CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19922

CHEMISTRY REVIEW(S)

Z. McD... 4

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 19-922 **CHEM.REVIEW #:** 8 **REVIEW DATE:** 29 Aug 96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12 Dec 88		
AMENDMENT BC	12 Aug 96	20 Aug 96	26 Aug 96

NAME & ADDRESS OF APPLICANT: Neurex
3760 Haven Avenue
Menlo Park, CA 94025-1012

DRUG PRODUCT NAME:

Proprietary:	Corlopam
Nonproprietary/USAN:	Fenoldopam mesylate (USAN, INN, BAN)
Code Name/#:	SK&F 82526-J
Chem.Type/Ther.Class:	1 S

PATENT STATUS: US 4,197,297, SmithKline Beecham (SB), expires 8 Apr 97.

PHARMACOL.CATEGORY/INDICATION: Antihypertensive

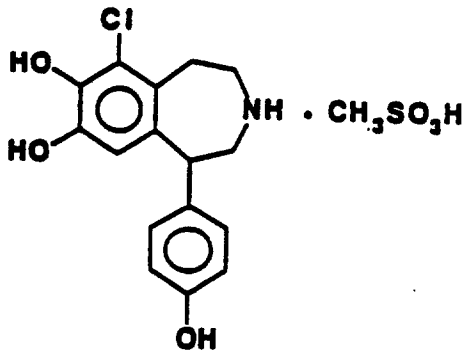
DOSAGE FORM: SVT

STRENGTHS: 5 mL ampules, 10 mg/mL

ROUTE OF ADMINISTRATION: Intravenous

DISPENSED: _x_ Rx ___ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



(R,S)-6-Chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1*H*-3-benzazepine-7,8-diol Mesylate

$C_{16}H_{16}ClNO_3 \cdot CH_3SO_3H$

305.76 (base) 401.87 (salt)

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable):

CONSULTS: Microbiology

REMARKS/COMMENTS:

A Request for Trademark Review, dated 16 Jan 96, was sent to the Labeling and Nomenclature Committee for review. Corlopam, the proposed trademark for this product, was found acceptable.

The information relating to sterility of the drug product has been reviewed by the Microbiology staff, and the submission is recommended for approval on the basis of sterility assurance. The review was dated 25 Jun 96.

An EER was sent to HFD-324, dated 28 Jun 96, requesting inspection of
for manufacture of the drug substance, and inspection of
for manufacture of the drug product. Response has not yet been received.

Validation of the analytical methods will be requested.

The amendment of 12 August 96 provides responses to the Agency's letter of 29 July 96. The deficiencies are repeated, followed by the applicant's responses and my comments.

The applicant apparently did not send a copy of the amendment to SAN-DO.

I had a telephone conference with Bonnie Horner and Dr. Shabbir Anik of Neurex on 28 Aug 96. Points discussed were incorporated in this review.

CONCLUSIONS & RECOMMENDATIONS:

APPROVAL is recommended as far as the chemistry, manufacturing and controls section of this application is concerned.

EER has not yet been returned.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/JShort/8/26/96
HFD-110/CSO
[redacted]
HFD-810/CHoiberg
R/D Init by: RWolters/9/3/96

James H. Short, Ph.D., Review Chemist
filename: N19-922.CR8

Roeder

FEB 26 1991

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
EVALUATION OF CHEMISTRY AND MANUFACTURING CONTROLS
Chemist's Review #6

NDA #: 19-922 Date Completed: 2/22/91

Applicant:

Product Names:

Proprietary:	Corlopam
Non-proprietary:	Fenoldopam Mesylate
USAN:	Fenoldopam Mesylate
Compendium:	Not yet assigned
Code name/number:	

Drug Classification: 1-C

Dosage Form(s) and Route(s) of Administration: Solution for intravenous injection, 2.5, 5 and 10 mL vials, 10 mg/mL

Pharmacological Category and/or Principal Indications: Antihypertensive

Structural Formula and Chemical Name: see Review #1

Initial Submission: 12/12/88

Amendment(s): 7/3/90

Supporting Documents: see Review #1

Related Documents: None

Remarks:

The amendment of 7/3/90 provides responses to our letter of 4/27/90 which conveyed deficiencies noted in CR#3. Our comments are repeated followed by the applicant's responses.

1. We do not agree with your statement in regard to batch size relating to the synthesis of the drug substance that "...there is no theoretical limitation to the batch size, and therefore any appropriate size is acceptable." Often problems are encountered in going to larger batches in different equipiment that may be necessary or changes in the quantities of solvents. We remind you that you are limited to synthesis of batches of fenoldopam starting with If you wish to synthesize larger or smaller batches the relevant information must be submitted to an annual report or supplement, as appropriate.

   RESPONSE: At this time we have no plans to synthesize larger or smaller batches other than what was submitted in NDA 19-922. However, when the decision is made to modify batch size for the synthesis of fenoldopam mesylate, it is expected that those changes will entail concomitant changes of all ingredients, with no alteration to the ratio of ingredients used in this synthesis. Such changes will be made in accordance with Good Manufacturing Practices with assurance that all in-process controls as well as final drug substance specifications will be met.

Changes in batch size that would require significantly different equipment or changes to ingredients in the synthesis will be submitted to the NDA for approval in accordance with 21 CFR 314.70(b)(1)(iv).

Satisfactory

Satisfactory

Conclusions and Recommendations:

NOT APPROVABLE

The information presented in this amendment is satisfactory, and no reply is deemed necessary.

The applicant has not yet responded to the deficiencies noted in Review #4.

James A Short
Chemist

cc:
Original
HFD-110
HFD-110/CSO
HFD-110/JShort
jhs/2/22/91/N19-922.CR6
R/D Init.: RWolters/2/25/91

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS
Chemist's Review #5

NDA #: 19-922 Date Completed: 4/13/90

Applicant: AF #: 14-935

Product Names:

Proprietary:	Corlopam
Non-proprietary:	Fenoldopam Mesylate
USAN:	Fenoldopam Mesylate
Compendium:	Not yet assigned
Code name/number:	

Drug Classification: 1-C

Dosage Form(s) and Route(s) of Administration: Solution for intravenous injection, 2.5, 5 and 10 mL vials, 10 mg/mL

Pharmacological Category and/or Principal Indications: Antihypertensive

Structural Formula and Chemical Name: see Review #1

Initial Submission: 12/12/88

Amendment(s): 4/3/90

Supporting Documents: see Review #1

Related Documents: None

Remarks:

The amendment of 4/3/90 provides for minor changes in the synthesis of the new drug substance. The changes are as follows.

Conclusions and Recommendations:

NOT APPROVABLE

The information presented in this amendment is satisfactory, and no reply is deemed necessary.

The applicant has not yet responded to the deficiencies noted in Reviews #3 and #4.

