CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20716

CHEMISTRY REVIEW(S)

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-716

DEC 11 1996

REVIEW #1 **DATE REVIEWED:** 9/17/96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	4-25-96	4-26-96	4-30-96
CORRESPONDENCE	5-29-96	6-03-96	6-12-96
CORRESPONDENCE	6-12-96	6-17-96	6-26-96
AMENDMENT	8-16-96	8-23-96	9-3-96

NAME & ADDRESS OF APPLICANT: Knoll Pharmaceutical Company
3000 Continental Drive, North
Mount Olive, New Jersey 07828-1234

DRUG PRODUCT NAME

- Proprietary: Vicoprofen® Tablets
- Established: Hydrocodone Bitartrate/ibuprofen
- Code Name/#: N/A
- Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY: Analgesic
DOSAGE FORM: Tablets, immediate release
STRENGTHS: 7.5/200 mg
ROUTE OF ADMINISTRATION: oral
DISPENSED: X Rx __ OTC
CONCLUSIONS & RECOMMENDATIONS:

This NDA is currently approvable due to numerous deficiencies.

cc:
Orig. NDA 20-716
HFD-550/Division File
HFD-550/Chem/CYaciw
HFD-550/CSO/LLoBianco
HFD-550/MO/JHyde
HFD-550/PK/DBashaw
HFD-550/Pharm/AWeir
filename: N20716C1.REV

Charlotte A. Yaciw
Charlotte A. Yaciw,
Chemist, HFD-550/830

Hasmukh B. Patel 11-18-96
Hasmukh Patel
Chemistry Team Leader, HFD-550

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-716

REVIEW #2 **DATE REVIEWED:** 2/24/97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	*4-25-96*	*4-26-96*	*4-30-96*
CORRESPONDENCE	*5-29-96*	*6-03-96*	*6-12-96*
CORRESPONDENCE	*6-12-96*	*6-17-96*	*6-26-96*
AMENDMENT	*8-16-96*	*8-23-96*	*9-03-96*
AMENDMENT	*12-16-96*	*12-24-96*	*1-02-97*
AMENDMENT	2-07-97	2-11-97	2-14-97

NAME & ADDRESS OF APPLICANT: Knoll Pharmaceutical Company
3000 Continental Drive, North
Mount Olive, New Jersey 07828-1234

DRUG PRODUCT NAME

- Proprietary: Vicoprofen® Tablets
- Established: Hydrocodone Bitartrate/ibuprofen
- Code Name/#: N/A
- Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY: Analgesic
DOSAGE FORM: Tablets, immediate release
STRENGTHS: 7.5/200 mg
ROUTE OF ADMINISTRATION: oral
DISPENSED: X Rx __ OTC

CONCLUSIONS & RECOMMENDATIONS:
This NDA is approvable although there are still deficiencies..

cc:
Orig. NDA 20-716
HFD-550/Division File
HFD-550/Chem/CYaciw
HFD-550/CSO/LLoBianco
HFD-550/MO/JHyde
HFD-550/PK/DBashaw
HFD-550/Pharm/AWeir
filename: N20716C2.REV

Charlotte A. Yaciw
Charlotte A. Yaciw,
Chemist, HFD-550/830

Hasmukh B. Patel 2-28-97
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JUL 7 1997

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-716

REVIEW #: 3 **DATE REVIEWED:** 6/27/97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	*4-25-96*	*4-26-96*	*4-30-96*
CORRESPONDENCE	*5-29-96*	*6-03-96*	*6-12-96*
CORRESPONDENCE	*6-12-96*	*6-17-96*	*6-26-96*
AMENDMENT	*8-16-96*	*8-23-96*	*9-03-96*
AMENDMENT	*12-16-96*	*12-24-96*	*1-02-97*
AMENDMENT	*2-07-97*	*2-11-97*	*2-14-97*
AMENDMENT	5-23-97	5-27-97	6-09-97

NAME & ADDRESS OF APPLICANT: Knoll Pharmaceutical Company
199 Cherry Hill Road
Parsippany, New Jersey 07054

DRUG PRODUCT NAME

Proprietary:	Vicoprofen® Tablets
Established:	Hydrocodone Bitartrate/ibuprofen
Code Name/#:	N/A
Chem.Type/Ther.Class:	3S
PHARMACOL. CATEGORY:	Analgesic
DOSAGE FORM:	Tablets, immediate release
STRENGTHS:	7.5/200 mg
ROUTE OF ADMINISTRATION:	oral
DISPENSED:	_X_ Rx __ OTC

CONCLUSIONS & RECOMMENDATIONS:
The CMC is now acceptable. This NDA may be approved with the Methods Validation paragraph.

cc:
Orig. NDA 20-716
HFD-550/Division File
HFD-550/Chem/CYaciw
HFD-550/CSO/~~SCook~~ Lutwiak
HFD-550/PK/DBashaw

Charlotte A. Yaciw
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Hasmukh B. Patel
Chemistry Team Leader, HFD-550

filename: N20716C4.REV

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20716

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

VICOPROFEN
HYDROCODONE BITARTRATE/IBUPROFEN
TABLETS

NDA 20-716

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION HFD-550

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-716
VICOPROFEN
HYDROCODONE BITARTRATE/IBUPROFEN
TABLETS

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required to under NEPA to consider the environmental impact of approving certain drug applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Vicoprofen Tablets, Knoll Pharmaceutical has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

* * *

Vicoprofen is a combination of hydrocodone bitartrate and ibuprofen administered orally as an immediate release formulation for the management of pain. This application allows sale of this product only by prescription. Typically, treatment is for a limited period. Production of the hydrocodone bitartrate will be at Mallinckrodt, St. Louis, Missouri. Production of the ibuprofen will be at Albemarle, Orangeburg, South Carolina. Production of the tablets will be at the Knoll manufacturing facilities in Whippany, New Jersey. Distribution will be from centers in the U.S.A. prior to sales to pharmacies.

Finished product will be sold in pharmacies, ultimate patient use and disposal will be mainly in residences.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging.

In the United States, unused or expired product will be

disposed of in approved incinerators and/or landfills. Federal and state waste permits and state air pollution control permits have been issued.

Empty or partially empty containers will be disposed of as trash by consumers and disposed of by the community's solid waste management system.

Neither the drug substances nor drug product are expected to be introduced into the environment via transportation or storage.

During the drug product manufacturing process at Whippany, New Jersey waste may result in air emissions, liquid waste streams and solids. Air emissions consist essentially of dust from the process and are controlled by filtering the exhausts. Liquid waste streams are discharged to an on-site waste water treatment facility and/or discharged into a local sewer system. Solid waste will be disposed of off-site at licensed disposal facilities.

Hydrocodone bitartrate, ibuprofen, and the other components of Vicoprofen Tablets are known not to be volatile and, therefore, release into the air would not be expected from therapeutic use or disposal.

Manufacture of Vicoprofen Tablets represents a portion of the total production at the facilities in Whippany, New Jersey. Land use will not be altered since existing Wyeth-Ayerst facilities will be utilized.

Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

* * *

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

7/11/97 Charlotte A. Yaciw
DATE PREPARED BY
Charlotte A. Yaciw
Review Chemist
HFD-550/830

7/11/97 Hasmukh B. Patel
DATE DIVISION CONCURRENCE
Hasmukh Patel
Chemistry Team Leader
HFD-550

7/16/97 Nancy B. Sager
DATE Approved
Nancy B. Sager
HFD-357
Center for Drug Evaluation and Research

Attachment:

FOIA copy of report (including MSDS)

ENVIRONMENTAL ASSESSMENT

(21 CFR 25.31a)

1. Date: April 2, 1996

2. Name of applicant: Knoll Pharmaceutical Company

3. Correspondence Address: 199 Cherry Hill Road
Parsippany, New Jersey 07054

4. Description of the proposed action:

a. Knoll Pharmaceutical is filing NDA #20-716, requesting approval to market Vicoprofen® Tablets. These tablets are indicated for the treatment of moderate to severe pain. They will be provided in one tablet size, containing 200.0 mg ibuprofen USP and 7.50 mg hydrocodone bitartrate USP.

b. The filing of the NDA was needed to obtain approval for the marketing of the drug product in the United States. This section of the NDA will assess the environmental aspects of the approval of the NDA.

c. Complete manufacturing addresses for all sites can be found at the end of section 4 c on page 3.

The ibuprofen will be manufactured by Albemarle Corporation, Baton Rouge, LA and the hydrocodone bitartrate by Mallinckrodt, St. Louis, MO. Both companies have submitted letters of authorization to Knoll Pharmaceutical Company, allowing reference to their Drug Master Files (DMF) covering the manufacture of these substances:

DMF 5381, Albemarle Corporation;
DMF 4884, Mallinckrodt Specialty Chemicals Company.

Copies of these letters of authorization are attached.

The tablets containing the two active ingredients will be formulated and packaged by Knoll Pharmaceutical Company at their plant at 30 North Jefferson Road, Whippany, NJ. The Vicoprofen® Tablets will be packaged in high density polyethylene bottles and as hospital unit dose polyethylene/aluminum backed blister packages. In addition, unit dose packaging will be performed by Reed-Lane, Inc., South Hackensack, NJ.

Manufacturer Addresses

Drug Substance

Ibuprofen	Hydrocodone Bitartrate
Albemarle Corporation Cannon Bridge Road Orangeburg, SC 29116-1028	Mallinckrodt Specialty Chemicals Company Mallinckrodt Drive and Second Avenue St. Louis, Missouri 63147

Drug Product — Vicoprofen Tablets

Knoll Pharmaceutical Company
30 North Jefferson Road
Whippany, New Jersey 07981

Packager — Unit Dose Package

Reed Lane, Inc.
550 Huyler Street
South Hackensack, New Jersey 07606

d. The sponsor plans to market the product in the United States where it will be supplied to individual patients by pharmacies, both independent and hospital-affiliated. Metabolites excreted by patients in urine and feces will be treated at local sewage treatment plants across the 50 states.

e. Unused drug product supplies will be disposed of by individuals as part of their municipal solid waste in the communities where they live. Pharmacies and hospitals will dispose of unused drug supplies as solid waste either to their municipalities or to private waste contractors, possibly for incineration.

The types of environments present at and adjacent to the production locations can be described as follows:

1) the manufacturing facility in Baton Rouge, LA: described in DMF 5381
2) the manufacturing facility in Chesterfield, MO: described in DMF 4884
3) the manufacturing and packaging facility in Whippany, NJ: suburban
4) the unit dose packaging facility in South Hackensack, NJ: suburban

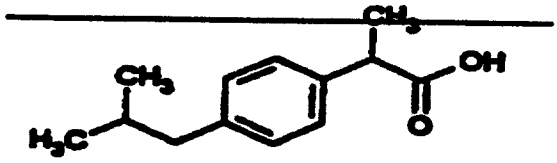
The types of environments where the product will be used and disposed of encompass the entire range of environments existing in the United States (possibly excepting wilderness): rural, suburban, and urban. Sewage treatment plants, landfills, and incinerators exist all across the United States and their placement is not confined to any one type of environment. It is impossible to know which of these various disposal facilities will be involved in the treatment and disposal of metabolized and/or unused Vicoprofen® Tablets.

5. Identification of chemical substances that are the subject of the proposed action:

DRUG SUBSTANCES:

Established or generic name:	Ibuprofen
CAS Reg. No.:	15687-27-1
Chemical name:	(±)-2-(p-Isobutylphenyl)propionic acid
Molecular name:	$C_{13}H_{18}O_2$
Melting point:	75-77°C
Molecular weight:	206.29
Impurity Limits:	Not more than 0.3% of any individual impurity, and the sum of all the individual impurities should not exceed 1.0%

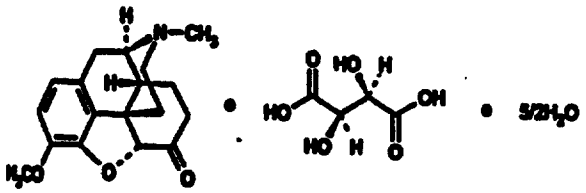
Structural formula:



DRUG SUBSTANCES (Continued)

Established or generic name:	**Hydrocodone Bitartrate**
CAS Reg. No:	**34195-34-1**
Chemical name:	**4,5 I -Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)**
Molecular formula:	$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$
Physical description:	**White needle-shaped crystalline solid**
Melting point:	**≈137 - 143°C**
Molecular weight:	**494.50**
Impurity Limits:	**Maximum 2.0%**

Structural formula:



DRUG PRODUCT

Vicoprofen® Tablets include the active ingredients, ibuprofen and hydrocodone bitartrate, at the level of 200.0 mg and 7.50 mg respectively. The inactive ingredients in these tablets consist of:

Core Tablet Ingredients:

Colloidal silicon dioxide NF	CASRN: 7631-86-9
Microcrystalline cellulose NF	CASRN: 9004-34-6
Croscarmellose sodium NF	CASRN: 74811-65-7
Corn starch NF	CASRN: 9005-25-8
Hydroxypropylmethylcellulose (HPMC) USP	CASRN: 9004-65-3
Purified water USP[1]	CASRN: 7732-18-5
Magnesium stearate NF	CASRN: 557-04-0

Film-coat Ingredients:

Opadry White YS-1-7003

Contains: hydroxypropyl methylcellulose USP (CASRN:9004-65-3),titanium dioxide USP (CASRN: 13463-67-7), polyethylene glycol NF (CASRN: 25322-68-3), and polysorbate 80 NF (CASRN: 9005-65-6)

Opadry Clear YS-3-7011

Contains: hydroxypropyl methylcellulose USP (CASRN: 9004-65-3), polyethylene glycol NF (CASRN: (25322-68-3), and polysorbate 80 NF (CASRN: 9005-65-6)

Purified water, USP[1]	CASRN: 7732-18-5

[1]Removed during processing

The specifications for the tablets call for each of the active ingredients to be present at no less than 90% and no more than 100% of the labeled amount.

6. Introduction of substances into the environment:

CAUSED BY PRODUCTION OF BULK DRUG SUBSTANCES:

A full description of the manufacturing facilities responsible for producing the bulk drug substances, Albemarle Corporation, 451 Florida Street, Baton Rouge, LA, and the Mallinckrodt Specialty Chemicals Company, Mallinckrodt and Second Avenue, St. Louis, MO, is given in their DMFs referenced previously. Approval of the NDA will have no adverse effect upon compliance with the current emissions requirements at either of these manufacturing sites. Certifications from both manufacturers will accompany this document in the confidential appendix (Appendix D Manufacturing Information).

Worker safety procedures in place will be adequate to assure worker safety in the manufacturer of the ibuprofen and hydrocodone bitartrate hemipentahydrate. The Material Safety Data Sheets are attached (Appendix B).

CAUSED BY FORMULATION AND PACKAGING OF DRUG PRODUCT

The formulation and packaging operation carried out at the Knoll Pharmaceutical Company facility at 30 North Jefferson Road, Whippany, NJ, complies with all applicable environmental regulations. Substances emitted and control measures used are as follows:

Substances emitted into the air:

Dust is collected during the manufacturing process by the following equipment, with an air emission permit certified by the State of New Jersey Department of Environmental Protection (NJDEP). The filtered air is discharged to the environment. The material from the dust collectors will be disposed by incineration with solid waste as described in the terrestrial ecosystem paragraphs.

NJDEP PERMIT NUMBER	EXPIRATION DATE	EQUIPMENT DESCRIPTION
080796	9/8/98	CY-802 Spencer Central Vacuum
080798	9/8/98	CY-801 Production Dust Collector
[079511	11/3/98	Despatch Tray Dryer]
107443	8/17/2000	Packaging Line #1 Cabinet Dust Collector
108106	10/5/95*	Packaging Lines #2 & #4 Cabinet Dust Collectors

*Note: This is a temporary permit renewing automatically every three months pending issue of a permanent permit by the NJDEP.

Fresh water, estuarine, and marine ecosystems:

All process water is discharged to POTW (Hanover Sewerage Authority), Industrial Sewer Discharge Permit No. D-9 (expiration date, March 31, 1996). Discharged process water complies with the provisions of the Federal Clean Water Act, New Jersey Water Pollution Control Act, and the Hanover Sewerage Authority requirements.

Terrestrial ecosystems:

Vicoprofen® Tablets are not a controlled substance. All discernible residues from manufacturing and distribution of the products are collected and disposed of by incineration at an EPA approved treatment, storage and disposal facility.

Knoll as a waste generator has an EPA ID number NJD058118308.

Approval of the NDA will have no adverse effect upon compliance with the current emissions requirements in Whippany, NJ.

Additional solid waste will be handled by disposal/incineration at Rollins Environmental Services, Inc., Rt. 322 and I-295, Bridgeport, NJ 08014. Rollins holds a permit, #NJD053288239, issued by the NJ Department of Environmental Protection, for this work, with an expiration date of March 31, 1994. (Note: Due to regulatory delays, permit renewal for Rollins Environmental Services, Inc. is still pending decision by the

NJDEP. The facility continues to operate under temporary approval by the NJDEP pending a final decision regarding the renewal application.)

