaminophen 500 mg

2. PERFORATIONS (rather than PERFORMATIONS)

B. Unit-dose blister

1. Vicodin tablet (rather than ~~———~~
It is our understanding that there is only one tablet per blister.

2. Delete the extra blank line beneath Hydrocodone Bitartrate. The "Warning" statement and Acetaminophen should both be repositioned.

C. We prefer: mg (rather than ~~—~~

Carton: Satisfactory as of November 10, 1986 submission.

Revise the unit dose label, then prepare and submit twelve final printed unit dose and carton labels.

Please let us have your response promptly.

Sincerely yours,

/S/ for 2-10-87

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

HFN-238 /S/ 2-6-87
HFN-230 /S/ 2/5/87
M.Seife/K.Johnson/Y.Mille/st/2-3-87
3224A Pg 1-2
Review Waiting Firm

APPEARS THIS WAY
ON ORIGINAL

Knoll Pharmaceuticals

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BASF Group

Draft Unit Dose Label - Not satisfactory
Carton Label - Satisfactory
and 1/16/86 both unacceptable
Note: S-011 must be approved with S-008 1/31 1/24/87

January 7, 1987

FDA SUPPL ACKNOWLEDGMENT
5011
DRAFT LABELING

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs & Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: ANDA 88-058/S-011 (Vicodin Unit Dose Labeling)

Dear Dr. Seife:

Reference is made to our pending supplemental application dated January 21, 1986, and to your letter of December 5, 1986. Enclosed for your review are four copies of the revised Vicodin Unit Dose Label. All of the comments in your December 5, 1986, letter have been incorporated.

Sincerly,

Robert J. McConnell /for RWA

Robert W. Ashworth, Ph.D.
Director, Drug Regulatory Affairs

RMc:lf
Enclosures

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JAN 9 1987

A Unit of BASF K&F Corporation
30 North Jefferson Road, Whippany, New Jersey 07981 (201) 887-8300 Telex 136466 Telefax (201) 887-8131

ANDA 88-058/S-011 S|008 009

Knoll Pharmaceuticals
Attention: Robert W. Ashworth, Ph.D.
30 North Jefferson Road
Whippany, New Jersey 07981

DEC 5 1986

Dear Sir:

Reference is made to your supplemental new drug application submitted pursuant to Section 314.70 of the Regulations, dated November 10, 1986, regarding your abbreviated new drug application for VICODIN (Hydrocodone Bitartrate 5 mg/Acetaminophen 500 mg) Tablets.

The supplemental application provides for unit dose packaging (4 sheets per carton, 25 tablets per sheet).

We have reviewed the draft material submitted and have the following comments:

1. Unit Dose Label - Not Satisfactory

Each unit dose blister must provide the following information.

A. Statement of contents controlled substance symbol and designation of dosage form

Hydrocodone bitartrate 5 mg CIII
(Warning: May be habit forming)
Acetaminophen 500 mg
Tab.

B. Lot number and expiration date

C. Corporate name

D. You may include additional information if there is room.

2. Carton Label - Satisfactory

Please revise the unit dose blister label, then prepare and submit twelve final printed unit dose and carton labels. (You may submit draft copy if you prefer.)

Please let us have your response promptly.

Sincerely yours,

/S/

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

/S/ 12-4-86 /S/ 12-2-86 /S/ /BR 12-5-86

HFN-238
M.Seife/K.Johnson/Y.Mille/st/11-26-86
2917A Pg 8
Review Waiting Firm

Knoll Pharmaceuticals

S-011 draft Unit Dose labels - Not satisfactory Revise + submit FPL - satisfactory draft Carton Labels - Satisfactory Prepare and submit FPL

Note: S-011 must be approved along with S-008 & S-009

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BASF Group

November 10, 1986

NDA SUPPL AMENDMENT
S/008 DRAFT LABELIN
009

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs & Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA NO. 88058 REF. NO. S/011
NDA SUPPL FOR Label Rev

Subject: ANDA 88-058/S-008, S-009

DRAFT LABELING

Dear Dr. Seife:

Reference is made to our pending supplemental applications dated January 21, 1986 and to your letter of November 4, 1986. Attached for your review are four copies of draft labels for the new packaging format.

