CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020667

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

TRADE NAME NOT GIVEN

(Pramipexole) USAN, INN

COMPRESSED TABLET 0.125, 0.25, 1.0, 1.25, 1.5 mg

NDA 20-667

THE UPJOHN COMPANY

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

(HFD-120)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-667

TRADE NAME NOT GIVEN

(Pramipexole) Tablets

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 Pramipexole, The UpJohn Company prepared an environmental assessment (attached) in accordance with 21 CFR 25.31a which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Pramipexole is a chemically synthesized drug which is administered as a tablet in the treatment of Parkinson's disease. The drug substance will be manufactured by Boehringer Ingelheim KG, Ingelheim am Rhein, Germany. The drug product will be manufactured by The UpJohn Company, Arecibo, Puerto Rico. The finished drug product will be used in hospitals, clinics and/or by patients in their homes.

Pramipexole may enter the environment from manufacturing sites, disposal of pharmaceutical waste, and from excretion from patients. Due to the relatively small projected use in this country, adverse environmental effects from distribution are not anticipated.

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. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages

will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

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

APPEARS THIS WAY
ON ORIGINAL

RETURN
MAY 8 1996

/S/

5/6/96
Date

PREPARED BY
Carl J. Berninger, Ph.D.
Environmental Scientist
Environmental Assessment Team
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

/S/

5/6/96
Date

CONCURRED
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment (FOI copy)
Material Safety Data Sheet for drug substance included

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Copies:

HFD-120

Jack Purvis
Original NDA 20-667
Division File for NDA 20-667

HFD-205

FOI Copy

HFD-357

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EA File
Docket File
C. Berninger 5/6/96

NON-CONFIDENTIAL

Pramipexole Tablets NDA
Item 3. Chemistry, Manufacturing and Controls
Part V. Environmental Assessment Report - Revised

TABLE OF CONTENTS - ENVIRONMENTAL ASSESSMENT

TABLE OF CONTENTS - ENVIRONMENTAL ASSESSMENT

ENVIRONMENTAL ASSESSMENT REPORT (EA)

1. DATE

December 8, 1995
February 22, 1996 (revision)

2. NAME OF APPLICANT

The Upjohn Company

3. ADDRESS

The mailing address and telephone number of The Upjohn Company are:

7000 Portage Road
Kalamazoo, Michigan 49001
Corporate telephone number: (616) 323-4000

4. DESCRIPTION OF THE PROPOSED ACTION

4.a. Requested Approval

This environmental assessment is submitted in compliance with 21CFR Part 25.31a to accompany the New Drug Application (NDA) #20-667 for pramipexole tablets.

4.b. Need for Action

This environmental assessment is required to accompany the NDA #20-667 for pramipexole tablets. Pramipexole tablets are indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

The first-year patient population is estimated to be 9,600.

4.c. Production Locations

- Drug Substance

The drug substance will be purchased by The Upjohn Company (Upjohn) from:

Boehringer Ingelheim KG
D-55216 Ingelheim am Rhein
Germany

- Drug Product

The drug product will be formulated and packaged at The Upjohn Manufacturing Company (UMC) in Arecibo, Puerto Rico, located south of Puerto Rico Highway No. 2 Km 60.0 (see non-confidential Appendix 1). This facility is in the Barceloneta Industrial Complex which was promoted by the Puerto Rico Industrial Development Corporation (PRIDCO) to attract pharmaceutical and other industrial plants. At this time, there are at least ten industries located in this industrial area. Some of those nearby companies include The nearest school is approximately three kilometers east of the project site, on PR Highway No. 2. Most of the land surrounding the site continues to be used for agricultural purposes with pineapples as the chief crop. The plant site occupies a portion of 94.3 hectares lying south of State Road PR-2 and 3 kilometers west of State Road PR-140 at Cruce Dávilla. About 13.8 hectares of the Upjohn land consist of karst formation [an area of irregular limestone in which erosion has produced fissures, sinkholes, underground streams, and caverns]. The remaining 80.5 hectares of the land that were formerly used for cultivation of sugar cane and for pasture are relatively flat in a tropical climate. The Upjohn Manufacturing Company consists of nine main buildings and some outside facilities and storage tanks.

4.d. Locations of Use

The ultimate use and disposal of the finished product will be mainly at residences, hospitals, and clinics, and nursing homes. Finished products will be stored in distribution centers throughout the U.S. prior to transportation for sale.