Also handling solid waste disposal/incineration will be Long Beach Recycling and Recovery, 70 Water Street, Long Beach, NY 11561, Permit #DLC 1-2809-00088/00006-0, issued by the NY Department of Environmental Conservation, expiration date May, 1995. (Note: Due to regulatory delays, permit renewal for Long Beach Recycling and Recovery is still pending decision by the NYDEC. The facility continues to operate under temporary approval by the NYDEC pending a final decision regarding the renewal application.)

CAUSED BY USE AND DISPOSAL

In order to assess the impact on the environment of the use and disposal of Vicoprofen® Tablets, certain assumptions about usage patterns and amounts have been made, which are confidential. Therefore, the calculation of the expected introduction concentration (EIC) entering into the aquatic environment has been included in a confidential appendix (Appendix D, Manufacturing Information).

7. Fate of emitted substances in the environment:

Vicoprofen® Tablets contain two active ingredients: ibuprofen and hydrocodone bitartrate. The fate of these two substances in the three major environmental compartments will be addressed.

Ibuprofen

(a) Air

Ibuprofen (molecular weight 206.29, m.p. 75-77□C) is a white crystalline solid at room temperature. Very little volatilization would be expected from this substance.

The drug product is a tablet which contains nearly 50% ibuprofen. Unused material, disposed of and landfilled, will not generate noticeable amounts of volatilized ibuprofen. Upon incineration, primarily carbon dioxide and water would be formed.

(b) Water

Ibuprofen is slightly soluble in water at pHs lower than neutral and, at pH 7.5, soluble to the extent of 6.56 mg/mL. Its pKa is ~5.2. Ibuprofen is very soluble in alcohol, methanol, acetone, and chloroform, slightly soluble in ethyl acetate.

c) Terrestrial ecosystems

If unused tablets are disposed of in landfills, much of the ibuprofen will remain essentially unchanged. Five types of forced degradation studies were performed on Vicoprofen tablets, including basic, acidic, oxidative, photolytic and heat conditions. Details of these experiments are given in Appendix C.

Only under conditions of acid hydrolysis was the amount of ibuprofen present at the end of the experiment less than 93% of the beginning amount.

As an organic compound in a landfill, ibuprofen will ultimately degrade to carbon dioxide and water, the same products that will be formed if the unused tablets are incinerated.

Hydrocodone Bitartrate

(a) Air

Hydrocodone bitartrate (molecular weight 494.5, m.p. ~137-143□C) is a white needle-shaped crystalline solid. Very little volatilization would be expected from this substance.

The drug product is a tablet which contains less than 2% hydrocodone bitartrate. Unused material, disposed of and landfilled, will not generate noticeable amounts of volatilized hydrocodone bitartrate. Upon incineration, primarily carbon dioxide and water would be formed.

(b) Water

Hydrocodone bitartrate has a water solubility of 63 g/L. In 95% alcohol, 8.2 g/L are soluble, and the material is insoluble in ether and chloroform.

In those tablets disposed of for sewage treatment, the hydrocodone bitartrate can be expected to to go into water solution. Even in landfills, the hydrocodone bitartrate will undoubtedly be leached out into water solution.

(c) Terrestrial ecosystems

Little of the hydrocodone bitartrate deposited in landfills will remain in solid form, given its water solubility.

The same forced degradation studies were performed on hydrocodone bitartrate as on ibuprofen: using basic, acidic, oxidative, photolytic and heat conditions (experimental details in Appendix C). Only in the case of basic hydrolysis was the amount of hydrocodone bitartrate recovered less than 86% of the amount at the beginning of the experiment.

8. Environmental effects of released substances:

(a) Air

Due to the small amounts of either ibuprofen or hydrocodone bitartrate expected to volatilize, the use and disposal of these products will not have any significant environmental effect on the air.

(b) Water

Even though ibuprofen is only slightly soluble in water, the amount of the substance entering any one sewage treatment plant will undoubtedly dissolve in the water, considering the very large quantities of water involved in the processes of Publicly Owned Treatment Works (POTWs). However, the amounts involved in any one sewage treatment plant will not be large enough to cause problems (EIC-Aquatic calculated, Appendix D).

Hydrocodone bitartrate is soluble in water and will be found in the treated effluent of POTWs wherever Vicoprofen is used. The amounts of this substance will be so small at any one location that no negative impacts related to its presence will be noted.

Both ibuprofen and hydrocodone bitartrate have been used for many years without report of toxic effects from their disposal.

(c) Terrestrial ecosystems

Ibuprofen will primarily remain unchanged in any landfill where it is placed, until it decomposes into carbon dioxide and water. The small portion of ibuprofen that may dissolve due to moisture in the landfill will not present any environmental problems.

If Vicoprofen tablets are disposed of in a landfill, hydrocodone bitartrate will dissolve if water is present and the solution will leach out of the solids. The amounts will be so small that no toxic effects will occur.

9. Use of resources and energy

Water and electricity used in the manufacture of Vicoprofen tablets at Whippany, NJ are described in Appendix D.

The solids emitted during the manufacture of Vicoprofen tablets and disposed of by incineration comprise an insignificant portion of the material incinerated at the waste facility. The same is true of the process water discharged to the Publicly Owned Treatment Works (POTWs) and the dust collected and disposed of.

The bulk ibuprofen and hydrocodone bitartrate are shipped from Louisiana and Missouri respectively primarily by truck. The amount of energy attributable to these shipments is not going to have a major environmental effect.

The finished product will be shipped from NJ by truck to about 50 wholesalers across the country. Some small amount of diesel fuel will be required for these shipments.

The amount of Vicoprofen tablets expected to be returned unused, based on previous experience, will probably be about 2 percent of the total production. This material will be picked up by Rollins Environmental Services for incineration. The energy used in this activity will be insignificant.

It was assumed that all of the Vicoprofen tablets prescribed for patients would be ingested, metabolized, and excreted, primarily ending up in POTWs across the country. The annual amount here is the production amount, disregarding the small portion returned unused. It is estimated that inflow to POTWs nationwide amounts to about 80×10^{12} lbs per year. This amount is so much larger than the annual production of Vicoprofen tablets (Appendix D) that the addition of the total amount of Vicoprofen tablets produced will not have a significant impact on the POTWs, either their operation or the content of their effluent.

The production and packaging of Vicoprofen tablets will take place in New Jersey, with the two active ingredients being manufactured in Louisiana and Missouri. There is no habitat of an endangered or threatened species close enough to any of the manufacturing or packaginig facilities for there to be a significant effect. Transport, use, and disposal of the material will take place across the entire United States, but the amounts in any one location will be small enough so as to have no significant effect on any endangered or threatened species in that location.

The manufacturing sites in New Jersey, Lousiana, and Missouri are not close to any properties listed in or eligible for listing in the National Register of Historic Places. Therefore, the manufacture will not adversely effect historic sites. Transport, use, and disposal of the material will be nationwide, but the amounts at any one location will not affect any historic place, assuming that existing highways, landfills, and POTWs have all been sited with reference to the impact on historic places in the area.

10. Mitigation measures:

Sound engineering design and controls, effective preventive maintenance programs, good manufacturing and disposal practices have all reduced the introduction of materials from the manufacturing and testing of this product into the environment.

Publicly-owned waste treatment plants, landfills, and incinerators meeting all regulatory requirements will provide the proper conditions for disposal of any unused drug product as well as the substances excreted by patients after use.

In the event of a spill of the bulk drug substance, either in the manufacturing site or while being transported, the procedures described in the Material Safety Data Sheets should be followed (refer to Appendix B). Measures to ensure worker safety are discussed in these documents.

Prescriptions for the drug product will not normally exceed one bottle containing 100 tablets to any one patient, so should a spill occur at this stage, no environmental damage will occur. The amounts of unused drug product discarded by individual patients will be so small at any one location that no environmental damage will occur if they are not transported properly to a landfill.

11. Alternatives to the proposed action:

An alternative which would prevent any possible contamination of the environment by this drug substance and/or product would be to discontinue manufacturing and not introduce the product into the market. However, this course of action would remove a useful drug which could benefit patients suffering from moderate to severe pain.

12. List of preparers:

NAME	TITLE	QUALIFICATIONS
D.J. Cajucom	Coordinator-IH and Ecology	Degree in Chemical Eng.
M.W. Fitch	Vice President Plant Operations	Pharmacy Degree
A. B. Sayigh	Executive Vice President, Parexel International Corp.	Ph.D. in Chemistry

13. Certification:

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm or agency responsible for preparation of the environmental assessment.

The undersigned official certifies that the EA summary document (pages 1-21) and Appendices A and B (pages 22-40) contain non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR § 1506.6

Date: 5/23/97

Susan F. Hamet
Signature of Responsible Official

Regulatory Affairs Associate
Title

14. References:

None

15. Appendices:

Non-confidential

A. Summary Data Table

B. Material Safety Data Sheets

Confidential

C. Test Reports of Fate and Effects

D. Manufacturing Information

ALBEMARLE™
CORPORATION

451 Florida Street
Baton Rouge, Louisiana 70801

Telephone: 504-388-8011
Facsimile: 504-388-7686

Health and Environment Department
Toxicology and Regulatory Affairs
Facsimile: 504-388-7046

August 28, 1996

Ms. Charlotte Yaciw
Division of Anti-inflammatory Analgesics
and Ophthalmic Drug Products
HFD-550
CDER
9201 Corporate Blvd.
Rockville, MD 20850

RE: ALBEMARLE CORPORATION CERTIFICATE OF ENVIRONMENTAL COMPLIANCE

Dear Ms. Yaciw:

This letter references your review of Knoll Pharmaceutical's NDA No. 20-716 for Vicoprofen (hydrocodone and Ibuprofen tablets). It serves to certify that Albemarle Corporation's Ibuprofen manufacturing site located at:

Cannon Bridge Road
P.O. Box 1028
Orangeburg, SC 29116-1028

is in compliance with local, State and Federal environmental assessment guidelines. Although not now required, an Environmental Assessment section is included in Albemarle's reformatted Drug Master File No. 5381 - Ibuprofen.

Please contact me if there are additional questions.

Sincerely,

ALBEMARLE CORPORATION

James S. Crawford, Ph.D.
Regulatory Advisor

MALLINCKRODT CHEMICAL

Mallinckrodt Chemical, Inc.
16305 Swingley Ridge Drive
Chesterfield, Missouri 63017-1777
Telephone (314) 530-2000

Mrs. Susan F. Hamet, Regulatory Associate
Knoll Pharmaceuticals
199 Cherry Hill Road
Parsippany, NJ 07054

Re: Compliance Certification -- Hydrocodone Bitartrate

Date: September 3, 1996

Dear Mrs. Hamet:

Mallinckrodt hereby certifies that its Hydrocodone Bitartrate production is in compliance with all Federal, State, and Local environmental and occupational regulations.

If you have any questions concerning this, please contact me.

Sincerely,

Steve Donatiello, P.E.
Environmental Program Manager
314-530-2032

APPENDIX A

SUMMARY DATA TABLE

SUMMARY DATA TABLE

	IBUPROFEN	HYDROCODONE BITARTRATE
Water solubility	very slightly soluble 0.04 mg/mL at pH 3.4 0.61 mg/mL at pH 5.6* 6.56 mg/mL at pH 7.5*	63 g/L
Dissociation constant	pKa = 5.2*	pKa = 3.6 in a 2% aqueous solution
Octanol/water partition coefficient	2.2**	
Vapor pressure	9×10^{-6} mmHg***	
Hydrolysis: base hydrolysis (1.0 N sodium hydroxide)	2.7% (8 hr)	17.3% (5 hr)
acid hydrolysis (1.0 N hydrochloric acid)	59.262% (2 hr)	- (8 hr)
Oxidation (3% hydrogen peroxide)	6.7% (8 hr)	13.3% (8 hr)
Photolysis (Sunlighter****)	0.7% (24 hr)	- (24 hr)
Heat (65°C for 24 hr)	no effect	no effect
Acute toxicity - oral	LD50 = 1255 mg/kg, mice (m) LC50 = 1050 mg/kg, rats (m)	hydrocodone: LD50 = 8.57 mg/kg, mice (s.c.)

* Loftsson, T; Olafsdottir, B.J.; Frioriksdottir, H. and Jonsdottir, S., Eur. J. Pharm. Sci., 1993, 1, 95-101.

** Estimated from log (solubility in hexane/solubility in water pH 5.6). Solubility in hexane was provided by Albemarle Corporation.

*** Ertel, K.D.; Heasley, R.A.; Koegel, C.; Chakrabarti, A.; and Carstensen, J.T., J. Pharm. Sci., 1990, 79, 552.

**** Sunlighter has a 100:1 ratio of the approximate acceleration over a full year of natural sunlight.

SOLUBILITY OF IBUPROFEN IN HEXANE

Solubility [illegible]	Temperature [illegible]
70.0	60.0
54.0	50.0
40.0	45.0
25.0	40.0
18.0	35.0
13.0	30.0
9.0	25.0
6.9	20.0
5.0	15.0
4.0	10.0
3.0	5.0
2.4	0.0
1.8	-5.0
1.5	-10.0
1.2	-15.0
0.9	-20.0
0.7	-25.0
0.6	-30.0

Record 1 of 1 - Derwent Drug File 1/92-12/94

93-39325
29 38 43 71
Loftsson-T; Olafsdottir-B-J; Frioriksdottir-H; Jonsdottir-S
Eur.J.Pharm.Sci. (1, No. 2, 95-101, 1993)
Cyclodextrin Complexation of NSAIDs: Physicochemical Characteristics.
The physico-chemical properties of the complexes of aspirin (Apodan), ibuprofen, methyl acetylsalicylate, methyl salicylate (Merck-Darmstadt), naproxen and tenoxicam (Sigma-Chem.) with cyclodextrins were investigated. All of these NSAIDs formed inclusion complexes with beta-cyclodextrin (beta-CD, Nihon-Shokuhin-Kako), 2-hydroxypropyl-beta-CD, 2-hydroxypropyl-gamma-CD (both Wacker), and a mixture of maltosyl/dimaltosyl beta-CD (Ensuiko). Addition of ethanol or propylene glycol to the aqueous CD solutions reduced the degree of complexation. Although ionization of the drug also reduced the degree of complexation, complexation with ionized drugs resulted in much larger total solubilization. NMR spectroscopy was used to study the structure of the inclusion complex of aspirin and beta-CD. (No EX).
4 Fig. 4 Tab. 24 Ref. (LP)
Department of Pharmacy, University of Iceland, IS-101 Reykjavik, Iceland.

Table 1
The effect of pH (i.e. the ionization of the drug molecule) on the solubilizing abilities of HPβCD MS 0.9 at 30.0 ± 0.2°C. The pK$_a$ values were obtained from Delgado and Reinero (1991)

HPβCD conc. (% w/v)	Solubility (mg/ml)								
	Ibuprofen (pK$_a$ 5.2)			Naproxen (pK$_a$ 4.2)			Tenoxicam		
	pH 3.4	pH 5.6	pH 7.5	pH 3.4	pH 5.6	pH 7.5	pH 4.6	pH 6.2	pH 9.9
0	0.04	0.61	6.56	0.0	0.52	9.18	—[a]	0.66	9.87
1	0.97	1.88	8.50	0.22	1.08	10.8	—	—	—
5	4.67	6.31	11.8	1.42	3.73	12.2	0.22	2.16	11.1
10	8.67	11.8	13.9	3.22	8.32	16.9	0.35	3.09	12.3
15	12.3	16.1	20.0	6.54	11.8	20.0	0.46	4.40	13.1

[a]Not determined.

of the inclusion complex between the salicylic acid derivatives and βCD. Assignment of the ^{1}H NMR peaks of salicylic acid, acetylsalicylic acid and βCD was simple and in the case of βCD based on previous work (Ueda and Nagai, 1980; Nishijo and Nagai, 1990). Fig. 2 shows the induced ^{1}H-chemical shifts of the βCD signals by salicylic acid and acetylsalicylic acid. The signals of protons located around the interior (i.e. H-3, H-5 and H-6) show a larger effect than the protons on the exterior of the cavity (i.e. H-1, H-2 and H-4) which clearly shows that the drug molecules form inclusion complexes with βCD. Much tion is a common method for increasing the aqueous solubility of ionizable drugs and in aqueous solutions CD complexation of ionized drug molecules can result in much larger total drug solubilization, i.e. the solubilization of a drug both due to CD complexation and ionization, than if either method was used by itself. Small lipophilic molecules such as ethanol or propylene glycol reduce the CD solubilization, possibly by occupying the lipophilic CD cavity and, thus, preventing the drug molecules from entering (Pitha and Hoshino, 1992).

