CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-726

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Femara™

(letrozole tablets)

NDA 20-726

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ONCOLOGIC DRUG PRODUCTS
(HFD-150)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-726

Femara

(Letrozole 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 **Femara (letrozole tablets)**, **Ciba-Geigy Corporation, Pharmaceuticals Division** has prepared an environmental assessment in accordance with 21 CFR 25.31a (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Letrozole is a synthetic drug that will be administered orally in the treatment of advanced breast cancer in post menopausal women. The drug substance and drug product will be manufactured by the applicant in Switzerland. Packaging operations will occur in the United States. The finished drug product will be used in hospitals, clinics and homes throughout the United States.

Letrozole may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites. The projected environmental introduction concentration from use is less than 1 ppb. CDER has routinely found that concentrations less than 1 ppb have no effect on relevant standard test organism, therefore the applicant has submitted a Tier 0 EA without format items 7, 8, 9, 10 and 11.

Disposal in the United States of the chemical substance may result from waste generated during packaging, returned, recalled or expired goods and user disposal of empty or partly used product and packaging. Packaging waste or returned, recalled or expired goods will be sent to licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures. 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, although

minimal quantities of unused drug may be disposed of in the sewer system.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

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. 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.

3/5/97 Nancy B Sager
DATE PREPARED BY
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Eric B Sheinin 3-10 97
DATE CONCURRED
Eric B. Sheinin, Ph.D.
Director, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

cc Original NDA 20-726
HFD-150 / Div Files
/ D. Spillman
/ P. Dietzc
/ L. Zhou
/ E. Tolgyesi
HFD-357 / EA file NDA #20-726²
/ Docket File
HFD-205 / FOI Copy

Non - Confidential

Environmental Assessment Information

Appendix I

BAUDEPARTEMENT
KANTON BASEL-STADT

ENVIRONMENTAL PROTECTION CERTIFICATE

1. The company CIBA-GEIGY LTD operates facilities for chemical and pharmaceutical manufacturing at the following address:

CIBA-GEIGY Ltd.
Klybeckstrasse 141
CH-4002 Basel
Switzerland

2. These production facilities may only operate in accordance with permits issued by the responsible Authorities. In the permits are laid down the purpose for witch buildings and plants may be used and the legal conditions with which the Company must comply.

3. The above-described permits also cover the preparation of the Active Substance

Femara (Letrozole)

4. All buildings and plants of the company CIBA-GEIGY LTD must comply with the federal and cantonal laws and regulations concerning safety, protection of the environment and working conditions.

5. The relevant departments of the Cantonal Authorities perform periodic inspections.

6. It can here be stated that the undersigned Governmental Office has proved the correct building and producing permits are given.

Basel, 15th July 1996

BAUDEPARTEMENT BASEL-STADT
Der Departementssekretär

Frauchiger

Lic. rer. pol. T. Frauchiger

02 MÜNSTERPLATZ 11 · CH-4001 BASEL TELEFON 061 267 60 91 · TELEFAX 061 267 91 50

A10

Ciba-Geigy AG
WerkStein
CH-4332 Stein

Dr.G.Schwalbach
Sicherheits- und Umwelt-
schutzdienst Werk Stein
Tel. 062 868 63 27
FAX 062 868 68 46

December 9, 1996

Self Certification of Compliance with respect to Environmental and Safety Laws and Regulations

1. The Company C i b a operates facilities for chemical and pharmaceutical manufacturing at the following address:

   Ciba-Geigy AG, Werk Stein
   Postfach
   CH-4332 STEIN

2. These production facilities may only operate in accordance with permits issued by the responsible Authorities. In the permit are laid down the purpose for which buildings and plants may be used and the legal conditions with which the Company must comply.

3. The above-described certification also covers the milling of

   FEMARA / AS (Letrozole)

   and the preparation of pharmaceutical products containing

   FEMARA / AS

4. All buildings and plants of C i b a must comply with the federal and cantonal laws and regulations concerning safety, protection to the environment, and working conditions.

5. The relevant departments of the Cantonal Authorities perform inspections.

6. Any subsequent increase in production at the above named facility is not expected to affect compliance with current emission requirements or compliance with environmental laws.

7. On the basis of the inspections performed , it can be confirmed that there exists no indication of violation of the applicable laws and regulations.