4.e. Disposal Sites

Disposal of drug substance or drug product may result from processing or distribution activities in the form of off-specification lots, returned goods, or from end user disposal of individual units of empty or partly empty finished product containers.

The present infrastructure at the proposed manufacturing sites provides for the following recovery and/or ultimate disposal mechanisms:

- Off-Specification Lots

Off-specification lots or rejected goods will be disposed of by incineration at Chambers Medical Technologies (CMT) in Hampton, South Carolina. [CMT has the following permits granted by the South Carolina Department of Health: air permit #1280-0021-CG; NPDES permit No. SC0042242.]

- Returned Goods

Returned goods of the drug product received at Upjohn will be incinerated in an on-site incinerator (interim status treatment storage and disposal facility).

- *Incinerator.* The incinerator is being operated as a Resource Conservation and Recovery Act (RCRA) interim status treatment storage and disposal facility under #MID000820381 in compliance with 40 CFR 264, Subpart O requirements. Additionally, 40 CFR 265.1(b) and Section 3005(e) of RCRA provide for the continued operation of an existing facility that meets certain conditions, until final administrative disposition of the owner's and operator's permit application is made.

The incinerator is a two-stage system: the primary chamber rotary kiln operates at a minimum of 700°F; the secondary chamber, where final destruction of the product and off-gasses occurs, operates at a minimum of 1,904°F. The incinerator is equipped with a pollution control equipment train designed to remove gaseous and particulate pollutants. The pollution control equipment consists of: a quench section, an acid-gas pre-scrubber, a scrubber, an entrainment separator, an induced draft fan, and an exhaust stack.

A hazardous waste RCRA Part B/Act 451, Part 111 permit application has been submitted to the Waste Management Division of the Michigan Department of Natural Resources (now the Michigan Department of Environmental Quality , MDEQ) in Lansing, Michigan. The Upjohn facility is operating under interim status provisions until action is taken on the permit application. MDEQ action on the permit application is expected in 1996. The State air permit issued on July 15, 1980 (#242-80), revised to incorporate the Act 451, Part 111 requirements, was approved on May 26, 1993.

All necessary permits are in place for the manufacture of this product to begin, as an existing interim status facility in accordance with Section 3005(e) of RCRA and Michigan Act 451, Part 111 licensing requirements.

Ash generated as a result of the incineration process will be sent to a permitted hazardous waste landfill. At the present time, Upjohn uses the following facilities:

- Chemical Waste Management, Trade Waste Incinerator Division, 7 Mobile Avenue, Sauget, IL, operating under EPA ID No. ILD 098 642 424 and Illinois Environmental Protection Agency No. IEPA 1631210009;
- Systech Environmental Corporation in Alpena, MI, operating under EPA ID No. MID981200835 and State Air Permit No. 587-93; or in Paulding, OH, operating under EPA ID No. OHD005048947 and State Air Permit Nos. 0363000002P016 and 0363000002P017;
- Continental Cement in Hannibal, MO, operating under EPA ID No. MOD054018288 and Air Permit No. 1086-004A;
- Upjohn may use other facilities for such disposal which are suitable for that purpose and properly permitted.

We have identified hazardous waste as well as air permits as given to us by these facilities, but there may be other permits and licenses applicable which are currently held by the facilities. While Upjohn has contracts with each of these facilities that require compliance with all applicable laws and regulations, Upjohn does not own, operate, or control these facilities. The waste stream profiles established with the hazardous waste landfill sites contain an affirmation by the facility of its compliance status. All facilities are audited and approved for use by Upjohn environmental auditors prior to the first shipment of waste from Upjohn to the site.

- Discarded Product in Hospital or Clinic Setting

Any discarded product or product containers generated in a hospital or clinic setting would typically be disposed in accordance with applicable Federal, State and local regulations.

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

Pharmaceutical Formulation

The material safety data sheet (MSDS) for the drug substance, pramipexole, is included as non-confidential Appendix 2.

The list of ingredients used in formulating the drug product, pramipexole tablets, is included as non-confidential Appendix 3.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

The drug substance and drug product are not expected to be introduced into the environment through transportation and storage. Product will be shipped in Department of Transportation (DOT) specification packaging. Pramipexole is not regulated as a hazardous material under current DOT regulations. Product ready for shipment will be stored in either the manufacturing facility or distribution centers. Both maintain security through limited access.

6.a. Substances Expected to be Emitted

Portions of the ingredients, as listed in non-confidential Appendix 3, may be released to the environment as a result of the proposed action.

Please refer to format item 6.b. for further specific disposal operations covering air, water, and solid waste streams.