Sincerely,

RECEIVED
NOV 17 1986
GENERIC DRUGS

Robert W. Ashworth, Ph.D.
Director
Drug Regulatory Affairs

RWA/kg

Attachment

A Unit of BASF K&F Corporation
30 North Jefferson Road, Whippany, New Jersey 07981 (201) 887-8300 Telex 136466 Telefax (201) 887-8131

ANDA 88-058/S-008, S-009

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

NOV 4 1986

Dear Mr. Ashworth:

Reference is made to your supplemental new drug applications submitted pursuant to Section 314.70 of the Regulations, dated January 21, 1986, regarding your abbreviated new drug application for Vicodin Tablets (5 mg Hydrocodone Bitartrate/500 mg Acetaminophen).

The supplemental applications provide for (1) S-008: Packaging of Vicodin Tablets in blister packages, and (2) S-009: Expiration dating for the new package.

We have reviewed the material submitted and have the following comments:

> We note from the physical description of the new blister packaging [100 tablets supplied as (4 sheets per carton, 25 tablets per sheet)] that it differs significantly from the previous blister packaging [100 tablets supplied as (4 boxes per carton, 1 roll per box, 25 tablets per roll)]. Because of this difference, it is necessary that unit dose and carton labels for the new packaging format be submitted for our review. Please submit this information.

Please let us have your response promptly.

Sincerely yours,

/S/ /for 11-4-86

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

/S/ 11/3/86

cc:
HFN-237
YMille/CChang/W[illegible]nane/tr/10/30/86
1121S
Review w/f

/S/ 11-3-86

/S/ 11-3-86

Knoll Pharmaceuticals

knoll

BASF Group

September 15, 1986

NDA SUPPL AMENDMENT
S/008
009

Marvin Seife, M.D., Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SUBJECT: **NDA 88-058/S-008, S-009**

Dear Dr. Seife:

Reference is made to our supplemental applications submitted January 21, 1986 regarding Vicodin Tablets and to your letter of March 19, 1986. The response to the comments detailed in your letter are provided herein.

1) A. Please provide a description of the physical characteristics of your blister package (size, dimensions, etc.).

Response: A sketch of the blister package with the pertinent dimensions is provided as Attachment I.

[redacted]

A Unit of BASF K&F Corporation
30 North Jefferson Road, Whippany, New Jersey 07981 (201) 887-8300 Telex 136466 Telefax (201) 887-8131

[redacted]

2) A. Accelerated stability data at challenge conditions may be used to justify a maximum expiration date of 18 months. Please revise your request for a 2 year expiration date or provide extended room temperature data.

Response: Based on the stability data provided, we are requesting an expiration date of 18 months.

[redacted]

C. [redacted]

Sincerely,

Robert W. Ashworth, Ph.D.
Director, Regulatory Affairs

RWA/kg

Attachments

4/21/86
1 of

Redacted 2

pages of trade secret and/or confidential commercial information

NDA 88-058/S-008, S-009

MAR 19 1986

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

Dear Mr. Ashworth:

Reference is made to your supplemental new drug applications submitted pursuant to Section 314.70 of the Regulations, dated January 21, 1986, regarding your new drug application for Vicodin Tablets (5 mg Hydrocodone Bitartrate/500 mg Acetaminophen).

The supplemental applications provide for (1) S-008; Packaging of Vicodin tablets in blister packages, and (2) S-009; Expiration dating for the new package.

We have reviewed the material submitted and have the following comments:

1. It fails to contain an adequate description of materials used for packaging and adequate information with respect to the characteristics of, and test methods employed for the drug package to assure their suitability for the intended use. In this regard:

   A. Please provide a description of the physical characteristics of your blister package (size, dimensions, etc.).

2. [redacted]

[redacted]

Please let us have your response promptly.