Basically, there are four different ways for the

APPENDIX B

MATERIAL SAFETY DATA SHEETS

ALBEMARLE CORPORATION
MATERIAL SAFETY CATA SHEET
451 FLORIDA STREET, BATON ROUGE, LA 70801
FOR EMERGENCIES ONLY - Phone (504) 344-7147

For Non-emergency Health & Safety Phone 1-800-535-3030
epresenting Albemarle Foreign Sales Corporation for Export Sales

ISSUE DATE: 08/25/94
SUPERSEDES: 01/08/91

IS CLASSIFICATIONS:
HEALTH: 2
FLAMMABILITY: 0
REACTIVITY: 1

35.3.0

PRODUCT IDENTIFICATION

PRODUCT NAME: Ibuprofen USP

CHEMICAL NAME: 2-(4-isobutylphenyl)propionic acid

CAS NO.: 15687-27-1

CHEMICAL FORMULA: C13H1802

CHEMICAL FAMILY: Carboxylic acid

SUMMARY OF HAZARDS

See ''Other Health Effects.''

OS HAZARDOUS COMPONENTS

CHEMICAL NAME	CAS NO.	NOTE	EXPOSURE LIMIT
2-(4-isobutylphenyl) propionic acid	15687-27-1	ND	Not established by OSHA/ACGIH.

NOTE: Carcinogenicity listing of components at concentrations greater than or equal to 0.1% indicated by: @=NTP; *=IARC; &=OSHA; +=ACGIH; **=OTHER; ND=Not Designated.

CHEMICAL AND PHYSICAL PROPERTIES

APPEARANCE/ODOR: White to off-white, crystalline powder/slight odor.

EMERGENCY PHONE NUMBER 344-7147 PRODUCT NAME: Ibuprofen USP

35.3.0

CHEMICAL AND PHYSICAL PROPERTIES (Con't)

VAPOR PRESSURE: < 0.1 mm Hg @ 38C/100F.

VAPOR DENSITY: 7.1 (air = 1).

SOLUBILITY IN WATER: Negligible.

SPECIFIC GRAVITY: < 1.0

MELTING POINT: 74-77C/165-171F (Range).

FIRE AND EXPLOSION HAZARDS

FLASH POINT(METHOD): Not applicable.

FLAMMABLE LIMITS: Not established.

EXTINGUISHING MEDIA: Dry chemical, water spray (fog), foam or carbon dioxide.

HAZARDOUS THERMAL DECOMPOSITION PRODUCTS: Include oxides of carbon.

SPECIAL FIRE FIGHTING PROCEDURES: Avoid breathing smoke and vapor.

FLAMMABLE LIMITS: Not established.

UNUSUAL FIRE AND EXPLOSION HAZARDS: The minimum dust concentration for explosion value of ibuprofen is lower than normal. Most dusts ignite at 0.05 oz/ft3. Ibuprofen dust will ignite at 0.025 oz/ft3. See "Additional Precautions" section for safety measures.

REACTIVITY DATA

STABILITY: Stable.

CONDITIONS TO AVOID: None.

MATERIALS TO AVOID: Alkaline substances.

HAZARDOUS POLYMERIZATION: Will not occur.

EMERGENCY PHONE NUMBER 344-7147 PRODUCT NAME: Ibuprofen USP 35.3.0

HEALTH HAZARDS

INHALATION: Not expected to be a primary route of exposure. Avoid breathing dust, may cause bronchoconstriction in persons with asthma or hypersensitivity to aspirin.

INGESTION: If ingested, not expected to be toxic. A small number of patients on therapeutic doses of Ibuprofen have developed vision changes, gastrointestinal symptoms, dizziness, headache, nervousness, tinnitus, skin rash, pruritis, blood dyscrasia, loss of appetite, fluid retention, bronchospasm, impaired renal function and allergic reactions. Adults are unlikely to develop serious toxicity. Through the use of good industrial hygiene practices, the ingestion of Ibuprofen will be far below therapeutic dose.

EYE CONTACT: Not expected to be an eye irritant.

SKIN CONTACT: Not expected to be a skin irritant.

CHRONIC EFFECTS OF OVEREXPOSURE: None known.

OTHER HEALTH EFFECTS: Literature data indicate that Ibuprofen causes allergic skin reactions. Avoid repeated or prolonged exposure to skin.

TOXICITY DATA: ORAL LD50 (rat) = 1.8 g/kg.

EMERGENCY FIRST AID PROCEDURES

INHALATION: Remove to fresh air. If not breathing, give artificial respiration, preferably mouth-to-mouth. If breathing is difficult, give oxygen. Get medical attention.

EYE CONTACT: Begin immediate eye irrigation with cool water.

SKIN CONTACT: Wash contaminated areas with soap and water.

INGESTION: Give two glasses of water. Do not induce vomiting. Get medical attention.

EMERGENCY PHONE NUMBER 344-7147 PRODUCT NAME: Ibuprofen USP

35.3.0

EXPOSURE CONTROL INFORMATION

EXPOSURE LIMITS: Not established by OSHA/ACGIH.

EYE PROTECTION: Chemical goggles.

PROTECTIVE GLOVES: Resistant to chemical penetration.

RESPIRATORY PROTECTION: NIOSH approved dust/mist respirator.

MECHANICAL VENTILATION: Recommended.

LOCAL EXHAUST VENTILATION: At source of dust.

OTHER: If repeated or prolonged skin contact or contamination of clothing is likely, protective clothing should be worn.

ENVIRONMENTAL PROTECTION

SPILLS OR LEAKS: Sweep or shovel spills into appropriate container for disposal.

DISPOSAL METHODS: Under the CERCLA/RCRA regulations currently in effect, this product is not regulated as a hazardous waste or material. Therefore, it may be disposed of as an industrial waste in a manner acceptable to good waste management practice and in compliance with applicable local, state and federal regulations.

STORAGE REQUIREMENTS: No special storage required. Store in cool, dry area.

ADDITIONAL PRECAUTIONS OR COMMENTS

Federal law prohibits dispensing without FDA approval. For manufacturing, processing, or repackaging only. It is recommended that all dust control equipment, milling systems, material transport systems, blenders and drying equipment involved in the processing of Ibuprofen

08/25/94

EMERGENCY PHONE NUMBER 344-7147 PRODUCT NAME: Ibuprofen USP

35.3.0

ADDITIONAL PRECAUTIONS OR COMMENTS (Con't)

contain explosion relief vents, explosion suppression systems, or oxygen-deficient environment. All conductive elements of the system that contact the dry powder should be electrically bonded and grounded. Explosion hazard can be reduced by good housekeeping, prevention of accumulation of dust on overhead, horizontal surfaces. In additions, a continuing effort should be made to control ignition sources.

REGULATORY INFORMATION

TSCA:
THIS MATERIAL IS IN COMPLIANCE WITH THE TOXIC SUBSTANCES CONTROL ACT (15 USC 2601 - 2629).
DOT DESCRIPTION/PROPER SHIPPING NAME:
Not regulated for transportation.

HAZARD CATEGORIES FOR SARA 311/312 REPORTING ARE INDICATED BELOW:

HEALTH	Immediate (Acute)	No
HEALTH	Delayed (Chronic)	No
PHYSICAL	Fire	No
PHYSICAL	Sudden Release of Pressure	No
PHYSICAL	Reactive	No
	Nuisance Mist/Dust Only	Yes

FOLLOWING ARE WHMIS CLASSIFICATIONS FOR THIS PRODUCT:
CLASS D, DIVISION 2B

COMPONENT NAME	CAS NO.	PERCENTAGE	REGULATION
2-(4-isobutylphenyl) propionic acid	15687-27-1	100.0	WHMIS-HC1

08/25/94

EMERGENCY PHONE NUMBER 344-7147 PRODUCT NAME: Ibuprofen USP

35.3.0

MSDS prepared by: Health & Environment Department
Albemarle Corporation

FOR ADDITIONAL NONEMERGENCY PRODUCT INFORMATION, CONTACT:

HEALTH AND ENVIRONMENT DEPARTMENT
ALBEMARLE CORPORATION
451 FLORIDA ST.
BATON ROUGE, LA. 70801
(800) 535-3030

THIS MATERIAL SAFETY DATA SHEET CONTAINS AT LEAST THE INFORMATION REQUIRED BY THE FEDERAL OSHA HAZARD COMMUNICATION RULE, 29 CFR 1910.1200(g) (2).

08/25/94

EXPLANATION OF MATERIAL SAFETY DATA SHEET TERMINOLOGY

EASE NOTE: THE FOLLOWING EXPLANATIONS ARE PROVIDED AS GENERAL INFORMATION
D MAY OR MAY NOT RELATE TO ITEMS APPEARING ON ANY ONE PARTICULAR MSDS.

HAZARDOUS COMPONENTS

V: Threshold Limit Value
armissible Exposure Limit
_: Time-weighted average concentration for a normal 8-hour workday.
EL: Short-Term Exposure Limit: 15-min. average exposure not to be exceeded.
OSH: National Institute for Occupational Safety and Health.
HA WEEL: Amer. Industrial Hygiene Assoc. Worker Environmental Exposure Limit.
P: National Toxicology Program.
RC: International Agency for Research on Cancer.
HER: May include preliminary data or studies not evaluated by other
encies.
GIH: American Conference of Governmental Industrial Hygienists.
HA: Occupational Safety and Health Administration.

CHEMICAL AND PHYSICAL PROPERTIES

PPEARANCE/ODOR: Description of material at normal temperature and pressure.
OILING POINT: Temperature at which the liquid boils.
ELTING POINT: Temperature at which a substance changes from solid to liquid.
APOR PRESSURE: The pressure exerted at a specified temperature by a vapor.
OLUBILITY IN WATER: The amount of the product that will dissolve in water.
PECIFIC GRAVITY: Ratio of the density of a product to the density water.
APORATION RATE: Ratio of the vaporization rate to a known material.
ERCENT VOLATILES: Percent of the product that will evaporate.
OUR POINT: Lowest temperature at which a liquid will flow from a container.
ISCOSITY: A measure of flow characteristics of a liquid.

FIRE AND EXPLOSION HAZARDS

LASH POINT (CLOSED CUP METHOD): Lowest temperature at which ignition will
ccur.
LA BLE LIMITS: Range of vapor concentrations at which the product will
n or explode in the presence of an ignition source.
_: The lower explosive limit
EL: The upper explosive limit.
XTINGUISHING MEDIA: Recommended fire fighting agents.
AZARDOUS THERMAL DECOMPOSITION PRODUCTS: Known hazardous chemicals resulting
rom heating.
NUSUAL FIRE AND EXPLOSION HAZARDS: Hazards pertaining to chemical reactions
n the presence of heat.

REACTIVITY DATA

TABILITY: Indicates susceptibility of the product to dangerously decompose.
ONDITIONS AND MATERIALS TO AVOID: Conditions and materials that may cause
ndesirable reactions or instability.
AZARDOUS DECOMPOSITION PRODUCTS: The hazardous materials produced from a
hemical reaction.
AZARDOUS POLYMERIZATION: Tendency to undergo a reaction releasing excess
ressure and heat.

HEALTH HAZARDS

INHALATION/EYE/SKIN/INGESTION: Immediate symptoms and effects of overexposure by skin or eye contact, breathing vapors or particles, and ingestion.
CHRONIC EFFECTS: Effects that may occur after repeated or prolonged overexposure or effects that may be long-lasting after acute exposure.
OTHER HEALTH EFFECTS: Includes medical conditions which may be aggravated by exposure to the product and hazards identified with components of a mixture.
TOXICITY: LD50 or LC50 is the dose level that kills half the animals tested.

EMERGENCY FIRST AID

INHALATION/EYE/SKIN/INGESTION: Emergency & first aid instructions for handling overexposure by inhalation, ingestion, and skin and eye contact.
NOTE TO PHYSICIAN: Gives licensed health care professional information on suggested indicated or recommended treatment.

EXPOSURE CONTROL INFORMATION

EYE PROTECTION: Necessary eye or face protection.
PROTECTIVE GLOVES: Indicates the need for and type of protective gloves.
RESPIRATORY PROTECTION: Respirator recommended for use during routine or emergency situations.
VENTILATION: Type (local/general) of ventilation recommended to capture contaminants or prevent the build-up of hazardous atmospheres.
OTHER: Other recommended personal protective equipment.

ENVIRONMENTAL PROTECTION

SPILLS AND LEAKS: Special precautions for clean-up of spills and leaks and preparation of chemical for disposal.
DISPOSAL METHOD: EPA classification and proper disposal procedure.
EPA: Environmental Protection Agency.
RCRA: Resource Conservation and Recover Act
STORAGE REQUIREMENTS: Any unusual requirements or precautions for storage.

REGULATORY INFORMATION

CERCLA: Comprehensive Environmental Response, Compensation and Liability Act.
DOT: Department of Transportation.
HTPQ: Higher Threshold Planning Quantity.
LTPQ: Lower Threshold Planning Quantity.
NJRTK: Determined by New Jersey to be a hazardous substance when present at concentrations greater than or equal to 1.0%.
NJRTK-SHH: Determined by New Jersey to pose a special health hazard when present at concentrations above 0.1%.
N.O.S.: Not otherwise specified.
PA. RTK (PENNSYLVANIA): Determined by Pennsylvania to be hazardous when present at concentrations greater than or equal to 1.0%.
PA. RTK-SHH (PENNSYLVANIA): Determined by Pennsylvania to be hazardous when present at concentrations greater than .01%.
PA. RTK-E (PENNSYLVANIA): Determined by Pennsylvania to be hazardous to the environment.
PROP 65-CA1 (CALIFORNIA): Determined by Calif. to cause cancer.
PROP 65-CA2 (CALIFORNIA): Determined by Calif. to cause reproductive toxicity.

RQ: Reportable Quantity.
SARA: Superfund Amendment Reauthorization Act.
SARA 302: An extremely hazardous substance listed in 40 CFR355.
SARA 313: Listed in 40 CFR 372.65. Has a de minimis cutoff of 1.0%.
SARA 313-CA: Listed in 40 CFR 372.65. Has a de minimis cutoff of 0.1%.
WHMIS: Canadian Workplace Hazardous Materials Information System.
WHMIS-CN1 (CANADA): On Canada's ingredient disclosure list (IDL) at 1.0%.
WHMIS-CN2 (CANADA): On Canada's ingredient disclosure list (IDL) at 0.1%.
WHMIS HC1: Hazardous under WHMIS at a threshold level of 1%.
WHMIS HC.1: Hazardous under WHMIS at a threshold level of .1%.

HYDROCODONE BITARTRATE

Material Safety Data Sheet

Effective Date: 10/25/93
Supercedes : 04/24/86

Mallinckrodt
16305 Swingley Ridge Dr
Chesterfield, Mo. 63017

Emergency Telephone Number
314/539-1600

Product Identification:

Synonyms: Morphinan-6-one, 4,5-alpha-epoxy-3-methoxy-17-methyl-tartrate(1:1); (Hydrocodone Bitartrate ARS-(FOR R&D USE ONLY)

Chemical Formula: $C_{18}H_{21}NO_3 \cdot C_4H_6O_4 \cdot 2.5\ H_2O$

Formula CAS No.: 34195-34-1
TSCA CAS No.: 143-71-5

Molecular Weight: 494.50

Hazardous Ingredients: Hydrocodone Bitartrate

PRECAUTIONARY MEASURES

DANGER MAY BE FATAL IF SWALLOWED. HARMFUL IF INHALED OR ABSORBED THROUGH SKIN. ALLERGEN. EXPOSURE MAY PRODUCE ALLERGIC RESPONSE. NARCOTIC.

Do not breathe dust.
Keep container closed.
Use only with adequate ventilation.
Wash thoroughly after handling.
Avoid contact with eyes, skin and clothing.

EMERGENCY/FIRST AID

In all cases call a physician immediately.
If swallowed, induce vomiting immediately as directed by medical personnel. Never give anything by mouth to an unconscious person. If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. In case of contact, immediately flush skin or eyes with plenty of water for at least 15 minutes.

SEE SECTION 5.

Physical Data — SECTION 1

Appearance:	White or slightly yellow crystals.
Odor:	Odorless.
Solubility:	6 g in 100 g of water.
Boiling Point:	Not applicable.
Melting Point:	ca.147°C (ca.297°F)
Specific Gravity:	No information found.
Vapor Density (Air=1):	No information found.
Vapor Pressure (mm.Hg):	No information found.
Evaporation Rate:	No information found.

Fire and Explosion Information — SECTION 2

FIRE:	As with most organic solids, fire is possible at elevated temperatures
Explosion:	Not considered to be an explosion hazard.
Fire Extinguishing Media:	Water spray, dry chemical, alcohol foam, or carbon dioxide.
Special Information:	In the event of a fire, wear full protective clothing and NIOSH-approved self-contained breathing apparatus with full facepiece operated in the pressure demand or other positive pressure mode.