Dr.G.Schwalbach

70 01 333 b

Non - Confidential

Environmental Assessment Information

Appendix II

Pharmaceuticals Division

ciba

Ciba-Geigy Corporation
556 Morris Avenue
Summit, NJ 07901-1398
Telephone 908 277 5000

Statement of Compliance

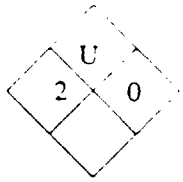
Ciba states that it is compliance with, or on a schedule to be in compliance with, all requirements set forth in all applicable Federal, state and local statutes and regulations, as well as permits, consent decrees and administrative orders applicable to the packaging of Femara 2.5 mg film-coated tablets at its Pharmaceutical production facility in Suffern, New York.

Non - Confidential

Environmental Assessment Information

Appendix III

ciba



MATERIAL SAFETY DATA SHEET

CIBA-GEIGY CORPORATION
PHARMACEUTICALS DIVISION
556 Morris Avenue
Summit, NJ 07901-1398

24 Hour Emergency Telephone Numbers:
Chemical Emergency Response Center: 1-800-888-8372
Medical Emergency: 1-908-277-5000

For Non-Emergency Situation/Technical Information: 1-908-277-5397 (9:00 AM - 5:00 PM E.S.T.)

SECTION 1. PRODUCT IDENTIFICATION

PRODUCT NAME:	**Letrozole**
Ciba Ident. No.:	146991.8
CLASSIFICATION:	Class III Compound
SYNONYMS:	Femara™ active substance, CGS 20267
THERAPEUTIC CATEGORY:	Treatment of breast cancer (nonsteroidal aromatase inhibitor)
GENERIC NAME:	None
CHEMICAL NAME:	4,4'-(1H-1,2,4-Triazol-1-ylmethylene)bis-benzonitrile
CHEMICAL FORMULA:	$C_{17}H_{11}N_5$
MOLECULAR WEIGHT:	285.31

SECTION 2. COMPOSITION/INFORMATION ON INGREDIENTS

COMPOSITION	CAS #	CONCENTRATION (% BY WT.)
Letrozole	112809-51-5	> 98%

SECTION 3. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW

****

REPRODUCTIVE HAZARD
EXPERIMENTAL TERATOGEN
MAY IMPAIR FERTILITY
AVOID CONTACT WITH EYES AND SKIN
AVOID BREATHING DUST

****

PRIMARY ROUTE(S) OF ENTRY: Inhalation

EFFECTS OF OVEREXPOSURE:

Skin:	Not an irritant.
Eye:	Not an irritant.
Inhalation:	Not known. Studies have not been performed to assess acute inhalation toxicity. Systemic effects from absorption is possible.
Ingestion:	Although this material has been found to be well-tolerated in animals after oral administration, its pharmacological mode of action suggests that it might possibly induce a variety of undesired effects. These effects, based on clinical experience, may include nausea, vomiting, depression and fatigue.

TARGET ORGAN EFFECTS: Not known. Letrozole has been found to accumulate in the skin, as well as produce changes in the liver and bone.

REPRODUCTIVE HAZARDS: Given its inhibitory effect on estrogen synthesis, the potential exists for Letrozole to inhibit uterine implantation of the fertilized egg, produce menstrual irregularities, and adversely affect the developing fetus.

CARCINOGENICITY: Studies have not been performed to assess carcinogenic potential.

ACGIH:	Not listed
EPA:	Not listed
IARC:	Not listed
MAK:	Not listed
NIOSH:	Not listed
NTP:	Not listed
OSHA:	Not listed

MUTAGENICITY: Not mutagenic in four test systems (see Section 11).

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE: Pregnancy; hypersensitivity to Letrozole

SECTION 4. EMERGENCY AND FIRST AID MEASURES

Skin Contact:	Wash contaminated area with soap and water.
Eye Contact:	Flush with running water for 15 minutes holding eyelids open.
Inhalation:	Remove to fresh air. Restore and/or support breathing as needed.
Ingestion:	Get medical attention immediately.

SECTION 5. FIRE FIGHTING MEASURES

Flash Point: Not applicable **Method Used:** Not applicable

Flammable Limits (% in air)
Lower: Not applicable Upper: Not applicable

Autoignition Temperature: Not available

Extinguishing Media: Use media suitable for fire in surrounding area.