Sincerely yours,

/S/

3/19/86

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

/S/ 3/18/86
Final Concurrence

/S/ 3/19/86

cc:
NWK-DO
HFN-237
CChang/WMarnane/tr/3/17/86
0625S
Review w/f

APPEARS THIS WAY
ON ORIGINAL

2/5/86
1 hr

Redacted 2

pages of trade secret and/or confidential commercial information

Orig

KNOLL PHARMACEUTICAL COMPANY
30 NORTH JEFFERSON ROAD, WHIPPANY, NEW JERSEY 07981

January 21, 1986

NDA NO. 88058 REF. NO. S/008
NDA SUPPL FOR Pkg Add VID

NDA NO. _____ REF. NO. S/009
NDA SUPPL FOR Exp Date

Marvin Seife, M.D., Director
Div. of Generic Drug Monographs
Office of the Associate Director for
Drug Monographs
National Center for Drugs & Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: Vicodin Tablets NDA 88-058, Packaging Supplement

Dear Dr. Seife:

Under the provisions of 21 CFR 314.70(b)(2)(vii), Knoll Pharmaceuticals is submitting a supplemental application to NDA 88-058 to provide for the packaging of Vicodin Tablets in blister packages.

The tablets will be packaged using the following components:

Blister: [redacted]

Backing: [redacted]

The supportive information is provided in the designated attachments:

Attachment A - Stability results for Vicodin Tablets stored in blister packages at 3 months (accelerated) and up to 6 months (room temperature), to support a 2-year expiration date.

Attachment B - Testing Standard used for Stability Analysis.

Attachment C - Letters of authorization to refer to [redacted] DMF [redacted] DMF [redacted] DMF [redacted] (Amendment 11) for the [redacted]

Attachment D - Testing standards for packaging components.

In addition, Knoll Pharmaceuticals makes the following stability commitment:

TELEPHONE (201) 887-8300 — TELEX: 136466

- The first three production lots of the product will be placed on stability. Yearly thereafter, at least one production batch will be added to the stability program.

- Results of the stability studies will be reported as they become available in periodic reports.

- We will withdraw from the market any batch found to fall outside the approved specifications for the drug.

Please address any comments/questions concerning this submission to the undersigned.

Sincerely,

Robert W. Ashworth, Ph.D.
Director
Drug Regulatory Affairs

RWA:js

Enclosure

Desk copy to: C. Chang

APPEARS THIS WAY
ON ORIGINAL

Orig

KNOLL PHARMACEUTICAL COMPANY
30 NORTH JEFFERSON ROAD, WHIPPANY, NEW JERSEY 07981

December 16, 1985

NDA NO. 88058 REF. NO. 5/006
NDA SUPPL FOR Pkg Add 100's

NDA NO. _____ REF. NO. 5/007
NDA SUPPL FOR Pkg Add 500's

Marvin Seife, M.D., Director
Div. of Generic Drug Monographs
Office of the Associate Director for
Drug Monographs
National Center for Drugs & Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: Vicodin Tablets NDA 88-058, Packaging Supplement

Dear Dr. Seife:

Under the provisions of 21 CFR 314.70(b)(2)(vii), Knoll Pharmaceutical Company is submitting a supplemental application to NDA 88-058 to provide for the packaging of Vicodin Tablets in plastic bottles.

The tablets will be packaged as follows:

a) 100 tablets in 160 cc white plastic [redacted] bottles using a [redacted] metal cap.

b) 500 tablets in 625 cc white plastic [redacted] bottles using a [redacted] metal cap.

The supportive information is provided in the designated attachments:

Attachment A - Stability results for Vicodin Tablets stored in plastic bottles at 3 months (accelerated) and up to 12 months (room temperature), to support a 2-year expiration date.