Reactivity Data — SECTION 3

Stability:	Stable under ordinary conditions of use and storage.
Hazardous Decomposition Products:	Carbon dioxide and carbon monoxide may form when heated to decomposition.
Hazardous Polymerization:	This substance does not polymerize.
Incompatabilities:	Alkaloid precipitants, strong acids and oxidizers, heavy metal salts.

Leak/Spill Disposal Information — SECTION 4

Ventilate area of leak or spill. Remove all sources of ignition. Clean-up personnel may require respiratory protection from dust. All clean-up operations should be witnessed by more than one individual. Spills: Carefully sweep up material into an appropriate container and save for reclamation or disposal. The amount of material collected should be assessed and documented. Disposal: Notify site Drug Enforcement Agency compliance officer and local DEA office for appropriate disposal procedures.

Ensure compliance with local, state and federal regulations.

Health Hazard Information — SECTION 5

A. Exposure/Health Effects

Inhalation:	Narcotic. Can irritate the nasal and respiratory surfaces; sneezing and breathing difficulties can result. Inhalation of appreciable amounts may cause lung edema and typical symptoms of narcosis. See Ingestion below.
Ingestion:	Narcotic, extremely toxic. Can cause nausea, dizziness and constipation. Large doses can lead to central nervous system depression, collapse, respiratory or cardiac arrest and death.
Skin contact:	Mild irritant, possibly capable of producing narcotic effects if absorbed through breaks, inflamed areas, etc.
Eye contact:	Mild irritant and narcotic if absorbed by this route.
Chronic Exposure:	Can lead to habituation or addiction.
Aggravation of Pre-existing Conditions:	Some individuals may become sensitized from exposure and develop skin rashes, coughs, stuffy nose, asthma, and other allergic complaints. Sensitivity may develop soon after immediate contact or after years of exposure.

B. FIRST AID

Inhalation:	Remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Call a physician.
Ingestion:	No information found.
Skin contact:	In case of contact, immediately flush skin with plenty of water for at least 15 minutes while removing contaminated clothing and shoes. Wash clothing before reuse. Call a physician immediately.
Eye contact:	In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. Call a physician.

C. TOXICITY DATA (RTECS, 1982)

Oral rat LD50: 375 mg/kg, investigated as a reproductive effector. ("Humans are probably much more sensitive." -- Gosselin, Smith, Hodge, "Clinical Toxology of Commercial Products" 5th Edition, 1984, p.II-239.)

Occupational Control Measures — SECTION 6

Airborne Exposure Limits:	None established.
Ventilation System:	A local exhaust system which captures the contaminant at its source is recommended to prevent dispersion of the contaminant into the workroom air.
Personal Respirators: (NIOSH Approved)	For conditions of use where exposure to the dust is apparent, a dust/mist respirator may be worn. For emergencies, a self-contained breathing apparatus may be necessary.
Skin Protection:	Wear protective gloves and clean body-covering clothing.
Eye Protection:	Use chemical safety goggles. Contact lenses should not be worn when working with this material. Maintain eye wash fountain and quick-drench facilities in work area.

Storage and Special Information — SECTION 7

Allergic responses in sensitive individuals will disappear if removed from exposure. Keep in a tightly closed container, stored in a cool, dry, ventilated area. Protect from physical damage and direct sunlight. CONTROLLED SUBSTANCE. Location of storage area must comply with all Drug Enforcement Agency regulations.

Addendum to Material Safety Data Sheet

REGULATORY STATUS

Hazard Categories for SARA Section 311/312 Reporting

Acute	Chronic	Fire	Pressure	Reactive
X	X			

Products or Components of Product:	CERCLA Sec.103 RQ lbs	RCRA Sec. 261.33	SARA EHS Sec. 302 RQ	SARA EHS Sec. 302 TPQ	SARA 313 Chemicals Name Chemical List	SARA 313 Chemicals Category
HYDROCODONE BITARTRATE (143-71-5)	No	No	No	No	No	No

SARA Section 302 EHS RQ:
Reportable Quantity of Extremely Hazardous Substance, listed at 40 CFR 355.

SARA Section 302 EHS TPQ:
Threshold Planning Quantity of Extremely Hazardous Substance. An asterick (*) following a Threshold Planning Quantity signifies that if the material is a solid and has a particle size equal to or larger than 100 micrometers, the Threshold Planning Quantity - 10,000 LBS.

SARA Section 313 Chemicals:
Toxic Substances subject to annual release reporting requirements listed at 40 CFR 372.65.

CERCLA Sec. 103:
Comprehensive Enviromental Response, Compensation and Liability Act (Superfund). Releases to air, land or water of these hazardous substances which exceed the Reportable Quantity (RQ) must be reported to the National Response Center, (800-424-8802); Listed at 40 CFR 302.4

RCRA:
Resource Conservation and Reclamation Act. Commercial chemical product wastes designated as acute hazards and toxic under 40 CFR 261.33

ALBEMARLE™
CORPORATION

725 Cannon Bridge Road
P. O. Box 1028
Orangeburg, SC 29116-1028

Telephone: 803-534-5781
Facsimile: 803-536-0981

May 8, 1997

Ms. Susan Hamet
Regulatory Associate
Knoll Pharmaceutical Company
199 Cherry Hill Road
Parsippany, New Jersey 07054

Dear Ms. Hamet:

Albemarle has been manufacturing ibuprofen for commercial distribution for about 19 years; the approval of the application by Knoll Pharmaceutical Company will not affect the qualitative composition of the emissions relating to the manufacture of the drug substance; the manufacturing site is currently in compliance with Federal, State, local/national emission requirements; and approval of this application will have no effect upon compliance with Federal, State, local/national emission requirements.

Sincerely,

D. R. Todd
Plant Manager

DRT:jw

MALLINCKRODT

Improving Healthcare and Chemistry

May 13, 1997

Mrs. Susan Hamet
Knoll Pharmaceutical Company
100 Cherry Hill Road
Parsippany, New Jersey 07054

Mallinckrodt
16305 Swingley Ridge Drive
Chesterfield, Missouri 63017-1777
Telephone (314) 530 2000

Dear Susan:

Re : VICOPROFEN APPROVAL LETTER NDA 20-716

In response to your request we submit the following:

I. An attached Environmental Assessment for our manufacture of Hydrocodone Bitartrate USP, DMF#4844. Please regard this document as Confidential.

II. We certify that:

A. Mallinckrodt has been manufacturing Hydrocodone Bitartrate USP for commercial drug production continuously for at least 20 years.

B. The approval of Knoll's VICOPROFEN application will not affect the qualitative composition of the emissions relating to the manufacture of Hydrocodone Bitartrate USP.

C. Mallinckrodt's St. Louis manufacturing site is currently in compliance with Federal, State, local/national emission requirements: and,

D. Approval of Knoll's VICOPROFEN application will have no affect upon compliance with Federal, State, local/national emission requirements.

Please notify us if you require more information.

Sincerely,

Gregory V. Rozman
Marketing Manager, Opiates

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20716

PHARMACOLOGY REVIEW(S)

550

AUG 30 1996

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
NDA 20-716

Andrea B. Weir, Ph.D.
Reviewing Pharmacologist

ORIGINAL SUMMARY

SUBMISSION DATE: April 25, 1996
CENTER RECEIPT DATE: April 26, 1996
REVIEWER RECEIPT DATE: May 2, 1996
DRAFT REVIEW COMPLETE: August 9, 1996

SPONSOR: Knoll Pharmaceutical Company
3000 Continental Drive, North
Mount Olive, New Jersey 07828-1234

DRUG: Vicoprofen (hydrocodone bitartrate/ibuprofen)

FORMULATION: The composition of Vicoprofen tablets, as defined on pages 083 to 085 of Volume 1.1, is shown below.

Composition of Vicoprofen Core Tablet

Ingredient	Function	mg/Tablet
Ibuprofen USP	Active ingredient	200.0
Hydrocodone bitartrate USP	Active ingredient	7.5
Colloidal silicon dioxide NF		
Microcrystalline cellulose NF		
Croscarmellose sodium NF		
Corn starch NF		
Hydroxypropyl methylcellulose USP		
Purified water USP		
Magnesium stearate NF		

Composition of Vicoprofen Film Coat

Ingredient	mg/Tablet
Purified water USP	Removed during processing

PROPOSED INDICATION: Management of moderate to severe pain.

RELATED DRUGS/INDs/NDAs: This drug product was developed under IND

RECOMMENDED DOSAGE: According to the proposed labeling (Volume 1.1, page 064), the recommended starting dosage is 1 tablet every 6 to 8 hours, which can be increased to 2 tablets every 6 to 8 hours. The dosage should not exceed 8 tablets in a 24-hour period (1660 mg actives = 1660 mg actives/50 kg = 33.2 mg/kg/24 hours). **[Reviewer's Comment:** The dose multiples for the nonclinical studies will be calculated using 33.2 mg/kg as the maximum clinical dose.]

BACKGROUND INFORMATION: Knoll Pharmaceuticals submitted IND for Vicoprofen on December 30, 1986. The reviewing pharmacologist, Dr. Conrad Chen, found it reasonably safe for the sponsor to initiate the clinical trials. The sponsor submitted NDA 20-716 to the FDA on April 25, 1996.

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NDA 20-716

SUMMARY/REVIEW OF NONCLINICAL STUDIES:

The toxicology studies that the sponsor submitted with this application are shown below. These studies were conducted using two developmental formulations (1:40 and 1:80 hydrocodone:ibuprofen) and the proposed marketing formulation (1:27 hydrocodone:ibuprofen).

Summary of Nonclinical Toxicology Studies Submitted with NDA 20-716

Study Number	Study Type	Species	Formulation
012-002	Acute toxicology	Rat	1:80
012-003	Acute toxicology	Mouse	1:80
012-008	Acute toxicology	Rat	1:40
84230	Repeat dose toxicology	Rat	1:27
012-004	Repeat dose toxicology	Rat	1:80
012-006	Repeat Dose toxicology	Rat	1:80
012-005	Repeat dose toxicology	Primate	1:80
012-007	Repeat dose toxicology	Primate	1:80
KNA/2/93	Reproductive toxicology	Rat	1:27
KNA/4A/93	Reproductive toxicology	Rabbit	1:27
KNA/1/92	Reproductive toxicology	Rat	1:27
KNA/3/93	Reproductive toxicology	Rabbit	1:27

I. General Toxicology

A. Acute Studies: The sponsor provided the three acute studies which are listed below. All three of these studies were conducted in compliance with GLP regulations at

•**Study 012-002 (Rat).** (Volume 1.5, pages 025 to 052. This study was conducted from February 14, 1986 to March 19, 1986.)

•**Study 012-003 (Mouse).** (Volume 1.5, pages 053 to 081. This study was conducted from February 13, 1986 to March 21, 1986.)

•**Study 012-008 (Rat).** (Volume 1.5, pages 082 to 114. This study was conducted from June 26, 1986 to July 28, 1986.)

1. Methods: The animals received the treatments shown below. All treatments were administered as a single oral (gavage) dose in 0.5% methylcellulose.

Treatment Protocol for Studies 012-002, 012-003, and 012-008

Study	Species	Treatment	n	Dose	
				mg actives/kg	mL/kg
012-002	Rat (Sprague-Dawley) (Crl:CD(SD)(BR))	Ibuprofen (IPN)	5♀	839	20
			5♂	1186	20
		Vicoprofen (VPN, 1:80)	5/sex	601	20
			5/sex	849	20
			5/sex	1201	20
			5/sex	1699	20
012-003	Mouse (CD-1)	Ibuprofen (IPN)	5/sex	1186	20
			5/sex	2373	20
		Vicoprofen (VPN, 1:80)	5♀	601	20
			5/sex	849	20
			5/sex	1201	20
			5/sex	1699	20
			10♀	2403	20
			5/sex	3398	20
012-008	Rat (Sprague-Dawley) (Crl:COB(SD)BR)	Ibuprofen (IPN)	5♀	505	20
			5♂	714	20
		Vicoprofen (VPN, 1:40)	5♀	366	20
			5/sex	518	20
			5/sex	732	20
			5/sex	1036	20

The animals were maintained for 14 days after treatment. Toxicity was assessed as shown below.

Toxicity Assessment for Studies 012-002, 012-003, and 012-008

Parameter	Methods
Observations	Animals were observed for mortality and clinical signs frequently on the day of treatment and twice daily thereafter for 14 days. A median lethal dose was calculated for VPN using probity analysis.
Body Weight	Body weights were obtained at the start of the study and 7 and 14 days after treatment.
Gross Necropsy	Gross necropsy examination was conducted on all animals that died during the course of the study and on all surviving animals on Day 14.

2. Results:

a. Observations: All treatment groups in the three studies displayed the following clinical signs after treatment with either VPN or IPN: prostration, labored respiration, lacrimation, hypothermia, ataxia, and hypoactivity. In general, these effects were dose-related.

In the rat studies, for IPN and VPN, deaths occurred at doses ≥ 505 mg/kg and ≥ 518 mg/kg, respectively. In mice doses ≥ 1186 mg IPN/kg (the lowest dose tested) and ≥ 601 mg VPN/kg resulted in deaths. The median lethal doses for VPN for the three studies are shown

below; the deaths in all three studies occurred within eight days of treatment. The majority of the animals that received IPN died before the end of the study; all deaths occurred within 11 days after treatment with IPN.

Median Lethal Doses for Studies 012-002, 012-003, and 012-008

Study	Species	Treatment	Median Lethal Dose (mg actives/kg)	
			♂	♀
21-002	Rat	VPN (1:80)	1006	802
21-003	Mouse	VPN (1:80)	1240	1512
21-008	Rat	VPN (1:40)	808	709

b. Body Weight: In general, the surviving animals in all three studies gained weight over the course of the study.

c. Gross Necropsy: The most prevalent findings in the VPN and IPN groups were in the gastrointestinal tract. The lesions, which were not confined to the animals that died prior to scheduled necropsy, are summarized in the table below.

Treatment-induced Gastrointestinal Lesions Identified in Studies 012-002, 012-003, and 012-008

Stomach	Small and Large Intestines
•Distention •Mucosal reddening •Dark or red fluid contents	•Mucosal reddening •Red or dark fluid or material contents •Adhesion to abdominal organs

3. Reviewer's Comment: These studies indicate that the toxicity of VPN is primarily due to the IPN component. The hydrocodone component does not appear to contribute significantly to the acute oral toxicity of VPN. In rats, the formulation did not influence toxicity. A no-observed-effect level (NOEL) was not identified for these studies. Because the formulations differ form the proposed clinical formulation, dose multiples were not be computed for these studies .

B. Repeat-Dose Studies

1. Definitive

[Reviewer's Comment: In some cases, sponsors need to conduct a repeat-dose study with the intended clinical formulation in a rodent and non-rodent. In the case of VPN, the sponsor requested a waiver from conducting the non-rodent study because the toxicity of the active components in VPN, IPN and hydrocodone, have been well-defined, and a non-rodent study would not likely provide any additional information. The FDA granted the sponsor a waiver for a non-rodent study with the 1:27 formulation.]

•Study 84230. A 13-Week Study of the Oral Toxicity of Vicoprofen (1:27) in the Albino Rat. (Volume 1.6, pages 002 to 468; and Volume 1.7, pages 002 to 225. This study was

conducted in compliance with GLP at
from October 16, 1989 to February 5, 1990.)

a. Methods: Rats received the treatments shown below by gavage in 1% methylcellulose. The control group received methylcellulose alone.

Treatment Study 84230

Study	Species	n	Duration	Treatment	Dose	
					mg actives/kg	mL/kg
84230	Rat Sprague-Dawley (Crl:CD®(SD)BR	20/sex	90 days	Control	0	10
				IPN	96	10
					128	10
				VPN (1:27)	33	10
					66	10
					99	10
					132	10

Toxicity was assessed as shown below.

Toxicity Assessment for Study 84230

Parameter	Method
Clinical observations	Rats were observed at least twice daily for mortality and signs of toxicity and received a detailed physical examination once weekly.
Body weight	Body weights were recorded weekly.
Food consumption	Food consumption was recorded weekly.
Clinical pathology	Samples of blood (on Days 5, 31, 59, and 87 for clinical chemistry and hematology and on Days 92/95 for prothrombin time and activated partial thromboplastin time), urine (on Days 9, 33, 61, and 89 for urinalysis), and feces (on Days 4, 30, 86, and 58/60 for occult blood) were obtained for analysis.
Necropsy	Necropsies were performed on all animals found dead during the study and on all surviving animals one day after the last treatment.
Organ weight	Organ weights (absolute and relative to body weight and brain weight) were obtained for the adrenals, brain, heart, kidneys, liver, ovaries, pituitary, spleen, testes, and thyroid with parathyroids.
Histopathology	All major tissues from the control, and high dose IPN and VPN groups were prepared for histopathological evaluation

b. Results:

(1) Clinical Observations: Male and female rats in the 128 mg/kg IPN and 132 mg/kg VPN group showed signs of rapid deterioration characterized by a reduced body temperature, pallor, dehydration, prominence of backbone, hunched posture, abdominal distention, and abnormal firmness of the abdomen. These events led to the death or premature sacrifice of 4/20 males in the 128 mg/kg IPN group and 3/20 males in the 132 mg/kg VPN group. Due to this mortality, two additional groups, 96 mg/kg IPN and 99 mg/kg VPN, were added to the study. The clinical signs

displayed by the 128 mg/kg IPN and 132 mg/kg VPN groups were not observed in the females from the 132 mg/kg VPN group or in any of the rats in the other treatment groups.