James P. Short
Chemist

cc:
Original
HFD-110
HFD-110/CSO
[redacted]
jhs/4/13/90/0073X
R/D Init.: RWolters/4/16/90

1990

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS
Chemist's Review #4

NDA #: 19-922 Date Completed: 4/6/90

Applicant: AF #: 14-935

Product Names:

Proprietary:	Corlopam
Non-proprietary:	Fenoldopam Mesylate
USAN:	Fenoldopam Mesylate
Compendium:	Not yet assigned
Code name/number:	

Drug Classification: 1-C

Dosage Form(s) and Route(s) of Administration: Solution for intravenous injection, 2.5, 5 and 10 mL vials, 10 mg/mL

Pharmacological Category and/or Principal Indications: Antihypertensive

Structural Formula and Chemical Name: see Review #1

Initial Submission: 12/12/88

Amendment(s): 3/13/90

Supporting Documents: see Review #1

Related Documents: None

Remarks:

The amendment of March 13, 1990 replies to comment 3 of our letter to the applicant dated 8/9/89, wherein we asked the applicant to delete the word "Injection" from their draft labels for cartons and immediate containers and replace it with "For intravenous Infusion." In their cover letter, the applicant agrees to this change. However, in the draft copies of the labels and labeling which they included in this amendment, in some places "Injection" was replaced with "Infusion." In some places the requested phrase is reproduced in print that is too small and is not on the main panel of the label.

1. In the draft PI, I believe the word "Infusion," which appears in the heading should be changed to "For Intravenous Infusion." In the Description section I believe the phrase "for intravenous administration" should be changed to "for intravenous infusion."

2. The main panels of the labels for the 2.5 mL and 5.0 mL vials contain only the word "Infusion." If space permits this should be changed to "For Intravenous Infusion - Dilute Before Administration." If space constraints require. "Intravenous" may be replaced with "IV."

3. The main panel of the label for the 10 mL vials also contains only the word "Infusion." This should be changed to "For Intravenous Infusion - Dilute Before Administration."

4. The main panels of the carton labels for all three strengths contain only the word "Infusion." This should be changed to "For Intravenous Infusion - Dilute Before Administration."

Conclusions and Recommendations:

NOT APPROVABLE

The deficiencies noted above will be conveyed to the applicant.

James H. Short
Chemist

cc:
Original
HFD-110
~~HFD-110/CSO~~
HFD-110/JShort
jhs/4/5/90/0073X
FINAL:sh/4/9/90
R/D Init.: RWolters/4/9/90

Rimcon

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS
Chemist's Review #3

NDA #: 19-922 Date Completed: 3/7/90

Applicant: AF #: 14-935

Product Names:

Proprietary:	Corlopam
Non-proprietary:	Fenoldopam Mesylate
USAN:	Fenoldopam Mesylate
Compendium:	Not yet assigned
Code name/number:	

Drug Classification: 1-C

Dosage Form(s) and Route(s) of Administration: Solution for intravenous injection, 2.5, 5 and 10 mL vials, 10 mg/mL

Pharmacological Category and/or Principal Indications: Antihypertensive

Structural Formula and Chemical Name: see Review #1

Initial Submission: 12/12/88

Amendment(s): 12/22/89

Supporting Documents: see Review #1

Related Documents: None

Remarks:

The amendment of 12/22/89 provides responses to our letter of 8/9/89, which conveyed deficiencies noted in Review #2. The deficiencies are repeated, followed by the applicant's responses and my comments.

3. In regard to your draft labels for the immediate containers and cartons, we note that these labels state that the contents are for "Injection." We believe you should use a more specific statement, such as "For Intravenous Infusion."

   Response. Revised labels will be provided as soon as they are available.

   Comment. Satisfactory.

Conclusions and Recommendations:

NOT APPROVABLE

The deficiencies noted above will be conveyed to the applicant.

James P. Shore
Chemist

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS
Chemist's Review #2

NDA #: 19-922

Date Completed: 7/17/89

Applicant:

AF #: 14-935

Product Names:

Proprietary:	Corlopam
Non-proprietary:	Fenoldopam Mesylate
USAN:	Fenoldopam Mesylate
Compendium:	Not yet assigned
Code name/number:	

Drug Classification: 1-C

Dosage Form(s) and Route(s) of Administration: Solution for intravenous injection, 2.5, 5 and 10 mL vials, 10 mg/mL

Pharmacological Category and/or Principal Indications: Antihypertensive

Structural Formula and Chemical Name: see Review #1

Initial Submission: 12/12/88

Amendment(s): 5/26/89

Supporting Documents: see Review #1

Related Documents: None

Remarks:

The amendment of 5/26/89 provides responses to the deficiencies conveyed in our letter of 2/17/89.

Original
Volume:Page Section

The changes/corrections listed above are acceptable.

EER was submitted 1/31/89 and was approved 2/3/89. Approval included manufacture of drug substance by
manufacture of drug product by
at
or by

In reviewing the applicant's draft labeling, I note that their immediate container labels contain the word "Injection." I believe that a more specific description should be used, such as "For Intravenous Infusion." This would conform with Dr. Kumkumian's memo of 4/24/89, and 21 CFR 201.100(b)(3). This suggestion will be made to the applicant.

Conclusions and Recommendations:

NOT APPROVABLE

Most of the information presented in this amendment is satisfactory. The remaining deficiencies will be conveyed to the applicant.

EER has been approved as noted above.

Methods Validation has not yet been requested.

James H. Short
Chemist

cc:
Original
HFD-110
HFD-110/CSO
HFD-110/JShort
jhs/6/28/89/0073X
R/D Init.: RWolters/7/18/89

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS
Chemist's Review #1

A. 1. NDA #: 19-922 Date Completed: 1/26/89

2. Applicant:

3. Product Name (s):

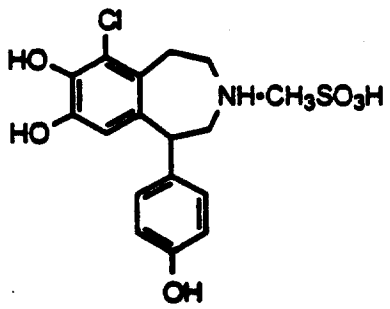
Proprietary:	Corlopam
Nonproprietary:	Fenoldopam Mesylate
USAN:	Fenoldopam Mesylate
Compendium:	Not yet assigned
Code Name/Number:	

4. Drug Classification: 1-C

5. Dosage Form and Route of Administration: Solution for intravenous injection, 2.5, 5 and 10 mL vials, 10 mg/mL

6. Pharmacological Category and/or Principal Indications: Antihypertensive

7. Structural Formula and Chemical Name:



6-Chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1H-3-benzazepine-7,8-diol Mesylate

Molecular Formula: $C_{16}H_{16}ClNO_3 \cdot CH_3SO_3H$

Molecular Weight: 305.76 (base)
401.87 (salt)

MP: 267-269.5° (dec)

8. Patent Information:

U.S. patent 4,197,297 covers composition of matter and use for treating hypertension and shock for its acid addition salts and esters. The patent expires 4/8/97.

9. Related Compounds: None

B. 1. Initial Submission: 12/12/88
Received CDER: 12/14/88
Assigned: 12/15/88

2. Amendments: None

3. Supporting INDs, NDAs, DMFs and Letters of Authorization:

4. Related Documents (INDs, NDAs, etc.): None

C. Remarks:

D. Conclusions and/or Recommendations:

NOT APPROVABLE

The deficiencies will be conveyed to the applicant.