Attachment B - Testing Standard used for Stability Analysis.

Attachment C - Letters of authorization to refer to [redacted]
DMF [redacted]
DMF [redacted]

Attachment D - Testing standards for 160 cc and 625 cc white plastic bottles, [redacted] metal caps.

In addition, Knoll Pharmaceutical Company makes the following stability commitment:

- The first three production lots of the product will be placed on stability. Yearly thereafter, at least one production batch will be added to the stability program.
- Results of the stability studies will be reported as they become available in periodic reports.
- We will withdraw from the market any batch found to fall outside the approved specifications for the drug.

Please address any comments/questions concerning this submission to the undersigned.

Sincerely,

Robert W. Ashworth, Ph.D.
Director
Drug Regulatory Affairs

RWA:js

APPEARS THIS WAY
ON ORIGINAL

Drug

KNOLL PHARMACEUTICAL COMPANY
30 NORTH JEFFERSON ROAD, WHIPPANY, NEW JERSEY 07981

October 23, 1984

SUPPL NEW CORRES
S/005

Marvin Seife, M.D., Director
Div. of Generic Drug Monographs
Office of the Associate Director
of Drug Monographs (HFN-530)
National Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: NDA Supplement, NDA 88-058
Vicodin Tablets, [redacted] Manufacture

Dear Dr. Seife:

This is in reference to our supplemental New Drug Application providing for a new tablet shape for Vicodin Tablets of [redacted] manufacture, NDA 88-058.

As discussed with Mr. C. Chang of your division, the modification does not involve a change in formulation and is being made solely to eliminate limited numbers of tablet breakage in bottles of 100's.

In light of the above, we wish to implement this change as soon as possible. Upon approval of this application, existing inventories of current Vicodin Tablets will be phased out and replaced by the new tablet shaped product.

Should you require any additional information regarding this application, please contact me at (201) 428-4014.

Sincerely,

A. C. Hanzas

A. C. Hanzas
Director
Drug Regulatory Affairs

ACH:mg

cc: Mr. C. Chang
Mr. J. Meyer

RECEIVED
OCT 24 1984
GENERIC DRUGS

TELEPHONE (201) 887-8300 — TELEX: 136466

KNOLL PHARMACEUTICAL COMPANY
30 NORTH JEFFERSON ROAD, WHIPPANY, NEW JERSEY 07981

Orig

FPL Container and carton labels and package insert labeling satisfactory 10/17/84

October 9, 1984

NDA NO. 88058 REF. NO. 5/004

NDA SUPPL FOR Label

FPL

NDA NO. REF. NO. 5/005

NDA SUPPL FOR Mfg Bus

Marvin Seife, MD, Director
Div. of Generic Drug Monographs
Office of the Associate Director
of Drug Monographs (HFN-530)
National Center for Drugs and
Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Subject: NDA Supplement for New Tablet Shape for NDA 88-058, Vicodin Tablets, ~~[redacted]~~ Mfg.

Dear Dr. Seife:

Under the provisions of 21 CFR 314.8 (a)(4)(iii), we are submitting a supplemental application to NDA 88-058 to provide for a change in the shape of Vicodin Tablets.

In support of this application we offer information under Items 4, 8h, 8n, and 8p of FDA Form 356H.

Customer reports of broken tablets in bottles of 100 have necessitated this change in tablet shape. Over the years, we have tried various packaging procedure modifications and shipping carton changes for bottles of 100. These changes have reduced but not eliminated the breakage problem. Vicodin Tablets are a Class III narcotic, therefore tablet breakage is an additional burden for the dispensing pharmacist since all tablets must be accounted for, including broken tablets. Broken tablets must be destroyed or returned to the manufacturer according to Drug Enforcement Administration procedure.

The change in tablet shape is from ~~[redacted]~~ to a capsule shaped tablet with rounded sides. The tablet identification imprint has been changed to the word "VICODIN" imprinted on one side from a ~~[redacted]~~ on the other side. The tablet is still bisected.