Special Fire Fighting Procedures and Precautions: Evacuate area and fight fire from safe distance.

Fire and Explosion Hazards: Do not release contaminated water which has been used to extinguish flames into surface waters, drains or ground water. Measures must be taken to retain the water used for extinguishing. Poisonous and irritating degradation products may be liberated from thermal decomposition.

Fire-Fighting Equipment: Wear full protective clothing and a pressure-demand self-contained breathing apparatus.

Decomposition Products: Oxides of carbon and nitrogen and other poisonous gases and vapors may be liberated when heated to decomposition.

NFPA Ratings: Health = 2 Flammability = U Reactivity = 0 Special Hazard = None
Hazard Rating Scales: 0 = Minimal 1 = Slight 2 = Moderate 3 = Serious 4 = Severe U = Unknown

SECTION 6. ACCIDENTAL RELEASE MEASURES

Steps to be taken if Material is Released or Spilled: Using appropriate protective equipment, sweep up and containerize spilled material. Avoid contamination of soils, sewage systems and waterways.

SECTION 7. HANDLING AND STORAGE

Storage Temperature (Min./Max.): Store material at temperatures above 2°C and below 30°C.

Shelf Life: Not known.

Special Sensitivity: Not known.

Handling and Storage Precautions: Store in tightly sealed containers and protect from temperatures below 2°C and above 30°C.

SECTION 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Eye Protection: Safety glasses with side shields.

Skin Protection: Wear protective gloves if direct handling of material is expected. If in solution, selection of gloves depends upon vehicle.

Respiratory Protection: A NIOSH-approved full-face respirator equipped with HEPA cartridges must be worn for open handling of kilogram quantities of material. If dissolved in solvents, use combination organic/HEPA cartridges.

Ventilation Requirements: Use physical barriers and separate ventilation (once-through air or HEPA-filtered recirculation with alarm). When there is potential exposure to Letrozole at or exceeding PIEL, process must be isolated from work area by glove box or other appropriate containment.

Additional Measures: Handle as a Class III compound *(see Safety Procedure G-14)*. Work with material only in designated areas. Avoid open handling of material. Avoid contact with eyes, skin and personal clothing. Decontaminate work areas and personal protective equipment after handling of material is completed.

Exposure Limits (Definition of terms):

ACGIH:	American Conference of Governmental Industrial Hygienists
Ceiling:	Ceiling Value
DTEL:	Derived Target Exposure Limit
MAK:	Federal Republic of Germany Maximum Concentration Values in the Workplace
NIOSH:	National Institute for Occupational Safety and Health
OSHA:	Occupational Safety and Health Administration [USA]
PEL:	Permissible Exposure Limit
PIEL:	Permissible Internal Exposure Limit [Ciba internal]
REL:	Recommended Exposure Limit
Skin (notation):	absorbed through skin
STEL:	Short Term Exposure Limit
TLV:	Threshold Limit Values
TWA:	Time-Weighted Average

Component	Exposure Limit
Letrozole	PIEL = 0.1 ug/m^3 (provisional TWA)

SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance :	crystalline powder	**Odor Threshold:**	not applicable
Color:	white to yellowish	**Odor Characteristics:**	odorless
pH:	7.2 (0.041 g/l sol. water @ 25°C)	**Vapor Pressure (mm Hg):**	$< 1.0 \times 10^{-7}$ torr
Boiling Point:	not applicable	**Vapor Density:**	not applicable
Melting/Freezing Pt:	184 - 185°C (363.2 - 365°F)	**Specific Gravity:**	not available
Solubility:	0.041 g/l at 25°C in water	**Partition Coeff. (log P):**	1.73 at 25°C
	120 g/l at 25°C in dichloromethane		
	6.25 g/l at 25°C in 96% ethanol		

SECTION 10. STABILITY AND REACTIVITY

Stable (yes/no): Yes, in dry and humid heat.

Hazardous Polymerization: Will not occur.

Conditions and Materials to Avoid: Not known.

Incompatibility: Not known

Hazardous Decomposition Products: Thermal decomposition may produce oxides of carbon and nitrogen.

SECTION 11. TOXICOLOGICAL INFORMATION

Eye Irritation: Not an irritant (rabbit).

Skin Irritation/Sensitization: Not a skin irritant (rabbit).