James W Short
Chemist

cc:
Orig.
HFD-102/CKumkumian
HFD-110
HFD-110/CSO
HFD-110/JShort
jhs/12/20/88/0057X
FINAL:sh/1/31/89
R/D Init: RWolters/1/31/89

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19922

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

CORLOPAM

(fenoldopam mesylate infusion)

NDA 19-922

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF
CARDIO-RENAL DRUG PRODUCTS
(HFD-110)

FINDING OF NO SIGNIFICANT IMPACT

NDA 19-922

CORLOPAM

fenoldopam mesylate infusion

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product 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 Corlopam (fenoldopam mesylate infusion), Neurex Corporation, Menlo Park, California, prepared an environmental assessment in accordance with 21 CFR 25.31a (a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Fenoldopam mesylate is a synthetic drug substance administered for the rapid and controlled lowering of elevated blood pressure. Fenoldopam mesylate is manufactured by Penn Chemicals B.V. (now known as Smith Kline Beecham Manufacturing Ltd), Currabinny, Carrigaline, County Cork, Ireland. The drug is filled into clear glass ampoules and sterilized by Oncology Division, Pharmacia, Inc., 4272 Balloon Park Road, NE, Albuquerque, New Mexico 87109-5801. Inspection, labeling and packaging is done at Pharmacia, Inc., 3700 Osuna NE, Albuquerque, New Mexico. All facilities are certified to operate in accord with applicable environmental regulations. The drug product will be used in hospital emergency suites and surgical suites.

The drug substance and its metabolites will be excreted in urine into the sewer system. Chemical and physical characteristics indicate that they will be restricted to the aquatic environment. No adverse environmental effects are anticipated because the Maximum Expected Environmental Concentration (MEEC) in the aquatic environment is much lower than 1 part per billion.

Disposal includes out of specification lots, returned, unused or expired product, empty or partly used product and packaging. These will be disposed at licensed incineration facilities and landfills. Empty or partially empty packages generated in American hospitals will be disposed according to their regulations. Minimal quantities of unused drug may be disposed in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed 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.

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.

July 16, 1996 Florian Zielinski
DATE PREPARED BY: Florian Zielinski, Review Chemist
Division of New Drug Chemistry I

7/18/96 Robert J Wolters
DATE DIVISION CONCURRENCE: Robert J Wolters,
Division of New Drug Chemistry I

7/23/96 Nancy B Sager
DATE APPROVED: Nancy B. Sager, Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment, pages 1 to 33 that includes:
Material Safety Data Sheet, pages 22 to 27, Appendix 5 and
Compliance Statements, pages 15 and 20, Appendices 1 and 4.

Original: NDA 19-922/ZMcDonald
HFD-357 FONSI File [NDA # 19-922]
HFD-357 Docket File
HFD-205 FOI COPY
HFD-110 Division File
HFD-110 CSO, Zelda McDonald
HFD-110 Review Chemist, Florian Zielinski

Review #2

NDA 19-922 Environmental Assessment #2

Review Notes for CORLOPAM Infusion
(50 mg fenoldopam mesylate free base in Type I clear glass ampoules)

1. Date: April 1996

2/3 Applicant: Neurex Corporation
3760 Haven Avenue
Menlo Park, CA 94025

4. Description of Proposed Action: The applicant submitted an environmental assessment according to 21 CFR 25.31 a (a) for approval of NDA 19-922 for Corlopam for short term management of elevated blood pressure in an acute critical care setting.

Need for Action: The drug product is intended to lower blood pressure when oral therapy is not appropriate.

Production Locations:

(a) Drug Substance:

Fenoldopam mesylate is a chemically synthesized drug substance manufactured by Penn Chemicals B.V. (now known as Smith Kline Beecham Manufacturing Ltd., Currabinny, Carrigaline, County Cork, Ireland. Total production to date is 303 kg (three 1 kg batches *plus* three 100 kg batches). Current inventory is expected to last at least 5 years. An alternative supplier such as Smith Kline Beecham, may be used in the future via an NDA Supplement.

Certification of compliance with local and national environmental laws by foreign manufacturing facilities required by Executive Order 12114 (21 CFR Section 25.50) is provided in Appendix 1, page 15.

(b) Drug Product:

The drug product is manufactured and sterilized by Oncology Division, Pharmacia, Inc., 4272 Balloon Park Road, NE, Albuquerque, New Mexico 87109-5801.
Inspection, labeling and packaging is done at Pharmacia, Inc., 3700 Osuna NE, Albuquerque, New Mexico.

These facilities are in typical industrial sites.

Locations of Use: The drug product will be administered to patients in hospitals.

Disposal Sites: Disposal includes out of specification lots, returned, unused or expired product and packaging. These will be disposed at licensed incineration facilities.
Permit information is provided for:

(a) Pharmacia, Inc., 4272 Balloon Park Road, Albuquerque, NM (generator),
(b) Rinchem Co (transporter / broker)
(c) Environmental Systems Co Inc. (final disposal)

Packaging waste generated in American hospitals and clinics will be disposed according to their regulations.

5. Identification of chemical substances that are the subject of the proposed action: 10 mg fenoldopam mesylate free base in 5 mL propylene glycol in aqueous citrate buffer (50:50). Sodium metabisulfite and nitrogen are components of the drug product. (See attached for details; pages 4 to 6 from EA). There are no impurities in the drug substance or drug product at levels greater than 1%.

6. Introduction of Substances into the Environment:

a. Manufacturing

A 5 year supply (approximately 300 kg) of drug substance was made in Ireland. Certification of compliance with environmental laws is provided, see 4 above.

The EIC is significantly below 1 part per billion. **The calculation of the EIC is provided in the** confidential appendix A, **page 35.** (The EIC for 500 kg fenoldopam mesylate emitted into the aquatic environment in 1 year is calculated to be 0.012 ppb)

The potential for introduction of the drug substance(s) into the environment during drug product formulation and packaging operations is extremely small.

All waste is incinerated.

b. Human use of the Drug Product

An environmental effect specifically attributed to the use of the drug product is not expected.

7. Fate in the Environment: Based on physicochemical properties, the drug substance and its metabolites will be restricted to the aquatic compartment.

8. Effects: The excreted drug substance and its metabolites are not expected to have any biological or environmental effects because of their very low concentration in the aquatic environment.

9. Resources and Energy: 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. Requirements for utilities, natural resources and land are unremarkable.

10. Mitigation: The facilities used to manufacture and dispose all substances associated with Corlopam are designed and operated to minimize and avoid potential environmental impacts. Environmental impacts are not expected.

11. Alternatives to the proposed action are not described because no potential adverse environmental impacts have been identified. Approval of the NDA is justified by consideration of environmental factors. Withholding approval (no action alternative) is not recommended because it will deny medical benefits to patients who require the drug product for the management of their condition.

12. Preparer, Michael Droege, PhD, Project Manager, Neurex Corporation, is qualified based on his education, experience and job title. (Resume is provided in Appendix 6, pages 28 to 33)

13. Certification dated July 10, 1996 is provided by Bonnie Horner, Senior Director, Regulatory Affairs, Neurex Corporation.

14. No references are provided (Acceptable).

15. The MSDS (Revised version dated June 22, 1993) for Fenoldopam Mesylate is provided on pages 21 to 26, Appendix 5.

Summary Evaluation: Complete & acceptable Environmental Assessment; FONSI will be prepared for approval by EA Team Leader

Florian Zielinski 7/16/96

Florian Zielinski
July 16, 1996

7/19/96

Original: NDA 19-922
HFD-110 Division File
HFD-110 CSO, Zelda McDonald
HFD-110 Review Chemist, Florian Zielinski

d. Locations of Use

The anticipated locations of use for CORLOPAM® (fenoldopam mesylate) infusion are hospital emergency rooms and surgical suites.

e. Disposal Sites

Rejected, expired, returned, and waste drug substance and product will be incinerated. The following permit numbers apply:

(1) Pharmacia at 4272 Balloon Park Road NE which includes 3700 Osuna NE - Large Quantity Generator - U.S. E.P.A. Permit number: NMD982552945.