We request your earliest review and approval of this supplemental application.

Sincerely,

A. C. Hanzas
Director
Drug Regulatory Affairs

JK/kg

Enclosure

cc: Charles Y. Chang (desk copy)
Jack L. Meyer (cover letter only)

Orig

KNOLL PHARMACEUTICAL COMPANY
30 NORTH JEFFERSON ROAD, WHIPPANY, NEW JERSEY 07981

July 17, 1984

Marvin Seife, MD
Director, Division of Generic Drugs (HFN-230)
Office of Drug Standards
National Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA SUPPL AMENDMENT
S/001
002

Subject: Vicodin^{R} (hydrocodone bitartrate 5mg and acetaminophen 500mg) Tablets, NDA 88-058/S-001, S-002

Dear Dr. Seife:

We refer to our supplements S-001, S-002 dated July 29, 1983, regarding the above referenced drug.

Reference is also made to your communications of January 31, 1984, February 24, 1984 and July 3, 1984 in which you requested submission of stability data at challenge conditions prior to approval of the supplements.

Pursuant to your request, we have attached updated stability results for [redacted] Vicodin Tablets (Lot #10760281R) at challenge conditions.

Based on the results of this testing, we request your approval of the [redacted] procedure (S-001) and a two-year expiration date for the [redacted] tablets (S-002).

Sincerely,

A. C. Hanzas
Director
Drug Regulatory Affairs

RRG:mg

attachment

RECEIVED
JUL 23 1984
GENERIC DRUGS

JUL 3 1984

NDA 88-058/S-001, S-002, S-003

Knoll Pharmaceutical Company
Attention: Mr. Agamemnon C. Hanzas
30 North Jefferson Road
Whippany, New Jersey 07981

Gentlemen:

Reference is made to your supplements dated July 29, 1983 and January 30, 1984 regarding your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vicodin (hydrocodone bitartrate 5 mg and acetaminophen 500 mg) Tablets.

Reference is also made to your communication dated May 7, 1984.

The supplemental applications provide for:

S-001	a ——— procedure.
S-002	two year expiration date for the ——— tablets.
S-003	a major control procedure change for the dosage form.

We have completed the review of these supplemental applications and request the following additional information:

Submit stability data at challenge conditions for the ——— Vicodin Tablets (#10760281R) as requested per your letters of January 31, and February 24, 1984.

Please let us have your response promptly.

Sincerely yours,

/S/ , /FOR 7-3-84

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologies

cc:
NWK-DO
HFN-230 /S/ 7-2-84
HFN-233
JMeyer/CChang/gp/7/2/84
R/d init. by: MSeife/JMeyer

REV W/F
3824A /S/ 7/2/84

Drug

KNOLL PHARMACEUTICAL COMPANY
30 NORTH JEFFERSON ROAD, WHIPPANY, NEW JERSEY 07981

May 7, 1984

NDA SUPPL AMENDMENT
5/003

Marvin Seife, MD, Director
Division of Generic Drugs (HFN-230)
National Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: VICODIN[R] (hydrocodone bitartrate 5mg and acetaminophen 500mg) Tablets, [redacted] manufacture), NDA 88-058. Amendment to Supplemental Application No. S-003

Dear Dr. Seife:

We refer to our supplemental application S-003, dated January 30, 1984, providing for a revised testing standard procedure (Registry No. T-770) for Vicodin Tablets [redacted] manufacture), NDA 88-058.

Attached, in response to your letter request of February 24, 1984, is the validation data for the revised new testing standard.

This information applies, and is being submitted concurrently, to our supplemental application S-020 for Vicodin Tablets [redacted] manufacture) NDA 85-667.

Please address any comments or inquiries regarding the attached material to the undersigned.