(2) Body Weight/Food Consumption: The body weight gains for the 13-week treatment period are shown below.

Body Weight Gains Following Treatment with IPN and VPN

Treatment Group	Mean Body Weight Gains (% of control)	
	Males (% of control)	Females (% of control)
Control	331.0 —	142.9 —
IPN 96 mg/kg	373.3 (113)	154.7 (108)
IPN 128 mg/kg	280.7 (85)	128.6 (90)
VPN 33 mg/kg	314.3 (95)	127.1 (89)
VPN 66 mg/kg	307.1 (93)	132.4 (93)
VPN 99 mg/kg	350.9 (106)	144.1 (101)
VPN 132 mg/kg	271.7 (82)	127.1 (89)

The weekly body weight values for males in the 128 mg/kg IPN and 132 mg/kg VPN groups were generally lower than the control value, with the differences almost consistently achieving statistical significance. Although differences in body were displayed by other animals, the differences seldom reached statistical significance.

Total food intake for the treatment period was slightly (< 10%) reduced in males that received 128 mg/kg IPN and 66 and 132 mg/kg VPN. The weekly food intake in these groups was generally less than the control, with statistically significant reductions being confined to the first five weeks of the study.

(3) Clinical Pathology: ***[Reviewer's Comment:*** *Clinical chemistry parameters were limited to BUN, alkaline phosphatase, glutamic pyruvic transaminase, glutamic oxaloacetic transaminase, glucose, creatinine, total protein (Day 87 only), albumin (Day 87 only), and A/G ratio (calculated, Day 87 only). In addition, the hematological assessment did not include a reticulocyte count. Ideally, the sponsor should have analyzed samples for additional clinical chemistry parameters, such as electrolytes, and reticulocyte counts. Considering, however, that the toxicity of IPN and hydrocodone are well-defined, the omission of these additional parameters is not considered a major deficiency.]* Treatment with IPN and VPN, primarily the high doses, resulted in significant erythroid depression at all time points. Reductions in RBC, HGB, and HCT were accompanied by increases in MCV, MCH, and MCHC. Data from male rats are shown below to illustrate this effect. In addition, males (128 mg/kg IPN on Days 59 and 87 and 132 mg/kg VPN on Day 31) and females (128 mg/kg IPN on Day 87 and 132 mg/kg VPN on Day 59) exhibited significant increases (36% to 48% greater than the control) in platelet counts.

Hematological Changes in Male rats Following Treatment with IPN and VPN

Day	Treatment	Parameter				
		RBC ($\times 10^6$)	HGB (g/dL)	HCT (%)	MCV (μM^3)	MCH (pg)
5	Control	6.72±0.258	14.7±0.59	42.6±1.32	63.6±0.67	22.0±0.19
	IPN 96 mg/kg	6.38±0.286	14.2±0.58	40.2±1.90	63.0±2.14	22.3±0.65
	IPN 128 mg/kg	5.86±0.414*	13.2±0.72*	37.6±2.23*	64.2±1.29	22.6±0.79
	VPN 33 mg/kg	6.71±0.095	15.1±0.61	42.6±1.35	63.5±1.90	22.5±0.89
	VPN 66 mg/kg	6.60±0.331	15.1±0.56	42.5±1.76	64.4±0.80	23.0±0.36
	VPN 99 mg/kg	6.40±0.512	14.1±0.80	40.6±2.18	63.6±2.06	22.0±0.63
	VPN 132 mg/kg	5.92±0.495*	13.0±1.13*	37.0±3.56*	62.5±1.49	22.0±0.33
31	Control	7.80±0.178	15.7±0.59	45.2±1.06	57.9±0.96	20.2±0.70
	IPN 96 mg/kg	6.61±0.409*	14.8±0.82	40.7±2.41	61.6±1.67*	22.4±0.79*
	IPN 128 mg/kg	5.56±0.974*	12.6±2.19*	35.6±5.87*	64.2±1.43*	22.6±0.51*
	VPN 33 mg/kg	7.52±0.232	15.7±0.79	43.8±1.93	58.3±1.41	20.9±0.69
	VPN 66 mg/kg	7.26±0.374	15.6±0.72	43.4±2.15	59.7±0.47	21.5±0.13*
	VPN 99 mg/kg	6.74±0.698*	14.9±1.19	41.6±3.44	61.8±1.83*	22.2±0.83*
	VPN 132 mg/kg	5.76±0.926*	13.2±1.52*	36.9±3.69*	64.5±3.84*	23.0±1.06
59	Control	8.18±0.365	16.0±0.75	44.4±1.99	54.3±2.35	19.6±0.98
	IPN 96 mg/kg	7.26±0.338	15.1±0.54	40.9±1.33	56.4±2.01	20.8±0.98
	IPN 128 mg/kg	5.94±1.165*	13.0±2.34*	36.8±5.82*	62.5±3.44*	22.0±0.61
	VPN 33 mg/kg	7.89±0.296	15.8±0.39	43.6±1.00	55.3±1.39	20.1±0.73
	VPN 66 mg/kg	7.82±0.411	16.0±0.68	44.3±1.87	56.7±1.11	20.5±0.39
	VPN 99 mg/kg	7.71±0.515	15.7±0.91	43.6±2.45	56.6±1.65	20.4±0.67
	VPN 132 mg/kg	6.79±0.897*	14.4±1.47	40.1±3.47	59.2±3.17*	21.3±0.93*
87	Control	8.44±0.318	15.7±0.56	43.9±1.80	52.0±2.22	18.6±0.89
	IPN 96 mg/kg	7.63±0.402	14.4±0.62	42.2±1.46	55.4±1.79	18.9±1.31
	IPN 128 mg/kg	6.45±1.135*	13.4±1.85*	37.1±4.67*	58.1±3.72*	20.8±1.00*
	VPN 33 mg/kg	8.03±0.358	15.8±0.44	43.2±1.22	53.8±1.38	19.7±0.61
	VPN 66 mg/kg	7.86±0.378	15.5±0.59	42.2±1.91	53.7±0.70	19.7±0.48
	VPN 99 mg/kg	7.33±1.257	14.5±1.48	40.1±6.86	54.7±0.84	20.0±1.91
	VPN 132 mg/kg	6.89±0.954*	14.3±1.58	38.5±3.66	56.2±2.52*	20.8±0.69*

*Statistically different from control

Males and females in the 128 mg IPN/kg and 132 mg VPN/kg group consistently exhibited statistically significant increases in serum BUN. These increases generally were of 30% to 50% higher than the control values. ***[Reviewer's Comment:*** *These findings were not considered toxicologically significant because the magnitude of the effect did not progress with treatment, and the values were within a reported normal range of 15 to 22 mg/dL (Ringler, DH and Dabich, L., 1979. The Laboratory Rat. Volume 1, Biology and Disease, pages 105 to 121. Academic Press.)]*

Urinalysis did not reveal any treatment-related effects.

Fecal occult blood was observed in a few rats that received 96 or 128 mg/kg IPN and in the 99 or 132 mg/kg VPN. In general, each animal demonstrated occult on one occasion only.

(4) Necropsy: Gross pathological findings were confined mainly to the gastrointestinal tract of the rats that received 128 mg/kg IPN and 132 mg/kg VPN. These findings are

summarized below. The incidence of these findings was generally low, and they were identified in the IPN and VPN high dose groups only.

Gross Pathological Findings in
Rats that Received 128 mg/kg IPN or 132 mg/kg VPN

Finding	128 mg/kg IPN		132 mg/kg VPN	
	Male	Female	Male	Female
Duodenum				
Discoloration	1/15	0/15	0/15	0/15
Foci dark	1/15	0/15	0/15	0/15
Thickening	0/15	0/15	2/15	1/15
Ileum				
Thickening	0/15	0/15	0/15	1/15
Jejunum				
Adhesion	1/15	0/15	0/15	0/15
Thickening	7/15	2/15	5/15	1/15
Dilatation	1/15	0/15	2/15	0/15
Discoloration	0/15	0/15	2/15	0/15
Area depressed	3/15	1/15	3/15	3/15
Area raised	0/15	0/15	1/15	0/15

(5) Organ Weight: Female rats that received 128 mg/kg IPN exhibited significant increases in relative liver (24.2% > control), kidney (19.3%> control), and spleen (49.1% > control) weight. Female rats that received 132 mg/kg VPN displayed significant increases in relative liver (11.6% > control) and spleen (20% > control) weight; females in the 99 mg/kg VPN group exhibited a 21.0% increase in relative spleen weight over the control value.

(6) Histopathology: Treatment-related findings are summarized in the table below. Other findings which were probably related to the inflammation in the abdominal cavity included plasmacytosis, lymph node hyperplasia, increased myopoiesis (primarily granulocytic) in the bone marrow, depletion of thymus lymphocytes, cortical necrosis of the thymus, and splenic changes. The histopathological findings were limited to the 128 mg/kg IPN and 132 mg/kg VPN groups. Thymic necrosis was observed only in the two male rats from the 132 mg/kg VPN group which were sacrificed prematurely.

Histopathological Findings in
Rats that Received 128 mg/kg IPN or 132 mg/kg VPN

Finding	128 mg/kg IPN		132 mg/kg VPN	
	Male	Female	Male	Female
Stomach				
Ulcer	1/15	0/15	0/15	1/15
Gastritis	2/15	5/15	0/15	3/15
Jejunum				
Peritonitis	1/15	0/15	2/15	2/15
Ulcer	4/15	3/15	3/15	3/15
Serositis	3/15	0/15	1/15	0/15
Jejunitis	0/15	0/15	0/15	1/15

Finding	128 mg/kg IPN		132 mg/kg VPN	
	Male	Female	Male	Female
Kidney				
Tubular basophilia	0/15	0/15	3/15	0/15
Interstitial nephritis	1/15	0/15	3/15	3/15
Papillary necrosis	0/15	0/15	0/15	1/15
Hydronephrosis	3/15	0/15	0/15	0/15

c. Reviewer's Comment: The no-observed-effect-level (NOEL) for VPN was 99 mg/kg. The toxicity of VPN is primarily due to the IPN component. The hydrocodone component does not appear to contribute significantly to the acute oral toxicity of VPN. The dose multiples for this study are provided below. The clinical doses used to calculate these multiples were 64 mg/kg (3200 mg/50 kg) for IPN and 33.2 mg actives/kg (32 mg/kg IPN and 1.2 mg/kg hydrocodone) for VPN. The dose for IPN represents IPN only, while the dose for VPN represents the total amount of active ingredients, IPN plus hydrocodone. The dose of IPN contained in the maximum recommend dose of VPN, 32 mg IPN/kg, is one-half that obtained from the maximum recommended dose of IPN, 64 mg/kg.

Dose Multiples for Study 84230

Dose	Multiple of Human Dose	
	mg/kg	mg/m²
96 mg/kg IPN	1.54	0.25
128 mg/kg IPN	2	0.33
33 mg/kg VPN	0.99	0.16
66 mg/kg VPN	1.98	0.33
99 mg/kg VPN	2.98	0.49
132 mg/kg VPN	3.97	0.66

2. Nondefinitive

•**Study 012-004. 7 Day Oral Rangefinding Study in Rats.** (Volume 1.5, pages 115 to 141. This study was conducted in compliance with GLP at from February 21, 1986 to March 3, 1986.)

•**Study 012-006. 30 Day Oral Toxicity Study in Rats.** (Volume 1.5, pages 173 to 409. This study was conducted in compliance with GLP at from March 3,1986 to April 2,1986.)

•**Study 012-005. Two Week Oral Rangefinding Toxicity Study in Cynomolgus Monkeys.** (Volume 1.5, pages 142 to 172. This study was conducted in compliance with GLP at from March 10,1986 to March 25,1986.)

•**Study 012-007. 30 Day Oral Subchronic Study in Cynomolgus Monkeys.** (Volume 1.7, pages 226 to 482. This study was conducted in compliance with GLP at

from March 31,1986 to April 30,1986.)

a. Methods: Rats and monkeys received the treatments shown by gavage. Methylcellulose (0.5%) was used as a vehicle in all of the studies; control animals received vehicle only.

Treatment Protocol for Repeat-Dose Studies

Study	Species	n	Duration	Treatment	Dose	
					mg active/kg	mL/kg
012-004	Rat (CD)	4/sex	7 or 10 days*	Vicoprofen (VPN, 1:80)	0 65 130 260 520	10 10 10 10 10
012-006	Rat (CD)	10/sex	29 or 30 days	Control Ibuprofen (IPN) VPN (1:80)	0 160 40 80 160	10 10 10 10 10
012-005	Cynomolgus monkey	1/sex	15 days	Control VPN (1:80)	0 25/300** 50 100 200	2 2 2 2 2
012-007	Cynomolgus monkey	3/sex	29 or 30 days	Control IPN VPN (1:80)	0 257 65 130 260	2 2 2 2 2

*Treatment of males in the control, low dose, and low-mid dose groups was extended from 7 to 10 days to "give a more thorough evaluation of the test material."
**On day 3 of the study, the dose was increased form 25 mg/kg to 300 mg/kg to increase the chance of producing toxic effects.

Toxicity was assessed as shown below.

Toxicity Assessment for Repeat-Dose Toxicology Studies

Parameter	Method
Clinical observations	Rats in all studies were observed at least twice daily for mortality and signs of toxicity.
Ophthalmologic examination	Rats and monkeys in the 30-day studies were examined during Week 4.
Body weight	Body weights were recorded weekly in all studies.
Food consumption	Food consumption was recorded weekly for all rat studies. In the monkey studies, food consumption was monitored and noted when abnormal.

Parameter	Method
Clinical pathology	In the 30-day rat study samples of blood (on Days 5 and 29 for hematology and clinical chemistry), urine (on Days 4 and 25 for urinalysis), and feces (on Days 2 and 24 for occult blood) were obtained. In the 30-day monkey study samples of blood (pretreatment and on Days 5 and 29 for hematology and clinical chemistry), urine (pretreatment and on Days 4 and 26 for urinalysis), and feces (on Days 4 and 26 for occult blood) were obtained.
Necropsy	In all studies, necropsies were performed one day after the last treatment.
Organ weight	Organ weights (absolute and relative to body weight)were obtained for the adrenals, brain, heart, kidneys, liver, pituitary, spleen, testes, and thyroid.with parathyroids in the 30-day rat and monkey studies.
Histopathology	All major tissues from all rats and monkeys in the 30-day studies were prepared for histopathological evaluation. Selected tissues from one male monkey from the 25/300, 50, and 100 mg VPN/kg group were examined.

b. Results:

(1) Clinical Observations: In the 7-day rangefinding study which was conducted in rats, all of the rats in the 520 mg/kg/day group died by Day 6. Beginning 3 days prior to death, these animals exhibited distended abdomens, diarrhea, pallor, hypothermia, and hypoactivity. Although no deaths occurred in the 260 mg/kg/day group, these animals exhibited pallor, hypoactivity, and diarrhea, all of which began on Day 4 and persisted until the end of the study. Rats in the 65 and 130 mg/kg groups did not exhibit any treatment-related clinical signs.

Rats in the 30-day study did not exhibit any treatment-related signs. On Day 17, one male from the 160 mg/kg VPN group was found dead. Although the cause of death was not determined, the death was considered treatment-related.

In the 15-day monkey study, the male that received 300 mg/kg was sacrificed in moribund condition on Day 7 of the study. Prior to sacrifice, the monkey exhibited hypoactivity, ataxia, and prostration.

Two deaths occurred during the 30-day monkey study, one on Day 30 in the 257 mg/kg IPN group and one on Day 10 in the 260 mg/kg VPN group. Prior to death, these two animals exhibited anorexia, emaciation, prostration, ataxia, and/or hypoactivity. The only other effect that was potentially treatment-related was an increase in emesis in the 257 mg/kg IPN group and in the 260 mg/kg VPN group.

(2) Ophthalmologic Examination: Neither the rats nor the monkeys in the 30-day studies exhibited any treatment-related effects.

(3) Body Weight/Food Consumption: In the 7-day rangefinding study which was conducted in rats, rats in the 260 mg/kg group displayed decreases in body weight and food consumption relative to the control group.