(2) The transporter/broker is Rinchem Company Inc. - U.S. E.P.A. Permit number: NMD00208627.

(3) The final disposal facility is Environmental Systems Company, Inc. - U.S. E.P.A. Permit number: ARD069748192.

At U.S. hospitals, pharmacies, or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy or clinic procedures.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

a. Nomenclature

i. *Established Name (U.S. Adopted Name-USAN)*

Fenoldopam Mesylate

ii. *Brand/Proprietary Name(s)*

CORLOPAM, CARLACOR, FEDOPAM

iii. *Chemical Names*

(1) Chemical Abstracts (CA) Index Name (inverted form)

1H-3-benzazepine-7,8-diol, 6-Chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl), methanesulfonate

(2) Systematic Chemical Name (uninverted form)

6-Chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1H-3-benzazepine-7,8-diol, methanesulfonate

b. Chemical Abstracts Service (CAS) Registration Number

67227-57-0

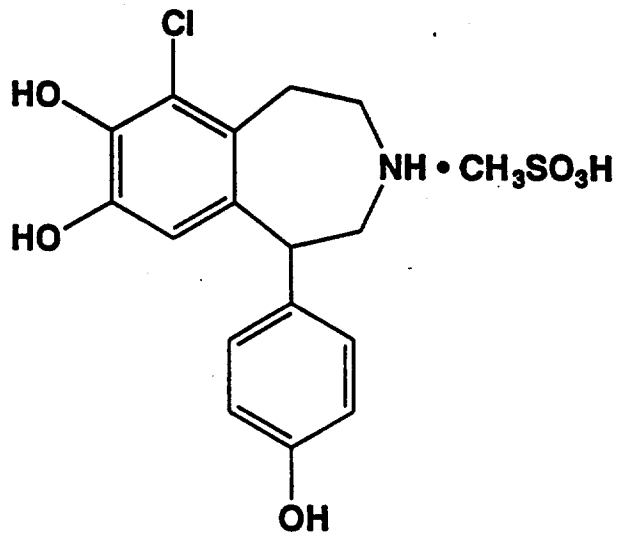
c. Molecular Formula

$C_{16}H_{16}ClNO_3 \cdot CH_3SO_3H$

d. Molecular Weight

401.87 g/mole (mesylate salt)
305.76 g/mole (free base)

e. Structural Formula



fenoldopam mesylate

f. Physical Description

Fenoldopam mesylate is a white to off-white powder.

g. Additives

The following inactive components are contained in the drug product:

Component	CAS Registration Number
sodium metabisulfite, NF	7681-57-4
citric acid anhydrous, USP	77-92-9
trisodium citrate dihydrate, USP	6132-04-3
propylene glycol, USP	57-55-6
water for injection, USP	7732-18-5
sterile nitrogen gas, NF	7727-37-9

JUL 25 1996

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed 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.

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.

July 16, 1996 Florian Zielinski
DATE PREPARED BY: Florian Zielinski, Review Chemist
Division of New Drug Chemistry I

7/16/96
DATE DIVISION CONCURRENCE: Robert J Wolters,
Division of New Drug Chemistry I

7/23/96
DATE APPROVED: Nancy B. Sager, Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment, pages 1 to 33 that includes:
Material Safety Data Sheet, pages 22 to 27, Appendix 5 and
Compliance Statements, pages 15 and 20, Appendices 1 and 4.

Original: NDA 19-922/ZMcDonald
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HFD-357 Docket File
HFD-205 FOI COPY
HFD-110 Division File
HFD-110 CSO, Zelda McDonald
HFD-110 Review Chemist, Florian Zielinski

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

CORLOPAM

(fenoldopam mesylate infusion)

NDA 19-922

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF CARDIO-RENAL DRUG PRODUCTS (HFD-110)

FINDING OF NO SIGNIFICANT IMPACT

NDA 19-922

CORLOPAM

fenoldopam mesylate infusion

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product 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 Corlopam (fenoldopam mesylate infusion), Neurex Corporation, Menlo Park, California, prepared an environmental assessment in accordance with 21 CFR 25.31a (a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Fenoldopam mesylate is a synthetic drug substance administered for the rapid and controlled lowering of elevated blood pressure. Fenoldopam mesylate is manufactured by Penn Chemicals B.V. (now known as Smith Kline Beecham Manufacturing Ltd), Currabinny, Carrigaline, County Cork, Ireland. The drug is filled into clear glass ampoules and sterilized by Oncology Division, Pharmacia, Inc., 4272 Balloon Park Road, NE, Albuquerque, New Mexico 87109-5801. Inspection, labeling and packaging is done at Pharmacia, Inc., 3700 Osuna NE, Albuquerque, New Mexico. All facilities are certified to operate in accord with applicable environmental regulations. The drug product will be used in hospital emergency suites and surgical suites.

The drug substance and its metabolites will be excreted in urine into the sewer system. Chemical and physical characteristics indicate that they will be restricted to the aquatic environment. No adverse environmental effects are anticipated because the Maximum Expected Environmental Concentration (MEEC) in the aquatic environment is much lower than 1 part per billion.

Disposal includes out of specification lots, returned, unused or expired product, empty or partly used product and packaging. These will be disposed at licensed incineration facilities and landfills. Empty or partially empty packages generated in American hospitals will be disposed according to their regulations. Minimal quantities of unused drug may be disposed in the sewer system.

ITEM 3

CHEMISTRY, MANUFACTURING, AND CONTROLS SECTION

D. ENVIRONMENTAL ASSESSMENT

NEUREX CORPORATION
3760 Haven Avenue
Menlo Park, CA 94025

ENVIRONMENTAL ASSESSMENT

SUMMARY DOCUMENT

Table of Contents

ITEM 3

CHEMISTRY, MANUFACTURING, AND CONTROLS SECTION

D. ENVIRONMENTAL ASSESSMENT

1. **DATE:** April, 1996

2. **NAME OF APPLICANT:** Neurex Corporation

3. **ADDRESS:** 3760 Haven Avenue
Menlo Park, CA 94025

4. **DESCRIPTION OF PROPOSED ACTION**

a. Requested Approval

Neurex Corporation has filed an NDA pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for CORLOPAM® (fenoldopam mesylate) infusion, 50 mg free base, packaged in Type I clear glass ampoules. An Environmental Assessment has been submitted pursuant to 21 CFR § 25.31a(a).

b. Need for Action

CORLOPAM® (fenoldopam mesylate) infusion is a well-tolerated and potent systemic and renal vasodilator, useful for the rapid and controlled lowering of elevated blood pressure. It is indicated for the short-term management of elevated blood pressure when oral therapy is not appropriate. It is anticipated that approved uses for CORLOPAM® (fenoldopam mesylate) infusion will primarily be in an acute critical care setting (hypertensive emergency, peri-operative blood pressure control, etc.).

c. Production Locations

Drug Substance Manufacturing:

A large quantity of the drug substance was previously manufactured in Ireland by Penn Chemicals B.V. (now known as SmithKline Beecham (Manufacturing) Ltd., Currabinny, Carrigaline, County Cork, Ireland). A certificate of compliance with applicable environmental laws and emission requirements for SmithKline Beecham (Manufacturing) Ltd., is provided in Non-confidential Appendix 1. There are no plans at this time to manufacture additional drug substance.