Oral Toxicity: $LD_{50} > 2000$ mg/kg (rat)
$LD_{50} > 2000$ mg/kg (mouse)
$LD_{50} = 200$ mg/kg (dog)

Dermal Toxicity: No data available.

Inhalation Toxicity: No data available.

Subacute/Subchronic: Multidose oral toxicity studies at doses of 30 to 50 mg/kg (3 months and 28 days, respectively) in rats and 3 to 5 mg/kg (3 months and 28 days, respectively) in dogs indicated the compound to be well tolerated, primarily resulting in alterations attributable to hormonal effects secondary to the pharmacologic action of the compound as an inhibitor of estrogen synthesis. These effects included changes in blood count, microscopic changes in several glandular tissues, and effects on male and female reproductive organs. Increased liver weights in rats (at 30 mg/kg) and dogs (at 3 mg/kg) were observed and were considered to be at least partially related to enzyme induction and increased levels of liver enzymes.

Chronic/Carcinogenicity: In a 6/12-month repeated administration study in rats, bone fractures were observed which could be correlated to alterations found in X-ray examinations (reduction in diameter and weight of the bones) and bone chemical analysis (increases in calcium and hydroxyproline). These observations were not found in dogs. The NOEL dose in rats and dogs was 0.3 mg/kg.

Mutagenicity: Negative in the following tests:

In vitro: Ames test; chromosome studies on Chinese hamster ovary cell line CCL 61; gene mutation test in Chinese hamster cells (V79)
In vivo: Rat micronucleus test

Reproductive Effects: In studies ranging between 14 days and 6 months, with repeated orally-administered doses in mice, rats, and dogs, effects on male and female genital organs were noted.

A teratology study in rats was conducted to evaluate maternal toxicity, embryotoxicity and fetotoxicity at daily oral doses of $\geq$ 0.003 mg/kg. Pregnant rats were dosed via gavage from gestation days 6 through 17. Evidence of teratogenicity was noted in the high dose group (0.03 mg/kg) and included malformations of domed head (5/220 fetuses) and fused cervical centrum/ vertebrae (1 fetus per each of 2 litters). These abnormalities were accompanied by maternal mortality, as well as increased resorptions and fetal deaths.

SECTION 12. ECOLOGICAL INFORMATION

Ecotoxicological Information

Microbial growth inhibition:

Species	Minimum Inhibitory Concentration (mg/L)
Aspergillus niger	> 1000
Trichoderma viride	> 1000
Clostridium perfringens	> 1000
Bacillus subtilis	> 1000
Nostoc sp.	> 1000

Invertebrate toxicity:	EC_{50} > 35 mg/l (48 hours)	Species: *Daphnia magna Straus* 1820
Fish toxicity:	LC_{50} > 37 mg/l (96 hours)	Species: rainbow trout
Sludge toxicity:	IC_{50} > 20.2 mg/l (29 days)	Species: activated sewage sludge
Algal toxicity:	EC_{50} > 100 mg/l (72 hours)	Species: *Scenedesmus subspicat*

Chemical Fate Information

Letrozole is not biodegradable (method of OECD guideline No. 301/B). Letrozole does not exert an immediate, harmful effect on aquatic organisms. When properly introduced into adequately prepared biological sewage-treatment plants, no reduction in the aerobic decomposition capacity of activated sludge is to be anticipated. Nonetheless, contamination of soil, drains, and surface waters should be avoided. Bioaccumulation in fish or other aquatic organisms can be ruled out.

SECTION 13. DISPOSAL CONSIDERATIONS

Waste Disposal Method: All wastes must be disposed of in accordance with local, state and federal laws and regulations. (Contact local or state environmental agency for specific rules).

EPA Hazardous Waste Number: None

SECTION 14. TRANSPORTATION INFORMATION

DOT Shipping Name:	Drugs N.O.I. NMFC 58770
DOT Hazard Class:	Not applicable
DOT Identification:	Not applicable
Packing Group:	Not applicable
Hazard Label:	Not applicable
Special Requirements:	Not applicable
Exceptions:	Not applicable
Non-Bulk Requirements:	Not applicable
Bulk Requirements:	Not applicable
Max. Passgr. Air/Rail:	Not applicable
Max. Cargo Only Air/Rail:	Not applicable
Reportable Quantity (lbs.):	Not applicable
Stowage:	Not applicable
Other Requirements:	Not applicable
Product Label:	Not applicable
Packing Group:	Not applicable

SECTION 15. REGULATORY INFORMATION

OSHA (Occupational Safety & Health Administration): This Material Safety Data Sheet contains the information required by the Federal OSHA Hazard Communication Standard (29 CFR 1910.1200).