Permits and other actions covering specific environmental regulations in force at UMC's chemical processing complex, including permit numbers and expiration dates where applicable, are summarized in the Permits Chart included as non-confidential Appendix 5 to include:

- Permit Description
- Regulatory Agency
- Permit No.
- Issue Date
- Expiration Date

See also The Upjohn Company's Permits Chart included as non-confidential Appendix 6 for an itemization of regulations and permits specific to the on-site approved incinerator.

6.b. Controls Exercised

- **Chemical Process**

See the letter dated 26 October 1995 from the Ministry for the Environment and Forestry (non-confidential Appendix 4) certifying Boehringer Ingelheim's (BI) manufacture in accordance with all German environmental laws and regulations.

- **Pharmaceutical Formulation**

- Air Emissions

Particulate emissions from the drug product are controlled through the use of the following equipment, with efficiencies at 99% by weight.

- dust collectors
- pre-filter system followed by HEPA filters for each dryer plus dust collector at the dryer room

This equipment is covered by the Puerto Rico Environmental Quality Board (EQB) under Temporary Air Operation Permit No. PFE-09-1194-1317-I-O [see Appendix 4 for a listing of permits/renewal status]

- Aqueous Waste Streams

Aqueous waste streams are generated from washes of process equipment at the pharmaceutical area. The equipment is washed with water and detergents [LC-30 or , alcohol 3A, or isopropyl alcohol These streams are discharged to the Puerto Rico Aqueduct & Sewer Authority (PRASA). [see Appendix 4 for a listing of permits/renewal status]

- Waste Solvents

The pramipexole tablets process does not generate waste solvents.

- Solid Waste

Residues from dust collectors and rags and towels used on cleaning of packaging lines and drying of small equipment parts are stored onsite at the container storage area (CSA) (permitted area for storage of hazardous, special, and nonhazardous wastes) prior to shipment to Chambers Medical Technologies (CMT) in Hampton, South Carolina. [CMT has the following permits granted by the South Carolina Department of Health: air permit #1280-0021-CG; NPDES permit No. SC0042242.]

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

The following regulations or standards are cited as applicable to the proposed action:

1. P.R. Public Law 9, The Environmental Public Policy Act of 1970, as amended (local regulation applicable to the Commonwealth of Puerto Rico):
   - Air Pollution Control Regulations
   - Water Quality Standards
   - Regulations for the Control of Hazardous and Non-Hazardous Wastes
   - Underground Injection Control Regulations
2. Puerto Rico Public Law #163 of May 3, 1949, as amended, The Puerto Rico Aqueduct and Sewer Authority, as amended.
3. P.R. Occupational Safety and Health Act of 1907, as amended (local regulation applicable to the Commonwealth of Puerto Rico).

- *Emission Requirements.* UMC 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 manufacture of the drug product, pramipexole tablets, at its facilities in Arecibo, Puerto Rico, as well as emission requirements set forth in applicable Federal, State, and local statutes and regulations applicable to the manufacture of the drug product, pramipexole tablets, at its facilities in Arecibo, Puerto Rico.

- *OSHA Requirements.* Upjohn certifies that it has comprehensive programs and practices in place addressing all applicable OSHA requirements.

6.d. Discussion of the Effect of the Approval on Current Emissions

Approval of the proposed action will not result in the modification of the UMC Puerto Rico site existing facilities.

Projecting to the fifth year of production, all discharges from the production of pramipexole tablets are permitted and will not affect compliance with current emission requirements. Waste water emission for this drug product will be of the permit limit.

6.e. Maximum Expected Environmental Concentration (MEEC)

Estimations of the theoretical maximum environmental concentration (MEEC) can be made using the following equation:

MEEC (ppm) = lbs/yr production X 8.9 E^{-9}

= (A)(B)(C)(D)(E)(F)

where:

A	=	pounds per year production
B	=	year/365 days
C	=	day person/150 gallons
D	=	1/264 million person US population
E	=	gallons/8.34
F	=	1 million

Utilizing the fifth-year production forecast of kg, the maximum environmental concentration that could be achieved is ppm. This concentration assumes complete and instantaneous release of the entire year's production, with no degradation.

These MEECs reflect the worst-case assumptions of instantaneous release and dispersion of the entire year's production with no allowance for biodegradation, hydrolysis, or other removal mechanisms.

CDER has routinely found that drugs at concentrations ppb have no significant effect on relevant standard test organisms and therefore are unlikely to have a significant effect on the environment. CDER has also determined that information for environmental assessment format items 7, 8, 9, 10, 11, and 15 will normally not be needed whose expected introduction concentration is less than 1 ppb.