Neurex will use three 100 kg batches of existing drug substance for product launch and commercial supplies. This inventory of drug substance is expected to last for at least 5 years. Additional drug substance may be available from SmithKline Beecham. Approximately 200 kg of the drug substance is stored in facilities in Puerto Rico and approximately 100 kg in Ireland. Neurex will also investigate sourcing from an alternative supplier once the product is launched and sales are established in the marketplace. If a new supplier is developed, Neurex will obtain the necessary regulatory approval prior to sourcing for commercial use.

Drug Product and Primary Packaging Operations:

These operations are being carried out under contract with Pharmacia Inc. Oncology Division (Pharmacia). The Pharmacia manufacturing facility where CORLOPAM® (fenoldopam mesylate) is compounded and filled is located at 4272 Balloon Park Road NE, Albuquerque, New Mexico 87109.

Pharmacia facilities located on the same block include the Research and Development building at 4200 Balloon Park Road NE; offices for materials planning, management information systems, and environmental health and safety at 4240 Balloon Park Road NE;

and Clinical Supply Services and engineering and finance at 4240 Balloon Park Road NE. These buildings are not involved with the CORLOPAM® (fenoldopam mesylate) infusion manufacturing process. Inspection of CORLOPAM® (fenoldopam mesylate) infusion ampoules and eventually labeling and packaging occurs at 3700 Osuna NE, a building approximately two miles from the manufacturing facility. A map showing the location of the facilities is attached as Non-confidential Appendix 2.

All sites are supplied with public utilities including natural gas, electricity, water, and sanitary sewers. The four buildings on Balloon Park Road are located in the Balloon Field Industrial Park in northeast Albuquerque. Surrounding facilities include business offices and light manufacturing. The two story 4272 manufacturing building, the adjacent one story 4240 building, and two asphalt parking lots cover about half of the Pharmacia owned property. Landscaped areas to the east and Pharmacia owned vacant land to the west show no signs of environmental stress. A former electronics firm directly east of the 4272 building used solvents that contaminated the groundwater beneath its property. None have been detected at Pharmacia. Prior to development as an industrial park, the site and adjoining areas were cultivated. The soils are classified as gravely fine sand loam.

The inspection, labeling, and packaging facility at 3700 Osuna is in a warehouse/office park. Surrounding areas also include business offices and light manufacturing.

Groundwater is 180 feet below the surface. Six city wells are located less than one mile south of the facility. The Rio Grande River is approximately 0.5 mile west of the building. Storm water is channeled to an arroyo that feeds into the river. The "arid continental" climate provides an average annual precipitation of 8 inches.

d. Locations of Use

The anticipated locations of use for CORLOPAM® (fenoldopam mesylate) infusion are hospital emergency rooms and surgical suites.

e. Disposal Sites

Rejected, expired, returned, and waste drug substance and product will be incinerated. The following permit numbers apply:

(1) Pharmacia at 4272 Balloon Park Road NE which includes 3700 Osuna NE - Large Quantity Generator - U.S. E.P.A. Permit number: NMD982552945.

(2) The transporter/broker is Rinchem Company Inc. - U.S. E.P.A. Permit number: NMD00208627.

(3) The final disposal facility is Environmental Systems Company, Inc. - U.S. E.P.A. Permit number: ARD069748192.

At U.S. hospitals, pharmacies, or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy or clinic procedures.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

a. Nomenclature

i. *Established Name (U.S. Adopted Name-USAN)*

Fenoldopam Mesylate

ii. *Brand/Proprietary Name(s)*

CORLOPAM, CARLACOR, FEDOPAM

iii. *Chemical Names*

(1) Chemical Abstracts (CA) Index Name (inverted form)

1H-3-benzazepine-7,8-diol, 6-Chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl), methanesulfonate

(2) Systematic Chemical Name (uninverted form)

6-Chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1H-3-benzazepine-7,8-diol, methanesulfonate

b. Chemical Abstracts Service (CAS) Registration Number

67227-57-0

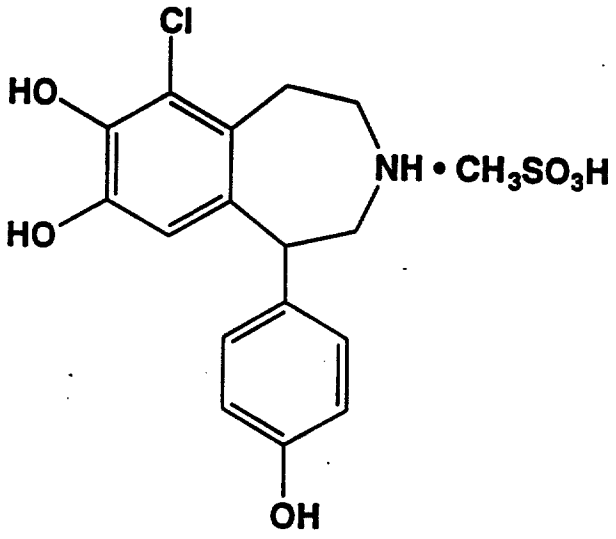
c. Molecular Formula

$C_{16}H_{16}ClNO_3 \cdot CH_3SO_3H$

d. Molecular Weight

401.87 g/mole (mesylate salt)
305.76 g/mole (free base)

e. Structural Formula



fenoldopam mesylate

f. Physical Description

Fenoldopam mesylate is a white to off-white powder.

g. Additives

The following inactive components are contained in the drug product:

Component	CAS Registration Number
sodium metabisulfite, NF	7681-57-4
citric acid anhydrous, USP	77-92-9
trisodium citrate dihydrate, USP	6132-04-3
propylene glycol, USP	57-55-6
water for injection, USP	7732-18-5
sterile nitrogen gas, NF	7727-37-9

h. Impurities

There are no known impurities in the drug substance or drug product at levels > 1%.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

a. Substances Expected to be Emitted

Since the drug substance is already manufactured, only drug product manufacturing and primary packaging operations will be performed. The drug product manufacturing and packaging operations are small volume and disposable items are used as much as possible for equipment that comes in contract with the drug product. All excess drug product and disposable equipment (filters, etc.) is incinerated. As a result, it is anticipated that any waste stream will contain only traces of the formulation components (see 5g) and no environmental impact is expected.

b. Controls Exercised

Not applicable (see 4e and 6a).

c. Citation of and Statement of Compliance with Applicable Emission Requirements

Drug substance was previously manufactured in Ireland and certification of compliance with environmental laws is provided in Non-confidential Appendix 1. A Table of applicable local, state, and federal emission requirements for the primary packaging operations at the Pharmacia facilities is presented in Non-confidential Appendix 3. Non-confidential Appendix 4 is a statement of compliance with the emission requirements set forth in the corresponding permits issued to Pharmacia. Non-confidential Appendix 5 contains the Material Safety Data Sheet for fenoldopam mesylate.

d. Discussion of the Effect of Approval on Compliance with Current Emission Requirements

The manufacturing and packaging operations required to produce the drug product will not impact Pharmacia's compliance with current emission requirements.

e. Expected Introduction Concentrations

i. *Expected Introduction Concentrations(EIC) from Use*

EIC calculations are provided in Confidential Appendix A. Since the environmental introduction concentration of CORLOPAM® (fenoldopam mesylate) is expected to be significantly below 1 ppb, the Tier 0 approach to Fate and Effects Testing is met.

ii. *Expected Introduction Concentration from Disposal*

Not applicable.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

Based on physiochemical properties, the drug substance and its metabolites will be restricted to the aquatic compartment.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

The excreted drug substance and its metabolites are not expected to have any biological or environmental effects because of their very low concentration in the aquatic environment.