During Week 1 of the 30-day rat study, body weight gain was decreased in the IPN group (males only, 31%, relative to the control group) and in the 160 mg VPN/kg group (37% and 42%, relative to the control group for the males and females,

respectively). Food consumption in all 3 of these groups was decreased approximately 10% relative to the control group.

In the 15-day monkey study, the body weight change of the treated monkeys did not differ from that of the controls.

In the 30-day monkey study, all female treatment groups exhibited a transitory weight loss at Week 4; the monkeys regained this weight by the end of the study. Food consumption was decreased throughout the study in the monkeys in the 257 mg/kg IPN group and in the 260 mg/kg VPN group

(4) Clinical Pathology: The male and female rats in the 160 mg/kg IPN and 160 mg/kg VPN groups (30-day study) exhibited a treatment-related decrease in RBC parameters. The nature of the effect was similar to that exhibited by the rats that received 128 mg/kg IPN and 132 mg/kg VPN in Study 84230. Unlike Study 84230, the 30-day study incorporated reticulocyte counts. The male and female rats in the 160 mg/kg IPN and 160 mg/kg VPN groups exhibited increases in reticulocyte counts (1.97 to 4.4 times the control value) following 30 days of treatment; with the exception of the female rats that received 160 mg/kg VPN, the increases were statistically significant. In addition, male and female rats that received 160 mg/kg IPN displayed significant increases in platelet counts (1.63 times greater than the control); females that received 80 or 160 mg/kg VPN exhibited increases of 1.41 and 1.85 times the control, respectively.

On Days 5 and 29, the male and female rats in the 160 mg/kg IPN and 160 mg/kg VPN group exhibited treatment-related decreases in albumin, globulin, and total protein. These decreases were generally statistically significant.

The urinalysis parameters in the rats that received IPN or VPN for 30 days did not differ from the control values.

Analysis of fecal samples from rats that received IPN or VPN revealed positive responses on Day 2 only (1 female in the 160 mg/kg IPN group and 4 females in the 160 mg/kg VPN group); all samples were negative on Day 24.

In the 30-day monkey study, treatment did not result in any changes in hematology, clinical chemistry, or urinalysis parameters. Analysis of fecal samples for occult blood revealed isolated positive results only (one male in the 260 mg/kg IPN group on Day 4 and on Day 26, and one control male on Day 26).

(5) Necropsy: In the 7-day rangefinding study which was conducted in rats, the animals in the 260 and 520 mg/kg/day groups displayed treatment-related lesions involving the kidneys (pale), liver (pale, white or yellow spots/area), and/or gastrointestinal tract (stomachs and small intestines distended with gas and a dark or yellow fluid and/or with pale mucosal surfaces, and small intestines with multiple, firm, yellow, red raised and/or pitted areas).

In the 30-day rat study, gross findings were identified in a limited number of high dose (160 mg/kg IPN or VPN) animals only. The gross findings included adhesion of the intestines to each other and to the mesentery (1/10 males that received 160 mg/kg VPN),

raised and/or thickened areas in the intestinal tract (1/10 males that received 160 mg/kg IPN and 1/10 males and 2/10 females that received 160 mg/kg VPN), and enlarged spleen (2/10 females that received 160 mg/kg IPN).

With the exception of the monkey that was sacrificed in moribund condition on day 7 of the study, the monkeys in the 15 day study did not exhibit any effects that were clearly treatment-related. The monkey that was prematurely sacrificed exhibited diffuse red areas in the stomach and the cecum.

In the 30-day monkey study, the only apparent treatment-related lesions were dark spots on the mucosal surface of the stomach of the female from the 260 mg/kg VPN group that died on day 10 of the study. Lesions identified in the gastrointestinal tract of treated and control monkeys were linked to parasites.

(6) Organ Weight: As shown in the table below, the male and female rats in the 30-day study exhibited increases in liver and spleen weight.

Liver and Spleen Weights in Rats Following Treatment with IPN and VPN

Treatment Group	Liver Weight		Spleen Weight	
	Absolute	Relative	Absolute	Relative
♂				
Vehicle	12.29	4.42	0.764	0.276
IPN 160	12.88	4.82*	1.051*	0.396*
VPN 40	13.20	4.53	0.809	0.279
VPN 80	12.63	4.44	0.820	0.288
VPN 160	12.71	4.67	1.128*	0.417*
♀				
Vehicle	7.06	3.93	0.524	0.294
IPN 160	9.60*	5.34*	1.062*	0.591*
VPN 40	7.58	4.27	0.581	0.326
VPN 80	7.37	4.28	0.635	0.367*
VPN 160	8.01	4.82*	0.794*	0.480*

* Statistically different from control

In the 30-day monkey study, treatment did not result in any significant effects on organ weight.

(7) Histopathology: Rats in the 30-day study exhibited treatment-related effects in the intestines, spleen, and liver. Intestinal lesions (chronic ulcers in the duodenum and ileum, and/or chronic serositis, and/or adhesions in the duodenum and ileum) were identified in 2 rats (1/10 males and 1/10 females) that received 160 mg/kg IPN and in 3 rats that received 160 mg/kg VPN (1/10 males and 2/10 females). In addition, all of these rats exhibited slight to severe hematopoiesis in the spleens. The total incidence of splenic hematopoiesis was 9/20 rats (2/10 males and 7/10 females) that received 160 mg/kg IPN, 3/20 rats (1/10 males and 2/10 females) that received 80 mg/kg VPN, and 7/20 rats (4/10 males and 3/10 females) that received 160 mg/kg VPN. Minimal to slight hepatic hematopoiesis was detected in the liver of 2/20 rats (both

female) that received 160 mg/kg IPN and 3/20 rats (1/10 males and 2/10 females) that received 160 mg/kg VPN.

The monkeys in the 15-day study did not exhibit any treatment-related effects.

In the 30-day monkey study, the only apparent treatment-related lesions identified were pyloric ulcers in one male that received 130 mg/kg VPN and in two females that received 260 mg/kg VPN.

c. **Reviewer's Comment:** Similar to the toxicity studies discussed previously in this review, the effects that were observed in these four studies are consistent with IPN-induced toxicity; the hydrocodone component does not appear to contribute to the toxicity profile. Because the formulations differ form the proposed clinical formulation, dose multiples were not be computed for these studies .

II. Reproductive Toxicology

A. Definitive

• **Study KNA/2/93. Vicoprofen (1:27), Oral (gavage) Rat Developmental Toxicity (Teratogenicity) Study.** (Volume 1.8, pages 069 to 255. This study was conducted in compliance with GLP at The study was completed on February 10, 1993.)

• **Study KNA/4A/93. Vicoprofen (1:27), Oral** (gavage) Rabbit, Developmental Toxicity (Teratogenicity) Study. (Volume 1.8, pages 358 to 521. This study was conducted in compliance with GLP at The study was completed on May 7, 1993.)

1. Methods: Rats and rabbits were treated with vicoprofen 1:27 (VPN) as shown below. All treatments were administered by gavage in a 1% carboxymethylcellulose vehicle. Rats were treated on Days 6 to 15 of pregnancy, rabbits on Days 6 to 18.

Treatment Protocols for Studies KNA/2/93 and KNA/4A/93

Study	Species/Strain	n	Dose	
			mg active/kg	mL/kg
KNA/2/93	Rat (Sprague-Dawley)	24 24 24 24 24	0 50 100 166 200	10 10 10 10 10
KNA/4A/93	Rabbit (New Zealand White)	16 16 16 16	0 10 33 95	2 2 2 2

The animals were sacrificed on Day 20 (rat) or Day 28 (rabbit) of pregnancy. Toxicity was assessed as shown below.

Toxicity Assessment for Studies KNA/2/93 and KNA/4A/93

Parameter	Methods
Observations	Observations were made for clinical signs and mortality at appropriate times after treatment.
Body weight	Body weights were obtained in rats on Days 0, 6 to 15, inclusive, and Day 20 of pregnancy; in rabbits on Days 2 to 18 of pregnancy, inclusive, and on Days 22, 25, and 28.
Food consumption	Food consumption was measured in rats on Days 0 to 6, 6 to 9, 9 to 12, 12 to 15, and 15 to 20 of pregnancy; in rabbits from Days 2 to 6 of pregnancy, inclusive, then every 2 days.
Necropsy	Necropsies were performed at the time of sacrifice. In rats and rabbits, the organs in the thoracic and abdominal cavities were examined. In rabbits, the mucosal surfaces of the stomach and duodenum and the renal pelvises were examined.
Cesarean observations	The ovaries were examined for the number of corpora lutea; the uterus was examined for implantation sites, live and dead fetuses, and early and late resorptions.
Fetal observations	The fetuses were weighed, sexed, and examined for external, visceral, and skeletal abnormalities.

2. Results:

a. Observations: Following 3 days of treatment, 13/20 dams in the 200 mg/kg/day group exhibited sedation, hunched posture, piloerection, pallor, hypothermia, slow respiration, and ptosis. Due this poor condition, all of the dams in the 200 mg/kg group were sacrificed for necropsy on Days 7 and 9 of pregnancy. All dams in the 166 mg/kg/day group displayed pallor on Days 8 to 20 of pregnancy. One dam from the 166 mg/kg/day group exhibited lack of muscle tone, piloerection, hypothermia, urogenital staining, perinasal staining, and ptosis; this rat was sacrificed on Day 10 of pregnancy.

The does did not exhibit any treatment-related effects.

b. Body weight: During the treatment period (Days 6 to 15 of pregnancy), rats in the 100 and 166 mg/kg groups exhibited significant decreases in body weight gain (20.6% and 60.3% relative to the control group, respectively); following treatment, body weight gain in these two groups was essentially the same as the control.

During the treatment period (Days 6 to 18 of pregnancy), the mean body weight gain of the does in the 95 mg/kg group was significantly decreased (44.4%) relative to that of the control group. Following treatment (Days 18 to 28 of pregnancy), the body weight gain in this group of does was significantly increased (34.6%) relative to the control group.

c. Food consumption: During the treatment period (Days 6 to 15 of pregnancy), the rats in the 100 and 166 mg/kg/day groups displayed significant decreases (7.9 to 17.9% and 22.4 to 39% less than the control value, respectively) in food consumption; at the end of the treatment period, food consumption in these groups was the same as in the control group.

During the treatment period (Days 6 to 18 of pregnancy), the does in the 95 mg/kg group exhibited a significant decrease in food consumption (~ 25%) relative to the control group; following treatment food consumption was similar to the control group.

d. Necropsy: At necropsy, 12/24 dams in the 200 mg/kg/day group exhibited one or more of the effects shown below. The dam in the 166 mg/kg/day group that was sacrificed on Day 10 of pregnancy exhibited excessive fluid in the abdominal cavity, pale liver and spleen, a distended stomach, adhesions between the small intestine and the mesentery and uterus, and dark and dehydrated cecum/colon contents. Dams from the other treatment groups did not exhibit these effects.

Necropsy Findings in Dams Following 200 mg/kg/day Vicoprofen

Effect	n
Peyers patches - enlarged	5/12
Intestinal adhesions to - itself/uterus/spleen/pancreas	6/12
Stomach/intestine - dilated	5/12
Small intestines - contents dark	2/12
Cecum/colon - contents dark	5/12
Cecum contents/fecal pellets - dehydrated	4/12
Spleen - enlarged	3/12
Intestines - surface blood vessels dilated	1/12
Mesenteric lymph nodes - enlarged	1/12

The does did not exhibit any treatment-related effects.

e. Cesarean observations: Neither the rats nor the rabbits exhibited any treatment-related effects.

f. Fetal observations: Rat fetuses did not display any treatment-related effects.

Although the rabbit fetuses did not exhibit an increase in the total number of minor abnormalities, the number of fetuses in the 95 mg/kg group with one or more nonossified metacarpals (3.9% of the fetuses, 5/16 litters) was significantly increased relative to the control group (0%). This effect was not observed in any fetuses from the 10 mg/kg group, but was observed in the 33 mg/kg group (3.2% of the fetuses, 3/15 litters). The sponsor did not statistically analyze the litter data.

The occurrence of major abnormalities ("Structural congenital abnormalities that impair or potentially impair the survival or fitness of the foetus were regarded as major abnormalities.") in the rabbit fetuses and litters is summarized in the table below. In the 95 mg/kg group, the percent of fetuses that exhibited any major abnormality was significantly increased relative to the control group. The historical range for fetuses with any abnormality is 0.0 to 4.2%. The sponsor did not statistically analyze the litter data. ***[Reviewer's Comment:*** *Although the number of fetuses and litters with any major abnormality was increased in the 95 mg/kg group, the relationship of this*

effect to treatment is not clear for several reasons. First, the control group did not contain the anticipated background level of major abnormalities; therefore, the treated groups were compared to an unusually low value. Second, the type of abnormalities observed in the 95 mg/kg group were diverse; the fetuses in the 95 mg/kg group exhibited 12 different abnormalities, 6 external/visceral and 6 skeletal, with only one abnormality occurring twice. In addition, the rabbit fetuses in the rangefinding study (see Study KNA 3/93) did not exhibit an increase in abnormalities following treatment of the does with 90 mg/kg VPN.]

Fetal Observations in Rabbits, Study KNA/4A/93

Category	Dose (mg actives /kg)							
	0		10		33		95	
	#	%	#	%	#	%	#	%
Fetuses with major external and visceral abnormalities	0	0	3	2.3	2	2.1	6	5.2
Litters with major external and visceral abnormalities	0	0	2	15.3	2	13.3	5	31.2
Fetuses with major skeletal abnormalities	0	0	3**	2.6	2	2.1	6	4.8
Litters with major skeletal abnormalities	0	0	3**	23.0	2	13.3	5	31.2
Fetuses with any major abnormality	0	0	4	4.3	3	2.8	9	7.4*
Litters with any major abnormality	0	0	3	23.0	3	20.0	7	43.7

* Statistically different from the control value.

** According to the summary table on page 388 of volume 1.8, the number of fetuses and litters in the 10 mg/kg with major skeletal abnormalities was two each. However, a review of the individual fetus/litter data on pages 461 to 462 of Volume 1.8 revealed in 1 fetus per litter from each of 3 litters.

3. Reviewer's Comment: The dose multiples for these studies are provided below. In rats, the NOEL for maternal toxicity was 50 mg/kg, for fetal toxicity was 166 mg/kg. In rabbits, the NOEL for maternal and fetal toxicity was 33 mg/kg (0.99 and 0.33 times the clinical dose based on body weight and surface area, respectively). The increase in major abnormalities in rats occurred at a dose that was essentially equivelant to the maximum human dose. Due to reasons cited above, however, the relationship of this response to treatment is not clear.

Dose Multiples for Study 84230

Dose		Multiple of Human Dose	
		mg/kg	mg/m²
Rat	50 mg/kg	1.50	0.25
Rat	100 mg/kg	3.00	0.50
Rat	166 mg/kg	5.00	0.83
Rat	200 mg/kg	6.00	1.00
Rabbit	10 mg/kg	0.30	0.10
Rabbit	33 mg/kg	0.99	0.33
Rabbit	95 mg/kg	2.86	0.95

B. Range-finding

• **Study KNA/1/92. Vicoprofen (1:27) Oral (Gavage) Rat Developmental Toxicity (Teratogenicity) Dose Ranging Study.** (Volume 1.8, pages 002 to 068. This study was conducted in compliance with GLP at from September 8, 1992 to February 10, 1993.)

• **Study KNA/3/93. Vicoprofen (1:27) Oral (Gavage) Rabbit Developmental Toxicity Dose Ranging Study.** (Volume 1.8, pages 256 to 357. This study was conducted in compliance with GLP from August 12, 1992 to February 19, 1993.)

1. Methods: Rats and rabbits were treatment with vicoprofen 1:27 (VPN) as shown below. All treatments were administered by gavage in a 1% carboxymethylcellulose vehicle. Rats were treated on Days 6 to 15 of pregnancy, rabbits on Days 6 to 18.

Treatment Protocols for Studies KNA/1/92 and KNA/3/93

Study	Species(Strain)	n	Dose	
			mg actives/kg	mL/kg
KNA/1/92	Rat (Sprague-Dawley) (Crl: CD(SD)BR(VAF plus))	5	0	10
		5	66.4	10
		5	132.8	10
		5	166.0	10
		5	332.0	10
KNA/3/2	Rabbit (New Zealand White)*	5	0	2
		5	10	2
		5	25	2
		5	70	2
		5	90	2

*The doses for the rabbit study were based upon the results of a preliminary study designed to establish a maximally tolerated dose in rabbits. The methods and results for the preliminary study were included in the report for Study KNA/3/2. A group of 5 non-mated female rabbits received the following series of oral (gavage) treatments with VPN: 16.6 mg/kg (Days 1 - 5), 33.2 mg/kg (Days 6 - 10), 66.4 mg/kg (Days 11 - 15), 99.6 mg/kg (Days 16 - 20), no treatment (Days 21 - 27), and 83 mg/kg (Days 28 - 32). One additional non-mated female received 90 mg/kg of VPN for 5 days. Toxicity was assessed by clinical observations, body weight and food consumption, and by necropsy. Treatment with 99.6 or 90 mg/kg resulted in a decrease in body weight and food consumption. Necropsy revealed healed ulceration in two of the females that received the varying doses of VPN; these ulcers were attributed to the 99.6 mg/kg treatment. The rabbits that received 90 mg/kg did not exhibit ulcers at necropsy. Based on these results 90 mg/kg was chosen as the high dose for the reproduction range finding study.