Respectfully,

R. O. Hanzas

A. C. Hanzas
Director
Drug Regulatory Affairs

RECEIVED
MAY 11 1984
GENERIC DRUGS

RRG:mg

Attachment

NDA 88-058/S-001, S-002

Knoll Pharmaceutical Company
Attention: Mr. Agamemnon C. Hanzas
30 North Jefferson Road
Whippany, NJ 07981

Gentlemen:

Reference is made to your supplements dated July 29, 1983 regarding your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vicodin (hydrocodone bitartrate 5 mg and acetaminophen 500 mg) Tablets.

Reference is also made to your communication dated January 4, 1984.

The supplemental applications provide for a ——— procedure and two year expiration date for the ——— tablets.

We have completed the review of these supplemental applications and request the following additional information:

Submit stability data at challenge conditions for ——— Vicodin Tablets (10750281R) prior to approval.

Please let us have your response promptly.

Sincerely yours,

/S/ FOR 1-31-84

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
National Center for Drugs and Biologics

cc: NWK-DD
HFN-530
JMeyer/CChan
R/D INITIAL JMeyer/MSeife
mm:1/27/84
Review

/S/ 1-30-84
/S/ 1/30/84

W/F

Drug

KNOLL PHARMACEUTICAL COMPANY
30 NORTH JEFFERSON ROAD, WHIPPANY, NEW JERSEY 07981

January 4, 1984

SUPPL NEW CORRES

Marvin Seife, MD
Director, Division of Generic Drug Monographs
Office of the Associate Director for
Drug Monographs
National Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Subject: Vicodin^{R} (hydrocodone bitartrate 5mg and acetaminophen 500mg Tablets, NDA 88-058/S-001, S-002

Dear Dr. Seife:

We refer to your letter of December 30, 1983 regarding our pending supplemental applications S-001 and S-002 for the above referenced drug.

You request submission of stability data at challenge conditions for ——— Vicodin Tablets (10760281R) when it becomes available. Results of stability testing under the requested conditions (37°, 75% humidity) should become available in early April 1984 (three-month data) and will be submitted promptly.

Based on the stability data previously submitted and our commitments noted in our letter of December 8, 1983, we request that approval of the supplements be granted.

Respectfully,

A. C. Hanzas

A. C. Hanzas
Director
Drug Regulatory Affairs

RRG:mg

RECEIVED
JAN 12 1984
GENERIC DRUGS

TELEPHONE (201) 887-8300 — TELEX: 136466

NDA 88-058/S-001, S-002

Knoll Pharmaceutical Company
Attention: Mr. Agamemnon C. Hanzas
30 North Jefferson Road
Whippany, NJ 07981

Gentlemen:

Reference is made to your supplements dated July 29, 1983 regarding your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vicodin (hydrocodone bitartrate 5 mg and acetaminophen 500 mg) Tablets.

Reference is also made to your communication dated December 8, 1983.

The supplemental applications provide for a ——— procedure and two year expiration date for the ——— tablets.

We have completed the review of these supplemental applications and request the following additional information:

Submit stability data at challenge condition for ——— Vicodin Tablets (10760281R) when it becomes available.

Please let us have your response promptly.

Sincerely yours,

/S/ D C

FOR 12-30-83

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
National Center for Drugs and Biologics

cc: NWK-DO
HFN-530
JMeyer/CChar /S/ 12-29-83
R/D INITIAL JMeyer/MSeife
mm:12/25/83 (3928c)
Review W/F
/S/ 12/29/83

Orig

KNOLL PHARMACEUTICAL COMPANY
30 NORTH JEFFERSON ROAD, WHIPPANY, NEW JERSEY 07981

December 8, 1983

NDA SUPPL AMENDMENT
S/001
002

Marvin Seife, MD
Director, Division of Generic Drug Monographs
Office of the Associate Director for
Drug Monographs
National Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Subject: Vicodin[R] (hydrocodone bitartrate 5mg and acetaminophen 500mg) Tablets, NDA 88-058/S-001,S-002

Dear Dr. Seife:

We refer to our supplemental new drug applications S-001 and S-002 for Vicodin[R] Tablets, and to your Agency's letter of October 7, 1983 requesting additional information in their regard.