9. USE OF RESOURCES AND ENERGY

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. Requirements for utilities, natural resources and land are unremarkable.

10. MITIGATION MEASURES

The facilities used to manufacture and dispose of all substances associated with CORLOPAM® (fenoldopam mesylate) are designed and operated to minimize and avoid potential environmental impacts. Environmental impacts are not expected.

11. ALTERNATIVES TO PROPOSED ACTION

Alternatives to the proposed action are not described because no potential adverse environmental impacts have been identified. Approval of the NDA is justified by consideration of environmental factors. Withholdings approval (no action alternative) is not recommended because it will deny medical benefits to patients who require the drug product for the management of their condition.

12. LIST OF PREPARERS

Michael Droege, Ph.D., Project Manager, Neurex Corporation, is qualified to prepare this EA based on his education, experience, and job title. (See Non-confidential Appendix 6 for resume.)

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 EA.

The undersigned official certifies that the EA Summary Document (pages 1-10), Appendices 1-6 (pages 12-33) contain non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR § 1506.6.

Bonnie Horner — 7/10/96

Bonnie Horner
Senior Director, Regulatory Affairs
Neurex Corporation

Date

14. REFERENCES

None

APPENDICES

Table of Contents for Non-Confidential and Confidential Appendices

NON-CONFIDENTIAL APPENDICES:

CONFIDENTIAL APPENDIX:

Environmental Assessment

Non-Confidential Appendices

Appendix 1

SmithKline Beecham (Manufacturing) Ltd.
Statement of Compliance with
Environmental Laws and
Emission Requirements

SB
SmithKline Beecham
Pharmaceuticals

COMPLIANCE STATEMENT

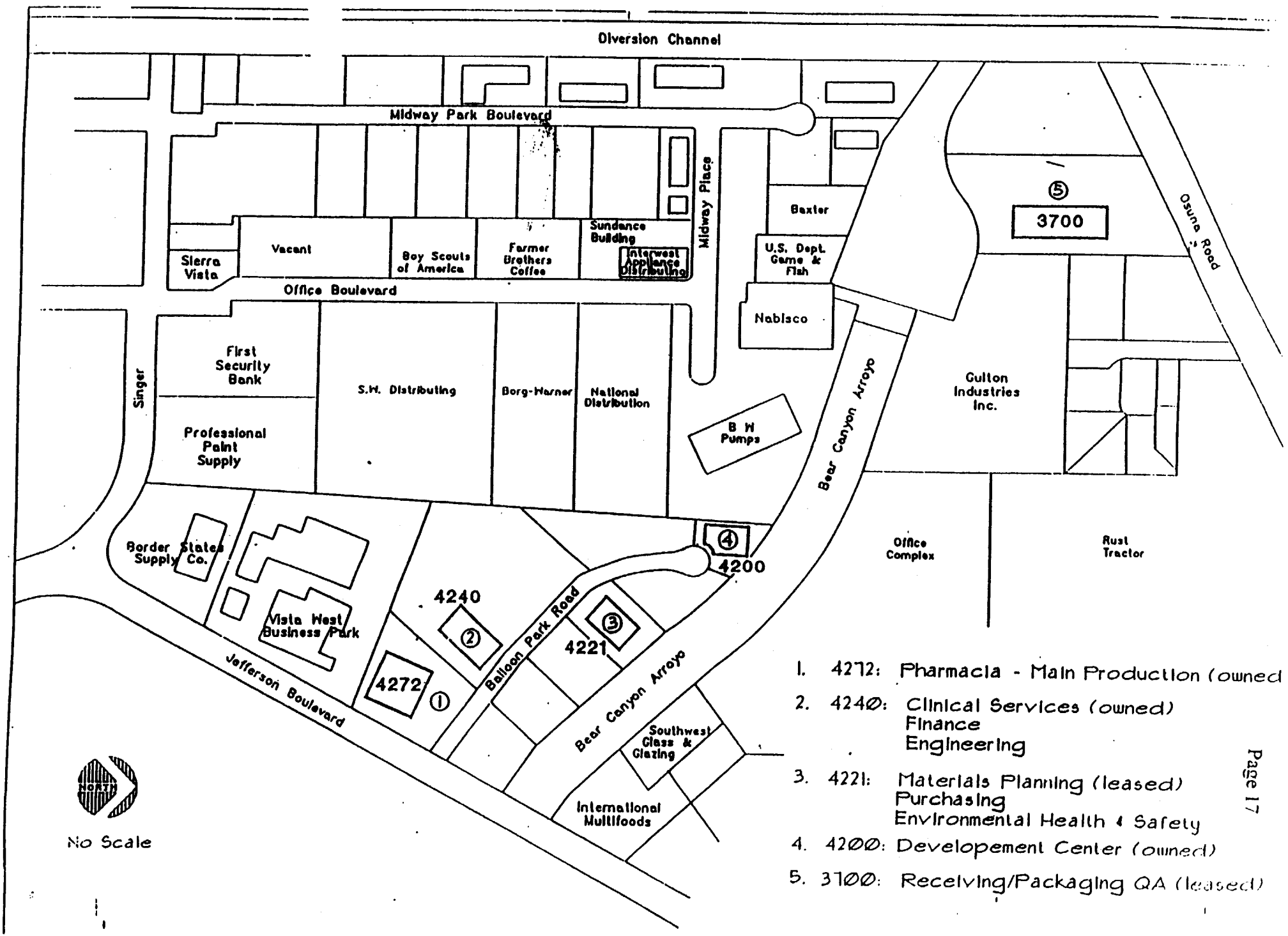
SmithKline Beecham(Manufacturing)Ltd. states that it is in compliance with, or on an enforceable schedule to be in compliance with,all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of it's ethical pharmaceutical products at it's facilities in Currabinny,Carrigaline.Co.Cork.Ireland.

F. A. Groege

Name : Dr.F.A.Groegel.
Title : Team Leader Quality Assurance/Regulatory Control.

Appendix 2

Map Showing the Location of the Pharmacia Facilities



1. 4272: Pharmacia - Main Production (owned
2. 4240: Clinical Services (owned)
   Finance
   Engineering
3. 4221: Materials Planning (leased)
   Purchasing
   Environmental Health & Safety
4. 4200: Developement Center (owned)
5. 3700: Receiving/Packaging QA (leased)

Appendix 3

Emission Permit Table

Permits for Pharmacia Facility			
Emission	**Authorizing Agency**	**Permit #**	**Expiration Date**
Wastewater	City of Albuquerque	2055A-5	January 31, 1998
Air Contaminants	City of Albuquerque	NM/001/00099	no expiration listed (issued 2/12/96)
Storm Water	U.S EPA	NMR00A557	no expiration listed (issued 4/4/96)
Large Quantity Generator	U.S. EPA	NMD982552945	no expiration listed

Appendix 4

Pharmacia Statement of Compliance with Emission Requirements Described in Applicable Permits

Pharmacia

Date April 15, 1996

Reference Full Compliance Statement

The undersigned official certifies that Pharmacia Inc. Oncology Division is, to the best of its knowledge, in full compliance with all applicable local, state, and federal laws regulating environmental emissions at Pharmacia's manufacturing operations.