The animals were sacrificed on Day 20 (rat) or Day 28 (rabbit) of pregnancy. Toxicity was assessed as shown below.

Toxicity Assessment for Studies KNA/1/92 and KNA/3/93

Parameter	Methods
Observations	Observations were made for clinical signs and mortality at appropriate times after treatment.
Body weight	Body weights were obtained in rats on Days 0, 6 to 15 and 20; in rabbits on Days 3, 6 to 18, 22, 25, and 28.

Parameter	Methods
Food consumption	Food consumption was measured in rats on Days 0 to 6, 6 to 9, 9 to 12, 12 to 15, and 15 to 20; in rabbits from Days 3 to 4 of pregnancy, then every 2 days.
Necropsy	Necropsies were performed at the time of sacrifice. The organs in the thoracic and abdominal cavities were examined. The mucosal surfaces of the stomach and duodenum and the renal pelvises were examined also.
Cesarean observations	At the time of sacrifice the animals were examined for the following: pregnancy status, number of corpora lutea, implantations, early/late resorptions, and dead and live fetuses.
Fetal observations	The rats fetuses were weighed, sexed, and examined for external abnormalities, the rabbit fetuses for external and visceral abnormalities.

2. Results:

a. Observations: The rats that received 332 mg/kg were sacrificed between Days 7 and 9 due to their moribund condition. Prior to sacrifice, these animals exhibited lethargy, general pallor, and an abnormal/hunched posture. The other treatment groups did not display any significant effect.

The rabbits did not display any signs of toxicity.

b. Body weight: Rats in the 132 and 166 mg/kg groups displayed a statistically significant decrease in body weight gain (32% and 40%, respectively, relative to the control group) for Days 6 to 15 of pregnancy.

During pregnancy, rabbits in the 90 mg/kg group displayed a slight, albeit consistent, decrease in body weight gain relative to the control group; however, the difference was not statistically significant.

c. Food consumption: Rats in the 166 and 332 mg/kg groups displayed a significant decrease in food consumption (33% and 84%, respectively, relative to the control group) for Days 6 to 9 of pregnancy.

In rabbits that received 90 mg/kg, food consumption was decreased relative to the control group on Days 14 to 18 of pregnancy; however, the decrease was not statistically significant.

d. Necropsy: All rats in the 332 mg/kg group exhibited adhesions between the gastrointestinal tract and the body wall, uterus, or liver and kidney. The gastrointestinal tract had ulcerated area, and the contents were dehydrated and blood-stained. The other groups did not exhibit any treatment-related findings.

The rabbits did not exhibit any treatment-related effects.

e. Cesarean observations: Neither species displayed any treatment-related effects.

f. Fetal observations: Neither species displayed any treatment-related effects. *[Reviewer's Comment: The study report provided a narrative only for the results of the external and visceral examination; no tabular presentation of data was included in the report.]*

SUMMARY:

I. Acute Toxicology: Acute toxicity studies were conducted in rats (1:80 and 1:40 blends) rats and mice (1:80 blend only). These studies indicate that the toxicity of VPN is primarily due to the IPN component. The hydrocodone component does not appear to contribute significantly to the acute oral toxicity of VPN. In rats, the formulation did not influence toxicity. All treatment groups in the these studies displayed the following clinical signs after treatment with either VPN or IPN: prostration, labored respiration, lacrimation, hypothermia, ataxia, and hypoactivity. In general, these effects were dose-related. In the rat studies deaths occurred at doses ≥ 505 mg/kg and ≥ 518 mg/kg following treatment with IPN and VPN, respectively. In mice, doses ≥ 1186 mg IPN/kg (the lowest dose tested) and ≥ 601 mg VPN/kg resulted in deaths. An NOEL was not identified for these studies.

II. Repeat Dose Toxicology: Male and female Sprague-Dawley rats received IPN (96 or 128 mg/kg/day) or VPN (1:27 blend at 33, 66, 99, or 132 mg/kg/day) for 90 days. Adverse effects were primarily limited to the 128 mg IPN/kg (2.00 and 0.33 times the maximum human dose, 64 mg/kg/day, based on body weight and surface area respectively) and the 132 mg VPN/kg groups (3.97 and 0.66 times the maximum human dose, 33.2 mg/kg/day, based on body weight and surface area, respectively), with very limited effects observed in the group that received 99 mg VPN/kg (2.98 or 0.49 times the human dose, based on body weight and surface area, respectively). Similar to the acute toxicology studies, the results of this study indicate that the toxicity of VPN is primarily due to the IPN component. The rats in the IPN and VPN high dose (128 mg/kg and 132 mg/kg, respectively) exhibited the following adverse effects: clinical signs which were limited to males and consisted of reduced body temperature, pallor, dehydration, prominence of backbone, hunched posture, abdominal distention, and abnormal firmness of the abdomen; death or premature sacrifice of 4/20 males in the 128 mg/kg IPN group and 3/20 males in the 132 mg/kg VPN group; significant erythroid depression, characterized by reductions in RBC, HGB, and HCT and increases in MCV, MCH, and MCHC throughout the study; increased organ weight for liver, kidney, and spleen; and gross and histopathological changes in the gastrointestinal tract which were consistent with IPN-induced toxicity. The NOEL for VPN was 99 mg/kg (2.98 and 0.49 times the clinical dose, based on body weight and surface area respectively.)

III. Reproductive Toxicology: Sprague-Dawley rats received 0, 50, 100, 166, or 200 mg /kg of VPN by gavage on Days 6 to 15 of pregnancy. Due to excessive toxicity, the dams in the 200 mg/kg group were sacrificed on Days 7 and 9 of pregnancy. All dams in the 166 mg/kg group (5.0 and 0.83 times the clinical dose, 33.2 mg/kg/day, based on body weight and surface area, respectively) exhibited pallor on Days 8 to 20 of pregnancy and decreased body weight gain (60.3% relative to the control group) during treatment. Dams in the 100 mg/kg (3.0 and 0.50 times the clinical dose based on body weight and surface weight, respectively) group exhibited a decrease in body weight gain (20.6% relative to the control group). The NOEL for maternal toxicity was 50 mg/kg (1.5 and 0.25 times the clinical dose, based on body weight and surface area, respectively). No treatment-related effects were detected in the cesarean or fetal observations for any treatment group. The NOEL for fetal toxicity was 166 mg/kg (5.0 and 0.83 times the clinical dose, based on body weight and surface area, respectively).

New Zealand White rabbits received 10, 33, or 95 mg/kg VPN by gavage on Day 6 to 18 of pregnancy. The does in the 95 mg/kg group (2.86 and 0.95 times the clinical dose based on body

weight and surface area, respectively) displayed a decrease in body weight gain (44.4% relative to the control) relative to the control group during treatment; the does did not exhibit any other signs of toxicity. No treatment-related effects were observed in cesarean parameters in any treatment group. Treatment with 95 mg/kg resulted in a statistically significant increase in the number of fetuses with any type of major abnormality (7.4% for the treated versus 0.0% for the concurrent control, with the historical range being 0.0 - 4.2%). The relationship of this effect to treatment is not clear for several reasons. First, the control group did not contain any major abnormalities; therefore, the treated groups were compared to an unusually low value. Second, the type of abnormalities observed in the 95 mg/kg group were diverse; the fetuses in the 95 mg/kg group exhibited 12 different abnormalities, 6 external/visceral and 6 skeletal, with only one abnormality occurring twice. In addition, the rabbit fetuses in the rangefinding study did not exhibit an increase in abnormalities following treatment of the does with 90 mg/kg. In addition to the major abnormalities, the fetuses in the 95 mg/kg group exhibited a significant increase in the percentage of fetuses (3.9% for the treated fetuses versus 0.0% for the control) with one or more nonossified metacarpals (a minor abnormality). The NOEL for maternal and fetal toxicity was 33 mg/kg (0.99 and 0.33 times the clinical dose based on body weight and surface area, respectively).

CONCLUSION: The studies that the sponsor submitted with this NDA adequately support the safety of vicoprofen. The toxic effects that vicoprofen produced did not differ from ibuprofen-induced toxicity.

RECOMMENDATIONS:

I. The pharmacology/toxicology recommendation for NDA 20-716 is APPROVAL.. The labeling should be modified as specified below.

II. **LABELING:** The Pharmacology/Toxicology labeling recommendations pertain to the "Carcinogenicity, mutagenicity, and impairment of fertility" and "Pregnancy" portions only.

A. It is recommended that the following statement be included in the labeling for "Carcinogenicity, mutagenicity, and impairment of fertility" .

The carcinogenic and mutagenic potential of Vicoprofen has not been investigated. The ability of Vicoprofen to impair fertility has not been assessed.

B. It is recommended that the section pertaining to the individual components of vicoprofen, ibuprofen and hydrocodone (Volume 1.1, pages 53 to 55, lines 360 to 388) be removed from the labeling. It is recommended that the portion of the labeling that pertains to vicoprofen (Volume 1.1, page 55, lines 390 to 403) be replaced with the following.

Pregnancy Category C. Vicoprofen, administered to rabbits at 95 mg/kg (2.86 and 0.95 times the maximum clinical dose based on body weight and surface area, respectively), a maternally toxic dose, resulted in an increase in the percentage of litters and fetuses with any major abnormality and an increase in the number of litters and fetuses with one or more nonossified metacarpals (a minor abnormality). Vicoprofen, administered to rats at 166 mg/kg (5.0 and 0.83 times the maximum clinical dose based on body weight and surface area, respectively), a maternally toxic dose, did not result in any reproductive toxicity. There are no adequate and well-controlled studies in pregnant

women. Vicoprofen should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Andrea B Weir Aug. 9, 1996

Andrea B. Weir, Ph.D.
Reviewing Pharmacologist

Concurred by Conrad H. Chen Aug. 30, 1996

cc:
Orig NDA 20-716
HFD-550/Division File
HFD-550/PM/Lobianco
HFD-550/Chem/Yaciw
HFD-550/Pharm/Weir
HFD-550/Hyde

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20716

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

SEP 23 1996

NDA: 20-716 (Re: IND)

Drug Name: Vicoprofen (ibuprofen 200mg + hydrocodone bitartrate 7.5mg)

Applicant: Knoll Pharmaceutical

Statistical Reviewer: Richard A. Stein Date of Review: 9/23/96

Correspondence Date: 4/25/96 FDA Stamp Date: 5/25/96

Reviewing Medical Officer: John Hyde, MD

Documents Reviewed: Vol. 1.1, 1.40-1.46, 1.48,

Indication: Management of moderate to severe pain

I. Introduction

One Vicoprofen tablet contains ibuprofen 200mg and hydrocodone bitartrate 7.5mg. It is for this dose that approval is being sought. Starting dosage is one tablet every 6-8 hours, which can be increased to 2 tablets every 6-8 hours. Dosage is not to exceed 8 tablets in a 24 -hour period. The half-life and time to peak concentration for hydrocodone are said to be 4.5 and 1.7 hours. For ibuprofen, these times are 2.2 and 1.8 hours. This review will examine the results of 7 protocols (10 studies): VP-01, VP-09, VP-12, VP-13, VP-21, VP-23, VP-29. Study VP-12 was for surgery in back pain. The remaining studies were done in post operative surgery. With the exception of studies VP-01-4, VP-12, and VP-13, where the male/female enrollment was about equal, the remaining 7 studies were done almost entirely in women. This is seen below.

No.	Study ID	N Sex(M,F,%F)	N Race(B,W,H)	Age(med.)
1	VP-01-1	17, 103, 85%	not known	28
2	VP-01-2	0, 120,100%	not known	32
3	VP-01-3	3, 117, 98%	not known	34
4	VP-01-4	63, 57, 48%	not known	55
5	VP-09	0, 119,100%	not known	27
6	VP-12	49, 16, 35%	not known	38
7	VP-13	102, 97, 50%	54, 116, 25	61
8	VP-21	0, 180,100%	0, 180, 0	26
9	VP-23	0, 240,100%	52, 187, 1	39
10	VP-29	0, 201,100%	40, 161, 0	40
Overall		234,1250,84%	234,1250, 26	36

The applicant submitted "FDA reviewer suggested 5-page summaries" for each of the 10 studies above. These analyses included results based on imputing data according to baseline observation carried forward (BOCF), last observation carried forward (LOCF), and worst of last and baseline observation carried forward (WOCF). Based on the electronic data furnished by Knoll, I have verified the computational aspects of the WOCF 5-page summary for study VP-23.

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II. Summary of Statistical Results

1. Statistically positive studies at the labeling dose (ibuprofen 200mg, hydrocodone 7.5mg) are tabled below.

	Effectiveness of	Contribution of	
Efficacy Variables	Vicoprofen	Hydrocodone	Ibuprofen
Relief of Pain	VP-21, VP-23	VP-23	VP-23
Time to Onset			
Time to Remedication	VP-21, VP-23		VP-23

2. There are no studies that lead me to believe that either component of Vicoprofen 200/7.5mg is detrimental to its analgesic effect.
3. Concerning the statistical contribution of ibuprofen and hydrocodone to Vicoprofen at doses at which no labeling is currently being sought:
   A. Studies VP-01-3 (pain) and VP-09 (pain, remedication) show that 10mg and 15mg hydrocodone contribute to the analgesic effectiveness of ibuprofen 400mg.
   B. Study VP-29 is the only study showing the analgesic contribution of ibuprofen to Vicoprofen, i.e., ibuprofen 400mg contributes to the effectiveness of hydrocodone 15mg (pain, remedication).
4. In the appendix, a statistically unsophisticated overview based on pain score data leads me to believe that Vicoprofen has onset in 15 to 25 minutes after dosing. Remedication will be needed "on average" about 6 hours after dosing. However, most studies are in women, so there is a potential for overestimating time to remedication in the general population of men and women.

III. Review by Study

With the exception of protocol VP-01, which had 4 studies, no distinction between protocol number and study number will be made. This should cause no confusion.

1. Protocol VP-01

Design

Protocol VP-01 (Vol. 1.46, pages 383-407) is designed as a randomized, unstratified, double-blind, placebo controlled, 6-week, parallel group study in acute postoperative pain. Forty patients with moderate or severe baseline pain are to enter each of 3 treatment groups. These 3 treatment groups are Vicoprofen (ibuprofen 400mg + hydrocodone 10mg), ibuprofen 400mg, and placebo. Post-dose pain evaluation data, which includes pain relief(PR) and pain intensity(PI), are recorded at 0 (baseline) and 30 minutes, and hours 1, 2, 3, 4, 5, 6.

Applicant's Statistical Results/VP-01

Four studies were conducted under Protocol VP-01. These were numbered VP-01-1 to VP-01-4 by the applicant. With the exception of study VP-01-4 (Kantor), these studies were carried out in women.

- In all 4 studies, the applicant has shown the statistical effectiveness of Vicoprofen 400/10mg for relief from pain and duration of action.
- Lacking a hydrocodone arm, none of these 4 studies were designed to show the contribution of ibuprofen to Vicoprofen.

- Hydrocodone showed a statistically significant contribution to Vicoprofen for relief of pain only in study VP-01-3. None of the 4 studies showed a statistically significant contribution for time to onset, or time to remedication.

2. Protocol VP-09

Design

Protocol VP-09 is a multicenter study carried out in two research facilities in Puerto Rico under Abraham Sunshine, MD, principal investigator. By protocol, this study is a double-blind, randomized, placebo controlled, 6-hour acute dental pain study designed to enter 40 patients with moderate or severe baseline pain in each of 3 treatment groups. These 3 treatment groups are Vicoprofen (ibuprofen 400mg + hydrocodone 15mg), ibuprofen 400mg, and placebo. Post-dose pain evaluation data, which includes pain relief(PR) and pain intensity(PI), are recorded at 0 (baseline) and 30 minutes, and hours 1, 2, 3, 4, 5, 6. The end of the investigational period is the time when the patient requests remedication.

Applicant's Statistical Results/VP-09

- The applicant has shown the statistical effectiveness of Vicoprofen 400/15mg with respect to placebo for the relief of pain, faster onset of action, and time to remedication.
- Lacking a hydrocodone arm, this study was not designed to show the contribution of ibuprofen to the effectiveness of Vicoprofen.
- The applicant has shown the statistical contribution of hydrocodone 15mg to the effectiveness of ibuprofen 400mg in relief of pain and onset of action, but not to time to remedication.