Since the calculated MEEC for pramipexole is ppb, the format items mentioned above have not been included.

In summary, based on worst-case analysis, pramipexole may reasonably be anticipated to be nontoxic according to the definition found at 21 CFR 25.15(b)(6).

Based on information in CDER's revised guidance document (see Reference 14.J.), information for this format item is not included for this document.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

Based on information in CDER's revised guidance document (see Reference 14.J.), information for this format item is not included for this document.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

Based on information in CDER's revised guidance document (see Reference 14.J.), information for this format item is not included for this document.

9. USE OF RESOURCES AND ENERGY

Based on information in CDER's revised guidance document (see Reference 14.J.), information for this format item is not included for this document.

10. MITIGATION MEASURES

Based on information in CDER's revised guidance document (see Reference 14.J.), information for this format item is not included for this document.

11. ALTERNATIVES TO THE PROPOSED ACTION

Based on information in CDER's revised guidance document (see Reference 14.J.), information for this format item is not included for this document.

APPEARS THIS WAY
ON ORIGINAL

12. LIST OF PREPARERS

Following is a listing of those persons, and corresponding qualifications, who participated in the preparation of this assessment. No government agency was consulted for this specific evaluation other than for routine implementation of ongoing environmental programs conducted at existing facilities.

Jeffrey S. Mehring	Environmental Quality and Safety Division Manager, Environmental Health Sciences Ph.D., Agriculture Professional experience: 24 years
Susan I. Shedore	Environmental Quality and Safety Division Environmental Technician A.A., Liberal Arts Corporate experience: 24 years
Evelyn Perez	Environmental Affairs Associate Environmental & Safety Unit B.S., Environmental Sciences Professional experience: 12 years
John S. Purvis	Supervisory Project Manager Food and Drug Administration CDER Rockville, Maryland

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13. CERTIFICATION

The undersigned officials certify that the information presented is true, accurate, and complete to the best of their knowledge.

The undersigned officials certify that the EA summary document (pages 1-12) and Appendices 1-7 (pages A 13 - A 25) contain non-confidential information and acknowledge that this information will be made available to the public in accordance with 40 CFR § 1506.6. **Appendix 8 (page A 26) contains confidential information that is not to be made available to the public.**

Randal L Senger — Feb 23, 1996

Randal S. Senger, Manager
Corporate Environmental Affairs
(telephone 616/323-5341)

Date

Jeffrey Mehring — 22 FEB 96

Jeffrey S. Mehring, Manager
Environmental Health Sciences
(telephone 616/323-4746)

Date

14. REFERENCES

A. Aerobic Biodegradation of Pramipexole in Water. Final Report #41293.

B. Aerobic Biodegradation of Pramipexole in Water. Draft Raw Data Package

C. Aerobic Biodegradation of Pramipexole in Water. Final Raw Data Package #41293R.

D. Aerobic Biodegradation of Pramipexole in Water. Quality Assurance Statement. Kalamazoo, Michigan: The Upjohn Co, April 17, 1995.

E. Determination of Air-Water Henry's Law Constant with Pramipexole. Final Report #42872. , December 7, 1995.

F. Determination of Air-Water Henry's Law Constant with Pramipexole. Final Raw Data Package #42872R. December 7, 1995.

G. Determination of Air-Water Henry's Law Constant with Pramipexole. Quality Assurance Statement. Kalamazoo, Michigan: The Upjohn Co, December 11, 1995.

H. Determination of the Aqueous Photodegradation of Pramipexole. Final Report #41592. September 15, 1995.

I. Determination of the Aqueous Photodegradation of Pramipexole. Quality Assurance Statement. Kalamazoo, Michigan: The Upjohn Co, September 28, 1995.

J. Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements. Center for Drug Evaluation and Research, CMC 6, November 1995.

K. Microbial Inhibition with Pramipexole. Final Report #41294. March 23, 1995.

L. Microbial Growth Inhibition with Pramipexole. Quality Assurance Statement. Kalamazoo, Michigan: The Upjohn Co, April 4, 1995.