Following are our responses to your comments:

1. The rationale for the ——— procedure:

   The ——— procedure is designed to ——— only ——— to the Knoll Pharmaceutical established testing standards, specifications and physical tablet characteristics. ——— will be performed after review and approval by the Quality Control Department.

2. Submit a commitment that you will notify FDA district office whenever a Vicodin ——— takes place.

   Knoll Pharmaceutical Company will notify our FDA district office whenever a Vicodin ——— takes place.

3. It is recommended that stability studies be performed on ——— Vicodin Tablets (10760281R) at challenged conditions (high humidity in addition to elevated temperature).

RECEIVED
DEC 12 1983

TELEPHONE (201) 887-8300 — TELEX: 136466

GENERIC DRUGS

Vicodin tablets control number 10760281R have been placed on stability testing at 37°/75% relative humidity. Samples will be tested after one month and three months at these conditions. Results of this testing will be reported in the next annual periodic report for Vicodin Tablets.

We trust the above information adequately responds to your request.

Please address any comments or inquiries regarding this information to me.

Respectfully,

A. C. Hanzas
Director
Drug Regulatory Affairs

RRG:mg

APPEARS THIS WAY
ON ORIGINAL

OCT 7 1983

NDA 88-058/S-001, S-002

Knoll Pharmaceutical Company
Attention: Mr. Agamemnon C. Hanzas
30 North Jefferson Road
Whippany, NJ 07981

Gentlemen:

Reference is made to your supplements dated July 29, 1983 regarding your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vicodin (hydrocodone bitartrate 5 mg and acetaminophen 500 mg) Tablets.

The supplemental applications provide for a ——— procedure and a two year expiration date for the ——— tablets.

We have completed the review of these supplemental applications and request the following additional information:

1. The rationale for the ——— procedure.

2. Submit a commitment that you will notify FDA district office whenever the ——— takes place.

3. It is recommended that the stability studies be performed on ——— Vicodin Tablets (# 10760281R) at challenged conditions (high humidity in addition to elevated temperature).

Please let us have your response promptly.

Sincerely yours,

/S/ on /for 10-7-83

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of the Associate Director for
Drug Monographs
Office of Drugs
National Center for Drugs & Biologics

cc:
NWK-DO
HFN-530
JLMeyer/CCha..
R/DinitJMeyer/MSeife
ft/cjl/10-5-83
rev w/

/S/ - 10-6-83

/S/ for J. L. Meyer
10-6-83

KNOLL PHARMACEUTICAL COMPANY
30 NORTH JEFFERSON ROAD, WHIPPANY, NEW JERSEY 07981

July 29, 1983 MD. NO. _____ REF. NO. 5002

NDA SUPPL. FOR 5-yr Date

NDA NO. 88-058 REF. NO. 5001

NDA SUPPL. FOR Control Rev

5-002
2yr expiration date

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of the Associate Director
of Monographs
Office of Drugs
National Center for Drugs & Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Seife:

Subject: VICODIN (hydrocodone bitartrate 5mg and acetaminophen 500mg) Tablets (manufacture)
NDA #88-058

Under the provision of 21 CFR, 314.8, we submit herewith a supplement to our abbreviated new drug application for Vicodin Tablets (manufacture), NDA 88-058. This supplemental application provides for a procedure and is set forth in Appendix A. Appendix B contains information relating to the stability of the Vicodin Tablets including the proposed expiration date.

Your earliest review and consideration in this matter is greatly appreciated. Please include this in the Administration's files for Vicodin Tablets of manufacture, NDA 88-058.

Sincerely,

Jeanmarie Kline /jr

A. C. Hanzas
Director
Drug Regulatory Affairs

JK/kg

Enclosure

TELEPHONE (201) 887-8300 — TELEX: 136466