Signature

4/16/96
Date

Vice-President, Development/QA
Title

A:\wp51\DEH 03 DISK\085DH.496

Pharmacia Inc.
Oncology Division
4272 Balloon Park Road, N.E.
Albuquerque, New Mexico 87109-5801
USA

Telephone
505-345-0500

Telefax
505-761-9335

Appendix 5

Material Safety Data Sheet for Fenoldopam Mesylate

SBMID Material Safety Data Sheet

10000134
Substance/Preparation
FENOLDOPAM MESYLATE

SB Number
82526-J (SKF)

1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION AND OF THE COMPANY/UNDERTAKING

SUBSTANCE/PREPARATION:
FENOLDOPAM MESYLATE
TRADENAMES/SYNONYMS:
CORLOPAM * FENOLDOPAM *
6-CHLORO-2,3,4,5-TETRAHYDRO-1-(4-HYDROXYPHENYL)-1H-3-BENZAZEPINE-7,8-D
IOL METHANESULPHONATE * SK&F 82526-J * SKF 82526-J * 82526-J (SK&F) *
82526-J (SKF)
CHEMICAL FAMILY:
Antihypertensive, dopamine agonist.
MOLECULAR FORMULA:
C16-H16-Cl-N-O3 . C-S-O3-H4
MOLECULAR WEIGHT:
401.878
EINECS NUMBER:
Not Assigned
ELINCS NUMBER:
Not Assigned
COMPANY:

2. COMPOSITION/INFORMATION ON INGREDIENTS

FENOLDOPAM MESYLATE CAS RN: 67227-57-0 MORE THAN 98%
CONTAMINANTS:
None.

3. HAZARDS IDENTIFICATION

PRIMARY ROUTES OF EXPOSURE:
Avoid breathing dust, skin contact, eye contact, ingestion
SKIN CONTACT:
Repeated contact can produce allergic skin reaction, based on reports of occupational exposures and effects in animals. Delayed signs of irritation can include redness or swelling.
EYE CONTACT:
Irritation can occur following direct contact, based upon animal studies. Repeated contact can produce allergic reactions involving the eyes, based on reports

of occupational exposures. Symptoms of immediate or delayed irritation can include redness, itching or swelling.

INHALATION:

Inhalation toxicity has not been determined, assume dust is toxic. Symptoms following overexposure might include flushing, headache, nausea, vomitting, hypotension or dizziness. Repeated contact can produce allergic reactions involving the lungs, based on reports of occupational exposures. Symptoms of allergic reaction might include increased secretions or difficulty breathing.

INGESTION:

Toxicity can occur following ingestion, based on animal studies. Symptoms following overexposure might include flushing, headache, nausea, vomitting, hypotension or dizziness.

CONDITIONS AGGRAVATED BY EXPOSURE:

Individuals taking certain medications that have cardiovascular effects may be more sensitive to the effects of this material.

4. FIRST-AID MEASURES

SKIN CONTACT:

Wash exposed area with soap and water, remove contaminated clothing and obtain medical assistance if irritation occurs, even if symptoms are delayed.

NOTE TO PHYSICIAN:

None

EYE CONTACT:

Wash eyes with water for at least 15 minutes than obtain medical assistance. Seek medical assistance even if symptoms of irritation are delayed.

NOTE TO PHYSICIAN:

None

INHALATION:

Move exposed subject to fresh air. See a physician if subject experiences difficulty breathing. If breathing has stopped, perform artificial respiration and seek immediate medical assistance. Seek medical assistance even if symptoms are delayed.

NOTE TO PHYSICIAN:

None

INGESTION:

In the event of swallowing this material, a properly trained person should induce vomitting but only if subject is fully conscious.

NOTE TO PHYSICIAN:

None

ANTIDOTES:

None Known

5. FIRE-FIGHTING MEASURES

FIRE CONTROL:
Use water, carbon dioxide, foam or dry powder suitable for surrounding fire.
SPECIAL FIREFIGHTING PROCEDURES:
Toxic gases containing carbon dioxide, chlorine and oxides of nitrogen are expected in fires of this material. Self-contained breathing apparatus is recommended for firefighters.

6. ACCIDENTAL RELEASE MEASURES

Scoop or shovel spilled material into a suitable container for recovery or disposal.

7. HANDLING AND STORAGE

HANDLING:
Use a fume hood when working with dust.
Local exhaust should be used when loading, unloading or milling this material.
STORAGE:
Store at room temperature in a dry area. Observe all federal, Sensitising.
state and local regulations when disposing of this material.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

EXPOSURE CONTROLS:
FENOLDOPAM MESYLATE:
SmithKline Beecham(PEL):
0.2 MG/M3 (30 MIN TWA, SENSITISER)
INDUSTRIAL HYGIENE METHOD:
SB/1001 gravimetric method.

PERSONAL PROTECTION:
LABORATORY:
RESPIRATORS:
If dust is present, a laboratory fume hood or approved respirator should be used.
GLOVES:
Wear impervious gloves.
EYE PROTECTION:
Wear safety glasses with sideshields.
HYGIENE PRACTICES:
- Wash hands and arms thoroughly after handling this material. Clean up spills immediately.

OTHER PROTECTIVE EQUIPMENT:
Wear lab coat with long sleeves.
PRODUCTION AND FORMULATON AREAS USING LARGE QUANTITIES:
RESPIRATORS:
Wear a respirator suitable for dust levels present and amount of dust being generated. Because of the possibility for allergic reactions, an air supplied

respirator may be needed for sensitive employees.

GLOVES:

Wear impervious gloves.

EYE PROTECTION:

Wear splash goggles when handling bulk quantities.

HYGIENE PRACTICES:

Shower at the end of each shift when handling this material in bulk quantities. Clean up spills immediately.

OTHER PROTECTIVE EQUIPMENT:

Wear clothing with long sleeves to avoid skin contact. An eye wash station should be available where bulk material is handled.

9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE:

White to off-white, odorless powder with a bitter taste.

FLASH POINT:

Not Determined

AUTOIGNITION TEMP:

Not Determined

LOWER EXPLOSIVE LIMIT:

UPPER EXPLOSIVE LIMIT:

MELTING POINT:

269-276 Degrees C (Decomposes)

BOILING POINT:

Not Applicable

SPECIFIC GRAVITY:

Not Determined

EVAPORATION RATE:

Negligible

VAPOR PRESSURE:

Negigible

PH OF AQUEOUS SOLUTIONS:

Not Determined

SOLUBILITY:

Slightly Soluble in water, propylene glycol and ethanol

10. STABILITY AND REACTIVITY

CONDITIONS TO AVOID:

None known.

INCOMPATABILITY:

None Expected

STABILITY:

Stable at room temperature.