15. APPENDICES

Non-Confidential

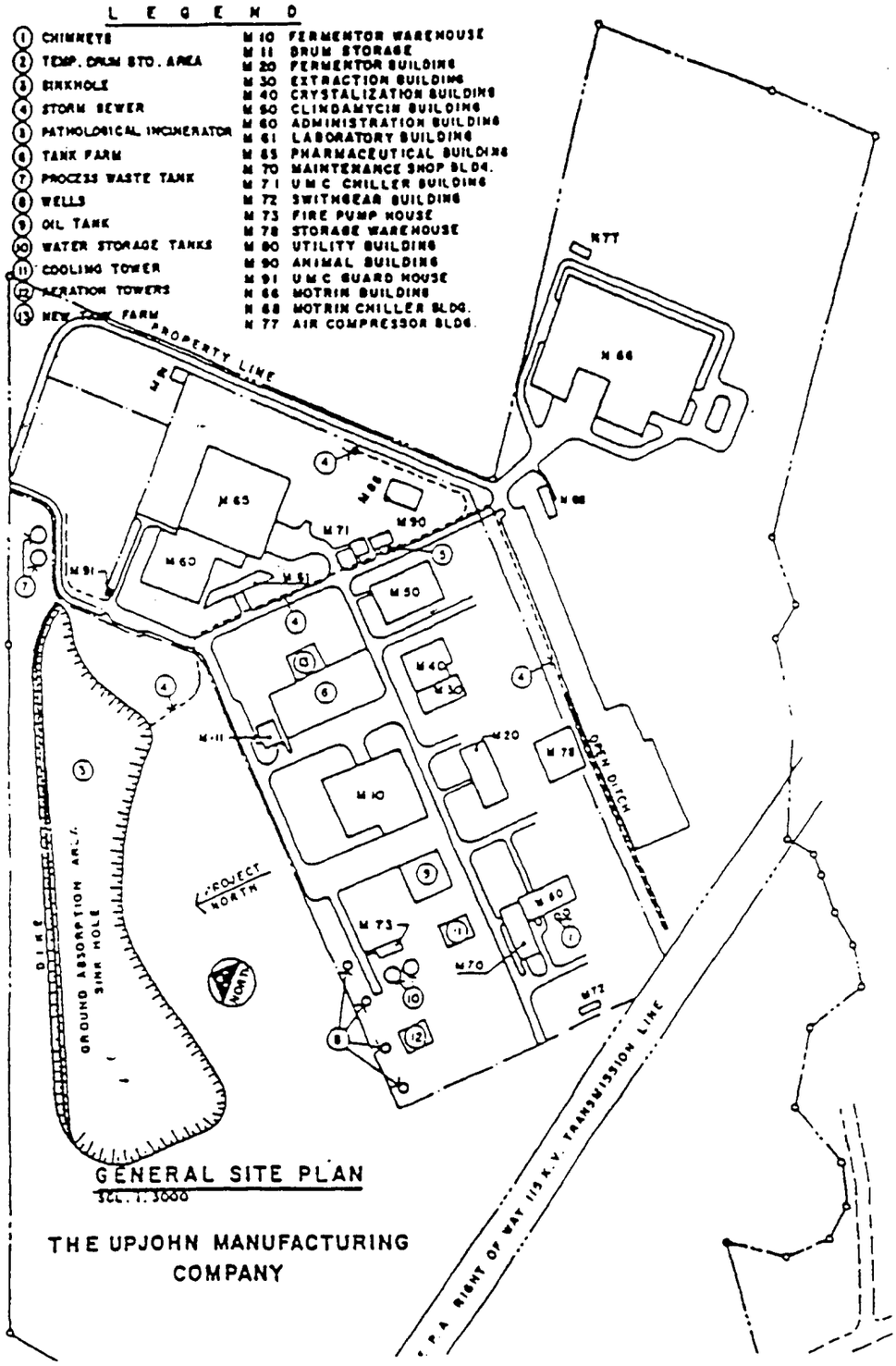
1 Map of UMC's Puerto Rico Pharmaceutical Manufacturing site complex
2 MSDS for the active ingredient, pramipexole
3 Pramipexole Tablets: List of Ingredients Used in Formulation
4 Certification letter covering BI manufacture: Ministry of the Environment and Forestry, Mainz, Germany
5 The Upjohn Manufacturing Company Permits Chart
6 The Upjohn Company Permits Chart
7 Chemical Summary