3. Protocol VP-12

Design

Protocol VP-12 is a single center (Dallas VanWagoner, MD), double-blind, randomized, 6-hour acute post surgical back pain pilot study designed to enter 15 patients with moderate or severe baseline pain in each of 3 treatment groups. These 3 treatment groups are Vicoprofen (ibuprofen 400mg + hydrocodone 10mg), ibuprofen 200mg, and ibuprofen 400mg. Post-dose pain evaluation data, which includes pain relief(PR) and pain intensity(PI), were recorded at minutes 0 (baseline), and 30 and at hours 1, 2, 3, 4, 5, 6. The protocol suggests there are four primary efficacy variables (Vol. 1.48, page 343): PID, SPID, PR and TOTPAR. Missing data are imputed by last observation carried forward.

Applicant's Statistical Results/VP-12

- Lacking a placebo, the basic statistical efficacy of Vicoprofen has not been shown.
- The statistical contribution of hydrocodone 10mg to Vicoprofen was not shown.
- Lacking a hydrocodone arm, the study was not designed to show the contribution of ibuprofen to the effectiveness of Vicoprofen.
- The 200 and 400 mg doses of ibuprofen could not be differentiated statistically from each other.

4. Protocol VP-13

Design

Protocol VP-13 is a single center (Dr. Honig), double-blind, randomized, placebo controlled, 8-hour acute postoperative pain study designed to enter 50 patients with moderate or severe baseline pain in each of 4 treatment groups. These 4 treatment groups are Vicoprofen (ibuprofen 400mg + hydrocodone 15mg), hydrocodone 15mg, ibuprofen 400mg, and placebo.

Post-dose pain evaluation data, which includes pain relief(PR) and pain intensity(PI), are recorded at minutes 0 (baseline), 20, 40, 60, 80, 100 and hours 2, 2.5, 3, 4, 5, 6, 8. The end of the investigational period is the time when the patient requests remedication. The protocol states there are four primary efficacy variables (Vol. 1.44, page 420): time-to-onset, time-to-peak, peak analgesic effect, and duration of analgesia. Blood samples are drawn following the 2-hour PI and PR evaluations and at study discontinuation to determine patient plasma drug concentrations.

Patients are allowed to remedicate at any time in the observation period with 200 mg ibuprofen tablets. Before remedicating, patients are encouraged, but not required to wait at least 1-hour and to wait until the pain level has increased to baseline levels.

Applicant's Statistical Results/VP-13

- The applicant has shown the statistical effectiveness of Vicoprofen 400/15mg in relief of pain and time to remedication.
- Neither ibuprofen nor hydrocodone showed a contribution to Vicoprofen in the relief of pain, in obtaining faster onset, nor in longer times to remedication.

5. Protocol VP-21

Design

Protocol VP-21, conducted at the Hospital Municipal de SanJuan, Puerto Rico, is a single center (Abraham Sunshine, MD), randomized, double-blind, placebo controlled, 8-hour acute postoperative pain study designed to enter 60 patients with moderate or severe baseline pain in each of 3 treatment groups. These 3 treatment groups are Vicoprofen (ibuprofen 400mg + hydrocodone 15mg), Vicoprofen (ibuprofen 200mg + hydrocodone 7.5mg), and placebo. Post-dose pain evaluation data, which includes pain relief(PR) and pain intensity(PI), are recorded at minutes 0 (baseline), 20, 40, 60, 80, 100 and hours 2, 2.5, 3, 4, 5, 6, 7, 8. The end of the investigational period is the time when the patient requests remedication. The protocol states there are four primary efficacy variables (Vol. 1.43, page 315): time to onset, time to peak, peak analgesic effect, and duration of analgesia.

Patients are allowed to remedicate at any time in the observation period. Before remedicating, patients are encouraged, but not required to wait at least 1-hour and to wait until the pain level has increased to baseline levels.

Applicant's Statistical Results/VP-21

- The applicant has shown the statistical effectiveness of both Vicoprofen 400/15mg and Vicoprofen 200/7.5mg in relief from pain, and time to remedication.
- Lacking a hydrocodone and an ibuprofen arm, this study was not designed to show the contribution of ibuprofen or hydrocodone to the effectiveness of Vicoprofen.
- There is no demonstrated difference in the effectiveness of the 200/7.5mg and the 400/15mg doses of Vicoprofen either in the relief of pain, onset of analgesia, or longer time to remedication.

6. Protocol VP-23

Design

Protocol VP-23, conducted in Birmingham, AL, is a single center (Gilder Wideman, MD), double-blind, randomized, placebo controlled, 8-hour acute postoperative pain study designed to enter 60 patients with moderate or severe baseline pain in each of 4 treatment groups. These 4 treatment groups are Vicoprofen (ibuprofen 200mg + hydrocodone 7.5mg), hydrocodone 7.5mg, ibuprofen 200mg, and placebo. Post-dose pain evaluation data, which includes pain

relief(PR) and pain intensity(PI), are recorded at minutes 0 (baseline), 20, 40, 60, 80, 100 and hours 2, 2.5, 3, 4, 5, 6, 8. The end of the investigational period is the time when the patient requests remedication. The protocol states there are four primary efficacy variables (Vol. 1.42, page 302): time-to-onset, time-to-peak, peak analgesic effect, and duration of analgesia. Blood samples are drawn following the 2-hour PI and PR evaluations and at study discontinuation to determine patient plasma drug concentrations.

Patients are allowed to remedicate at any time in the observation period with 200 mg ibuprofen tablets. Before remedicating, patients are encouraged, but not required to wait at least 1-hour and to wait until the pain level has increased to baseline levels.

Applicant's Statistical Results/VP-23

- The applicant has shown the statistical effectiveness of Vicoprofen 200/7.5mg in relief from pain, and time to remedication.
- Both ibuprofen and hydrocodone make a statistically significant contribution to the relief from pain of Vicoprofen, but only ibuprofen was shown to make a statistical contribution to longer time to remedication.
- There is no demonstrated effect of the contribution of either ibuprofen or hydrocodone in obtaining faster onset of action for Vicoprofen.

7. Protocol VP-29

Design

Protocol VP-29 is a single center (Gilder Wideman, MD), double-blind, randomized, placebo controlled, 8-hour acute postoperative pain study designed to enter 60 patients with moderate or severe baseline pain in each of 4 treatment groups. These 4 treatment groups are Vicoprofen 400/15mg, hydrocodone 15mg, ibuprofen 400mg, and placebo. Post-dose pain evaluation data, which includes pain relief(PR) and pain intensity(PI), are recorded at minutes 0 (baseline), 20, 40, 60, 80, 100 and hours 2, 2.5, 3, 4, 5, 6, 7, 8. The end of the investigational period is the time when the patient requests remedication. The protocol states there are four primary efficacy variables (Vol. 1.41, page 247): time-to-onset, time-to-peak, peak analgesic effect, and duration of analgesia. Blood samples are drawn following the 2-hour PI and PR evaluations and at study discontinuation to determine patient plasma drug concentrations.

Patients are allowed to remedicate at any time in the observation period with 200 mg ibuprofen tablets. Before remedicating, patients are strongly encouraged, but not required to wait at least 1-hour and to wait until the pain level has increased to baseline levels.

Applicant's Statistical Results/VP-29

- The applicant has shown the statistical effectiveness of Vicoprofen 400/15mg in relief from pain, and time to remedication.
- Ibuprofen 400mg makes a statistically significant contribution to the effectiveness of Vicoprofen in time to remedication and relief from pain.
- Hydrocodone makes a statistically significant contribution to time to remedication and to the relief of pain at one hour and at hours 4 through 8. Given that 42% of the patients in the hydrocodone treatment group have remedicated by hour 4, the contribution of hydrocodone at hours 4-8 to the relief of pain can be questioned because there is so much imputed data.
- There is no demonstrated effect of the contribution of either ibuprofen or hydrocodone in obtaining onset of action for Vicoprofen.

IV. Reviewer's Comments

i) In CFR Part 300, Subpart B, it is stated:

> "Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug."

This statement introduces conditions to be satisfied. Two of these conditions are:

1. The dosage of each component is such that the combination is safe and effective.
2. Each component of the combination must contribute to the claimed effects.

It is my opinion that the wording of the CFR could lead the reader to believe that statements 1 and 2 are totally independent. However, I will show that if one were to consider statements 1 and 2 as independent, an undesirable, but logical, result would follow.

For brevity, let us call the combination drug AB. Let the component drugs be called A and B. It is significant that, unlike condition 1; condition 2, like the CFR statement, contains no reference to the dose of A or B in the combination AB.

For ease of discussion, suppose that approval of a combination drug AB is sought for a tablet containing 100 mg of drug A and 100 mg of drug B.

A. According to condition 1, it must be shown that AB, containing 100 mg A and 100 mg B, is safe and effective. This is reasonable.

B. According to condition 2, the contribution of drug B to the combination AB can be shown by formulating AB tablets containing a small amount, say 1 mg of drug A and 100 mg of drug B. The contribution of B to AB would require simply that modified tablet AB be shown more effective than 1 mg of drug A alone. The failure to mention dose in the statement of the contribution of the components of a combination drug has a logical ramification that is not necessarily reasonable.

   In the limiting case scenario, as the amount of drug A goes to zero, the drug A tablet reduces to a placebo, and the drug tablet AB reduces to drug B alone. Then, showing the contribution of B to AB would reduce (in the limit) to showing that drug B is better than placebo. The same argument applies to the contribution of drug A. Therefore, in the limiting case, if no dose constraints are present; to show the contribution of A and B to combination drug AB reduces to showing A and B are better than placebo.

   Thus, if a combination drug were made up of two properly chosen already marketed drugs, condition 2, i.e., the contribution of each component would be automatically satisfied without ever needing to make a within-study comparison AB to A or AB to B.

ii) Vicoprofen has been almost entirely tested in the post-operative surgery model in women. The only study not conducted in post operative surgery was VP-12 which contained about 50% men, 50% women and did not provide evidence of effectiveness.

V. Conclusions

1. Three requirements for the effectiveness of Vicoprofen 200/7.5mg have been satisfied as follows:
   a. Vicoprofen 200/7.5mg has been shown statistically significantly more effective than placebo in the post-operative surgery model in women.
   b. Hydrocodone provides a statistically significant increase to the effectiveness of ibuprofen in the post-operative surgery model in women since the 3 successful studies involved a total of 3 men.
   c. Ibuprofen provides a statistically significant increase to the effectiveness of hydrocodone in the post-operative surgery model in women.

   The following table specifically addresses these points.

	Effectiveness of	Contribution of	
Efficacy Variables	Vicoprofen 200/7/5mg	Hydrocodone	Ibuprofen
Relief of Pain	VP-21, VP-23	VP-09*, VP-23, VP-01-3**	VP-23, VP-29*
Efficacy at 30 min.		VP-09*	
Time to Remedication	VP-21, VP-23		VP-23, VP-29*

* Study tested Vicoprofen 400/15mg.
** Study tested Vicoprofen 400/10mg.

2. The data reviewed leads us to believe that in women, Vicoprofen 200/7.5mg begins to have analgesic effect about 15 to 25 minutes after being taken, and has a median time to remedication of about 6 hours. However, both these studies were carried out entirely in women. The efficacy data for one of these two studies was in Puerto Rico and involved only Hispanic women. Since some believe that women are more tolerant of pain, and women of native Hispanic culture are still more tolerant of pain, the apparent estimates of the performance of Vicoprofen, particularly time to remedication, may overstate what might be expected.

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Archival: NDA 20-716

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Appendix

Time to Remedication

1. If, in the study of analgesia, there is an efficacy variable/measure that a statistician might intuitively feel to be less encumbered by subjectivity and assumptions, it is Time to Remedication in acute analgesic clinical trials. This is the time interval between when a patient receives an analgesic to alleviate his/her pain and when that patient requests more analgesic.
2. If there is a statistical estimator of a population parameter in the statistical arsenal that is robust, insensitive to spurious within-study data, it would seem to be the median.

Items 1 and 2 above would lead one to conclude that the median time to remedication would be one of the more stable quantities of interest in common acute pain trials.

This idea meets reality in these Vicoprofen trials. Only studies VP-21 and VP-23 studied Vicoprofen at the desired labeling dose. The tolerance for pain seems to vary significantly around the world. Study VP-21 had 60 Vicoprofen patients who had a median time to remedication of 10.54 hours and study VP-23 had 59 Vicoprofen patients who had a median time to remedication of 3.00 hours. In VP-23, Puerto Rican women underwent post operative surgery. In study VP-21, women in Alabama underwent post operative surgery.

The following table orders the estimates of time to remedication to provide a perspective of variability across the Vicoprofen trials submitted:

Study	Vicoprofen Dose in mg (1)	No. Patients	Median Hours to Remedication	95% Confidence Limits
VP-12	400/10	15	2.08	1.08 - 6.50
VP-23	200/7.5	59	3.00	1.33 - 4.67
VP-13	400/15	50	3.96	2.50 - 5.00
VP-01-1	400/10	40	4.17	2.33 - 5.50
VP-29	400/15	50	5.00	3.33 - 7.00
VP-01-4	400/10	40	6.08	4.33 - 9.00
VP-01-3	400/10	40	6.46	4.92 - 7.58
VP-01-2	400/10	40	10.50	8.75 - 12.75
VP-21	400/15	60	10.50	9.67 - 11.25
VP-21	200/7.5	60	10.54	9.92 - 11.33
VP-09	400/15	40	11.58	10.75 - 23.67

(1) ibuprofen dose/hydrocodone dose

One can note from this relatively short table that in the first 4 rows, the upper 95% "confidence" bound does not even reach as high as the lower 95% bound for the final 4 row estimates in this table.

This reviewer sees little need for sophistication at this point in taking an overview of the data presented above. It looks like the time to remedication is about 6 hours and that any estimate between 4 and 9 hours is not too unreasonable were it not for the fact that I believe this estimator is biased and too large.

Time to Onset of Relief from Pain

Time to onset (minutes) was approximated by computing 30/mean PRID. Stopwatch measurements were not available except for time to meaningful relief. The following table orders the estimates of time to onset of relief from pain in the same manner as was previously done for time to remedication:

Study	Vicoprofen Dose in mg (1)	No. Patients	Minutes to Onset	95% Confidence Limits
VP-09	400/15	40	12	10 - 16
VP-21	400/15	60	13	11 - 16
VP-23	200/7.5	59	13	11 - 16
VP-29	400/15	50	14	12 - 19
VP-21	200/7.5	60	17	14 - 21
VP-01-3	400/10	40	18	13 - 29
VP-01-1	400/10	40	20	16 - 28
VP-01-2	400/10	40	21	15 - 32
VP-12	400/10	15	22	14 - 63
VP-01-4	400/10	40	23	16 - 37
VP-13	400/15	50	26	20 - 39

(1) ibuprofen dose/hydrocodone dose

Again without sophistication, one can take a rough overview of this data. It would appear that time to onset of Vicoprofen 200/7.5 mg takes about 17 minutes with any estimate between 15 and 25 minutes as not too unreasonable.

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Contribution to Combined Drug Effect at Labeled Dose Levels

Combination drug policy does not state that "Two or more drugs may be combined in a single dosage form when each component makes a contribution at labeled dose to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug."

The search for studies that show the effectiveness of Vicoprofen 200/7.5mg along with the contributions of ibuprofen 200mg and hydrocodone 7.5mg is limited by the design proper of the studies submitted. The table below displays certain relevant features of the studies reviewed.

	Study VP-						
Study feature relative to label	01	09	12	13	21	23	29
Used Labeled Vicoprofen dose			Yes		Yes	Yes	
Designed to show the contribution of ibuprofen				Yes		Yes	Yes
Designed to show the contribution of hydrocodone	Yes	Yes	Yes	Yes		Yes	Yes
Placebo controlled	Yes	Yes		Yes	Yes	Yes	Yes
Total number of positive features:	2	2	2	3	2	4	3

It is clear from this table that only study VP-23 was designed to be fully able to show Vicoprofen 200/7.5mg meets statistically each of the criteria:

It is more effective than (1) placebo, (2) ibuprofen 200mg, and (3) hydrocodone 7.5mg. This table further shows:

- Only study VP-21 is, by design, capable of joining study VP-23 in showing Vicoprofen 200/7.5mg is more effective than placebo.
- Only study VP-12 is, by design, capable of joining study VP-23 in showing the contribution of 7.5mg hydrocodone to Vicoprofen 200/7.5mg.
- No study is, by design, capable of joining study VP-23 in showing the contribution of 200mg ibuprofen to Vicoprofen 200/7.5mg.

Without need for statistical analysis, it follows that any finding of the contribution of ibuprofen 200mg to the efficacy of hydrocodone 7.5mg can't be based on the studies above. Combination drug policy is not as stringent as the 3 criteria just stated.

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