HAZARDOUS POLYMERIZATION:

Not Expected

HAZARDOUS DECOMPOSITION PRODUCTS:

Not Determined

FIRE AND EXPLOSION HAZARDS:

Expected to be negligible.

11. TOXICOLOGICAL INFORMATION

LETHALITY:
Oral LD50 values were 1048 mg/kg in male rats, 1275 mg/kg in female rats, 1657 mg/kg in male mice and 1840 mg/kg in female mice.

INHALATION TOXICITY:
Not determined but allergic reaction is possible, as described under sensitisation below.

SKIN IRRITATION:
This material was classified as a non-irritant to rabbit skin. No visible signs of irritation resulted after direct application in rabbits.

EYE IRRITATION:
This material was classified as a moderate irritant in rabbit eyes. Moderate redness or swelling resulted up to 5 days after direct application in rabbits.

SENSITISATION:
This material was classified as a strong sensitizer to guinea pig skin. Delayed irritation occurred in most guinea pigs used to test for allergic reaction or sensitization (maximization test). Reports of allergic reactions in some employees working with this material also indicate that this effect can occur following contact in humans. Assume that repeated contact with this material can produce allergic reaction involving skin, eyes or lungs.

MUTAGENICITY:
This material is not considered to be mutagenic or genotoxic following numerous laboratory tests (Ames test, CHO/HGPRT forward mutation assay and mouse micronucleus test).

CARCINOGENICITY:
This material is not listed as a carcinogen by SB, IARC, NTP or OSHA. Lifetime studies with mice and rats demonstrated no evidence for carcinogenicity.

REPRODUCTIVE EFFECTS:
No teratogenic effects (birth defects) or embryotoxicity resulted in studies with rats or rabbits. Rat studies showed no adverse effects on male or female reproduction.

PHARMACOLOGIC EFFECTS:
This material is a dopamine agonist used to treat medical conditions, such as acute renal disease, severe hypertension and congestive heart failure.

12. ECOLOGICAL INFORMATION

Not Determined

13. DISPOSAL CONSIDERATIONS

Store at room temperature in a dry area. Observe all federal, state and local regulations when disposing of this material.

14. TRANSPORT INFORMATION

For hazardous materials, the mode of shipment will determine the applicable IATA (air), IMCO (ocean) OR CFR49 (truck) regulations

regarding method of packaging, labeling and declaration.

15. REGULATORY INFORMATION

EUROPEAN UNION CLASSIFICATION AND LABELLING REQUIREMENTS:

FIRE CLASSIFICATION
Not classified as a significant fire hazard
HEALTH CLASSIFICATION
Harmful Irritant

ENVIRONMENTAL CLASSIFICATION
(Leave blank)
RISK PHRASES:
To be determined
SAFETY PHRASES:
Avoid contact with skin and eyes. (S24/25)
In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. (S26)
Wear suitable protective clothing and gloves. (S36/37)
SYMBOL:
Saint Andrew's Cross.(Xn) & Saint Andrew's Cross.(Xi)

16. OTHER INFORMATION

HAZARD LABELLING:
**** NOT CLASSIFIED AS A SIGNIFICANT FIRE HAZARD ****
**** HARMFUL & IRRITANT & SENSITISING ****
**** CAUTION - ENVIRONMENTAL HAZARD NOT FULLY IDENTIFIED ****
** AVOID CONTACT WITH SKIN AND EYES.
** IN CASE OF CONTACT WITH EYES, RINSE IMMEDIATELY WITH PLENTY OF WATER AND SEEK MEDICAL ADVICE.
** WEAR SUITABLE PROTECTIVE CLOTHING AND GLOVES.
** TARGET ORGAN- NO SPECIFIC TARGET ORGAN EFFECTS KNOWN.
** SYMBOL: SAINT ANDREW'S CROSS.(XN) & SAINT ANDREW'S CROSS.(XI)

REFERENCES:
SB HAZARD DETERMINATION

DATE APPROVED: 07 September 89 DATE REVISED: 22 June 93

Appendix 6

Resume of EA Preparer

MICHAEL W. DROEGE

Present Position: Manager, CORLOPAM® Development
Neurex Corporation
3760 Haven Avenue
Menlo Park, CA 94025
(414) 853-1500

Education:

Stanford University; Stanford, CA
Postdoctoral Fellow (1984-1986)

University of Oregon; Eugene, OR
Ph.D. in Chemistry (1984)

Concordia College; Moorhead, MN
B.A. in Chemistry (1978)

Professional Experience:

NEUREX CORPORATION (7/95 to present)

Project Manager (7/95 to present)

Responsible for coordinating drug development project activities for a late stage venture capital and corporate-partner funded biopharmaceutical company.

Manager, CORLOPAM® Development (12/95 to present)

Operations manager for the CORLOPAM ® (fenoldopam mesylate) drug development program.

NYCOMED SALUTAR (9/91 to present)

Manager, Exploratory Research (2/93- 3/95)
Group Leader, Exploratory Research (9/91-2/93)

Head of the Exploratory Research Department (3/94- 3/95)

Responisble for management and technical oversight of all drug discovery programs.

Project Leader for New X-ray Contrast Media (9/91- 3/95)

Technical and administrative leader for a drug discovery program focused on developing new chemical entities to be used as *in vivo* x-ray constrast agents.

LAWRENCE LIVERMORE NATIONAL LABORATORY [LLNL] (9/86 to 9/91)

Project Leader (1/87-9/91)
Member of Technical Staff (9/86-9/91)

Project Leader and Primary Investigator (1987 to 9/91)

Responisble for management and technical oversight of a multi-disciplinary project (chemistry, chemical engineering, microbiology, biochemistry, computations) for the discovery and development of novel energy utilization processes.

Member of Chemistry & Materials Sciences Technical Staff (9/86 to 9/91)

Principal Investigator for research tasks supporting internal LLNL programs

CATALYTICA INC., MOUNTAIN VIEW, CA (11/84 to 9/86)

Technical consultant.

Patents and Applications:

1. Sanderson, W.A.; Droege, M.W. "Iodated Boranes." 1994, PCT Int. Appl. and separate US Patent Appl.

2. Berg, A.; Droege, M.; Fellmann, J.; Klaveness, J.; Rongved, P. "Improvements in or Relating to Polymeric Materials." 1994, PCT Int. Appl.

3. Almen, T.; Berg, A.; Chang, C.A.; Droege, M.; Dugstad, H.; Fellmann, J.; Kim. S.H.; Klaveness, J.; Rocklage, S.; Segal, B. "Contrast Medium." 1992, PCT Int. Appl., WO 9217215.

4. Droege, M.W.; Coronado, P.R.; Hair, L.M. "Tanatalum Oxide Aerogel." 1992 US Patent Application; LLNL Case No.: IL-8743.

Publications/Presentations:

1. Satcher, J.H., Jr.; Balch, A.L.; Olmstead, M.M.; Droege, M.W. "An Unsymmetrical, doubly Bridged Diiron(II) Complex with Readily Accessible Coordination Sites." Inorg. Chem. 1996, 35, 1749-1750.

2. Droege, M.W.; Kim, S-H.; Segal, B.; Watson, A.; Almén, T.; Christoffersson, J-O. "A New Class of *In Vivo* X-Ray Contrast Agents Based on Heavy Element Clusters." Nature 1996, submitted for publication.

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