Confidential

8 Five-Year Marketing Figures

NON-CONFIDENTIAL
APPENDIX 1

Map of UMC's Puerto Rico Pharmaceutical Manufacturing Site Complex



GENERAL SITE PLAN

SCL. 1: 3000

THE UPJOHN MANUFACTURING COMPANY

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APPENDIX 2

Material Safety Data Sheet
Pramipexole

NON-CONFIDENTIAL
APPENDIX 2

MATERIAL SAFETY DATA SHEET

Revision Date: November 21, 1995
Agent ID#: 54

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

COMMON NAME: PRAMIPEXOLE
SYNONYMS: 104632-26-0 - CAS NUMBER
(S)-4,5,6,7-tetrahydro-N6-propyl-2,6-benzothiazolediamine
dihydrochloride monohydrate
U-98,528E - UPJOHN U#
MOLECULAR FORMULA: C10-H17-N3-S.2HCl.H2O
USE: Investigational drug for the treatment of Parkinson's disease.
MANUFACTURER/SUPPLIER: PHARMACIA & UPJOHN INC
7171 PORTAGE RD
KALAMAZOO, MI 49001-0199
TELEPHONE NUMBERS: (616) 323-5122 - (24 HOURS)
(616) 323-7555 - (8:00 a.m. - 4:30 p.m.)
(616) 385-7358 - (SAMPLE REQUEST/TECHNICAL ASSISTANCE)

2. COMPOSITION/INFORMATION ON INGREDIENTS

INGREDIENT 1
COMMON NAME: Pramipexole
CHEMICAL NAME: (S)-4,5,6,7-tetrahydro-N6-propyl-2,6-benzothiazolediamine
dihydrochloride monohydrate
% BY WEIGHT: 100 %
CAS NUMBER: 104632-26-0
EXPOSURE LIMIT(S):
UPJOHN EXPOSURE LIMIT-TWA: 7 UG/M3

3. HAZARDS IDENTIFICATION

PRIMARY ROUTE(S) OF EXPOSURE: Skin contact, eye contact, ingestion and inhalation. As a hydrochloride, the substance is soluble in water, methanol and ethanol. The absorption from the gastrointestinal tract is

very good. Absorption after inhalation of dusts and aerosols, after contact with the eyes and, under certain circumstances, absorption of solutions through the intact skin are to be expected. It is expected that as the free base, the compound will penetrate intact skin very easily; this can lead rapidly to high blood levels, especially after skin contact with solutions in hydrophobic solvents.

EFFECTS OF OVEREXPOSURE: Overexposure to this material may lower blood pressure (especially when standing upright; nausea, vomiting, weakness, headache, dizziness and reduced heart rates. Hallucinations and confusion is possible with exposure to high concentrations.

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE: Hypotension.

4. FIRST AID MEASURES

EYES: Flush with water for 15 minutes. Hold eyelids open to assure complete contact with water.

SKIN: Wash with soap and water. Remove contaminated clothing.

INHALATION: Remove from exposure.

INGESTION: Call a physician.

ANTIDOTE: The antidote for pramipexole is metoclopramide {Reglan(R)}. It is diluted and administered as a continuous intravenous infusion.

NOTES TO PHYSICIAN: The compound exerts highly potent agonistic effects in special pharmacological models of pre- and postsynaptic dopamine D2 receptors. Depending on the animal species investigated and the dose administered, sedation or agitation, decrease in blood pressure, drop in heart rate, sterotypic behavior, vomiting and reduction in sleeping time were observed as general pharmacodynamic effects. In case of intoxication, the patient should not be placed in an upright position. If there is a severe drop in blood pressure, the shock recovery position (elevation of the legs) can be recommended. If the patient vomits, it must be ensured that the airways are kept free and vomit is not aspirated.

5. FIRE FIGHTING MEASURES

FLASH POINT: Not applicable (solid).

EXTINGUISHING MEDIA: Water, carbon dioxide, or dry chemical.

FIRE-FIGHTING PROCEDURES: Wear self-contained breathing apparatus and full body protective equipment.

UNUSUAL FIRE OR EXPLOSION HAZARDS: As with all finely divided organic powders, it is advisable to eliminate explosion hazards by methods such

as grounding mechanical equipment in contact with the material to prevent the buildup of static electricity, inerting the atmosphere or controlling dust levels.
HAZARDOUS COMBUSTION PRODUCTS: Carbon monoxide. Carbon dioxide. Sulfur oxides. Nitrogen oxides. Acrid, flammable fumes may develop.

6. ACCIDENTAL RELEASE MEASURES

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED: Remove ignition sources; control the generation of dust/vapors; provide ventilation and respiratory, skin and eye protection to prevent overexposure. Keep out of drains; prevent entry to surface water, groundwater and soil. Vacuum (with HEPA-filtered and explosion-proof equipment) or scoop spilled material and place in container.

7. EXPOSURE CONTROLS/PERSONAL PROTECTION

RESPIRATORY PROTECTION: Approved respirator or dust mask.
VENTILATION: Local exhaust at point of manufacture or use.
PROTECTIVE GLOVES: Rubber.
EYE PROTECTION: Safety glasses with side shields.

8. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE/PHYSICAL STATE: White, crystalline powder.
MELTING RANGE: 298 - 301 C (568 - 574 F) (with decomposition)
MOLECULAR WEIGHT: 302.27
SOLUBILITY IN WATER: > 10 % (at 20 C)
VAPOR PRESSURE: Negligible.
VOLATILITY: Negligible.

9. TOXICOLOGICAL INFORMATION

ACUTE STUDIES:
SKIN IRRITATION (RABBIT): Non-irritating.
INTRAVENOUS TOXICITY: Single intravenous doses of 10 to 100 micrograms were well tolerated in normal, healthy individuals. Adverse effects were mild and included headache and fatigue. Hypotension and other adverse effects may occur at higher doses.
INTRAVENOUS LD50 (RAT): 210 MG/KG (approximate)
INTRAVENOUS LD50 (MOUSE): 155 MG/KG (males)

IV LD50 for female mice is 188 mg/kg.
ORAL TOXICITY (HUMAN): In safety and tolerance studies in normal, healthy individuals, single oral doses up to 100 micrograms were well tolerated. Hypotension was observed at doses of 100 micrograms or above. The single oral maximum tolerated dose of 400 micrograms was established.
ORAL LD50 (RAT): 548 MG/KG (females)
Oral LD50 for male rats is >800 mg/kg.
ORAL LD50 (MOUSE): 1,700 MG/KG (approximate)
OTHER STUDIES:
GENOTOXICITY: Negative in the Ames assay, Micronucleus test, Cell Transformation assay in SHE cells, and the Chromosome Aberration assay in CHO cells.
REPRODUCTION/FERTILITY: No treatment-related effects were observed in rats at oral dosages of 0.1 mg/kg. Decreased fertility and low birth weight were observed at higher oral dosages of 2.5 mg/kg.
TERATOGENICITY: Studies in rats and rabbits revealed no teratogenic effects.

10. DISPOSAL CONSIDERATIONS

WASTE DISPOSAL METHOD: Dispose of by incineration in accordance with applicable international, national, state, and/or local waste disposal regulations.

11. SHIPPING REGULATIONS

Not regulated for transportation by the United States Department of Transportation (DOT), International Maritime Organization (IMO), or International Air Transport Association (IATA). May be subject to state and/or local transportation requirements.

12. OTHER INFORMATION

REVIEWED BY: Environmental Health Sciences.
DISCLAIMER: The MSDS information is believed to be correct but should only be used as a guide. Pharmacia & Upjohn, Inc. disclaims any express or implied warranty as to the accuracy of the MSDS information and shall not be held liable for any direct, incidental or consequential damages resulting from reliance on the information.

13. LABELING

UPJOHN PRECAUTIONARY LABEL CODE(S): P
HAZARD: POTENT MATERIAL.
SIGNAL WORD: DANGER!
STATEMENT OF HAZARD/RISK PHRASE: May cause immediate and serious adverse effects.
PRECAUTIONARY MEASURES: Do not get in eyes, on skin, on clothing. Avoid breathing dust, vapor, mist or gas. Keep container closed. Use with adequate ventilation. Wash thoroughly after handling.

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APPENDIX 3

Pramipexole Tablets: Ingredients Used in the Formulation

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APPENDIX 3

Pramipexole Tablets: Ingredients Used in the Formulation

Name	CAS No.	M.W.	Formula	Appearance
Colloidal silicon dioxide	7631-86-9	60.09	SiO_2	Fine white powder
Corn starch	9005-84-9	162.06	$C_{16}H_{10}O_5$	White powder
Magnesium stearate	557-04-0	591.2	$C_{36}H_{70}MgO_4$	Fine white powder
Mannitol	69-65-8	182.17	$C_6H_{14}O_6$	White powder
Povidone	9003-39-8	N/A	$(C_6H_9NO)_x$	Off-white powder
Pramipexole	104632-26-0	302.27	$C_{10}H_{21}Cl_2N_3OS$	White crystalline powder

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

NON-CONFIDENTIAL
APPENDIX 5

The Upjohn Manufacturing Company Permits Chart

NON-CONFIDENTIAL
APPENDIX 5

THE UPJOHN MANUFACTURING COMPANY PERMITS CHART

PERMIT DESCRIPTION	REGULATORY AGENCY	PERMIT NO.	ISSUED	EXPIRES
Air Operating Permit	Puerto Rico Environmental Quality Board (EQB)	PFE-07-0391-0331-I-II-O	02/24/92	02/24/94[1]
Temporary Air Operating Permit	EQB	PFE-09-0694-0731-I-O	6/20/94	12/31/95
Extension to Temporary Air Operating Permit	EQB	PFE-09-1195-1427-I-O	submitted to EQB 11/2/95	[2]
Underground Injection Control (Class VI)	Puerto Rico EQB	UIC 84-0253	10/20/92	10/19/97
Wastewater Discharge Permit	Puerto Rico Aqueduct & Sewer Authority (PRASA)	GDA-93-202-051	11/18/95	11/18/97
Well Water Extraction Franchise	Puerto Rico Department of Natural & Environmental Resources	RF-95-92	06/18/92	07/18/95[2]
Biomedical Waste Generator	Puerto Rico EQB	DBM-07-91-9-0028-R-95	9/19/95	11/20/97
RCRA Part B	U.S. EPA	PRD-090398074	12/26/91	12/26/96

[1]Permit renewal application submitted on time; EQB sent letter extending permit until Title V permit is issued in 1995-1996.
[2]Permit renewal applications submitted on time; they remain in effect until acted upon.

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APPENDIX 6

The Upjohn Company Permits Chart

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APPENDIX 6

THE UPJOHN COMPANY PERMITS CHART

PERMIT DESCRIPTION	REGULATORY AGENCY	PERMIT NO.	ISSUED	EXPIRES
Air Consent Judgment	Michigan Department of Natural Resources, Air Quality Division		03/15/91	08/01/96
Air Use Permit	MDNR, Air Quality Division	923-92	03/29/94	
National Pollutant Discharge Elimination System (NPDES)	Michigan Department of Natural Resources Michigan Water Resources Commission	MI0002941	09/20/90 reissued 12/1/95, effective 3/1/96	10/1/2000
RCRA/Michigan Hazardous Waste Management Act 451/Part 111 (On-site Incinerator)	Michigan Department of Natural Resources Waste Management Division	Incinerator operated as a RCRA Interim Status Treatment Storage and Disposal Facility under #MID 000820381 pending action on Act 451/ Part 111 permit application.		
Michigan Air Pollution Act 348 (On-site Incinerator)	Michigan Department of Natural Resources Air Quality Division	242-80	07/15/80 (revised to incorporate the Act 64 requirements) approved 05/26/93	non-expiring until modified

PERMIT DESCRIPTION	REGULATORY AGENCY	PERMIT NO.	ISSUED	EXPIRES
Wastewater Discharge Permit	City of Kalamazoo Industrial Pretreatment Program	The City of Kalamazoo Sewer Use Ordinance and Sewer Use Regulations/Industrial Control Document	03/25/94	03/31/99
Chemical Process Water Management (CPWM) Injection System (Class 1 wells) Underground Injection Control Permit	U.S. EPA, Region 5 Safe Drinking Water Act	MI-077-1W-0001 MI-077-1W-0002	07/09/93	10/27/96

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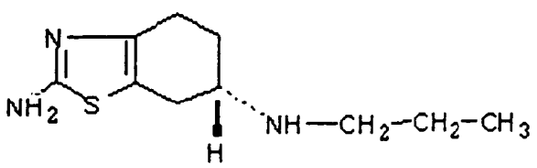
APPENDIX 7

Chemical Summary

APPENDIX 7

CHEMICAL SUMMARY

Structure



• 2 HCl
• H_2O

Chemical name	(S)-2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazol dihydrochloride monohydrate
CAS Registry number	104632-26-0
Upjohn U-number	98528E
USAN approved generic name	Pramipexole
Empirical formula	$C_{10}H_{21}Cl_2N_3OS$
Molecular weight	302.27
Melting point	296-301°C with decomposition
Appearance	white crystalline powder
Solubility, water (mg/mL)	> 20%

mechanism also occurs, and may therefore be affected, in humans has been reincorporated.

/S/

APPEARS THIS WAY
ON ORIGINAL

Thomas D. Steele, Ph.D.
Pharmacologist

cc: Div. File N20667, HFD-120
G. Fitzgerald, Ph.D. /S/ 5/14/97
J. Feeney, M.D.
T. Wheelous, R.Ph.
T. Steele, Ph.D.

APPEARS THIS WAY
ON ORIGINAL