OSHA PSM (Product Safety Management): Not listed

NJ TCPA (Toxic Catastrophe Prevention Act): This product contains NONE of the substances subject to the reporting requirements of Section NJAC 7:31 of this act.

TSCA (Toxic Substance Control Act): Not listed

CERCLA (Comprehensive Response Compensation & Liability Act): Not listed

SARA Title III (Superfund Amendments & Reauthorization Act):

Section 302 Extremely Hazardous Substances:	Not applicable (R&D exemption)
Section 311/312 Hazard Categories:	Acute health effects; chronic health effects
Section 313 Toxic Chemicals:	Not listed

RCRA (Resource Conservation & Recovery Act): Not listed

Other State Regulatory Information:

New Jersey: NJ RTK Threshold Planning Quantity = 10,000 lbs.

Other USA Regulations: None

California Proposition 65: The following statement is made in order to comply with the California Safe Drinking Water and Toxic Enforcement Act of 1986: *This material is not known to the State of California to cause cancer or reproductive toxicity.*

Canada:

WHMIS Ingredient Disclosure List
Not listed

EEC Classification (European Economic Community):

Warning Symbol: T
Risk Phrases:
R60 - May impair fertility.
R33 - Danger of cumulative effects.
Safety Phrases:
S53 - Avoid exposure - obtain special instructions before use.
S45 - In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).
S22 - Do not breathe dust.
S36/37 - Wear suitable protective clothing and gloves.

SECTION 16. OTHER INFORMATION

Reason for Issue: 08 Jul 96 - Addition of environmental fate and effects data (Section 12).
03 Apr 96 - Addition of results from teratology study in rats (see Section 11).

Supercedes:	03 Apr 96		
Written By:	C. Perino	**Date:**	08 Jul 96
Approved By:	J. Sinno	**Date:**	08 Jul 96

To the best of our knowledge, the information contained herein is accurate. However, Ciba-Geigy Corporation does not assume any liability whatsoever for the accuracy or completeness of the information contained herein except for the product's administration/use as intended. Final determination of the suitability of any material is the sole responsibility of the user. All materials may present unknown hazards and should be used with caution. Although certain hazards are described herein, we cannot guarantee that these are the only hazards which exist.

Non - Confidential

Environmental Assessment Information

Appendix IV

Peter Leung
Environmental Compliance Officer/Air, HS&E

EMPLOYMENT

Mr. Leung has been employed by Ciba Corporation, Pharmaceuticals Division in Summit, New Jersey since June 1991. As Compliance Officer/Air, Mr. Leung has the responsibility of regulatory compliance for all air emissions for the Summit site. Prior to joining Ciba, Mr. Leung worked for Stone and Webster Engineering Corporation as an environmental engineer.

PROFESSIONAL ACTIVITIES

Mr. Leung is a member of the American Institute of Chemical Engineers and the Air and Waste Management Association.

EDUCATION

Mr. Leung holds a Bachelor degree in Chemical Engineering from The Cooper Union, School of Engineering.

Steve J. Lesko, CSP
Environmental Compliance Officer/Waste, HS&E

EMPLOYMENT

Mr. Lesko has been employed by Ciba Corporation, Pharmaceuticals Division in Summit, New Jersey since May 1994. As Environmental Compliance Officer/Air, Mr. Lesko has the responsibility of regulatory compliance for all medical, hazardous and non-hazardous pharmaceutical wastes for the Summit site. In addition to the Environmental Compliance Officer/Waste responsibilities, Mr. Lesko is also currently responsible for managerial and daily operations of the Environmental section for the Division.

Prior to assuming the above-noted responsibilities, Mr. Lesko was employed by Ciba Corporation, Pharmaceuticals Division and held the position's of Compliance Auditor and Industrial Hygienist since November, 1988. Before joining Ciba, Mr. Lesko worked as an Industrial Hygienist for Beecham Laboratories, an Associate Industrial Hygienist for Clayton Environmental Laboratories and as an Industrial Hygiene Technologist for Princeton Testing Laboratories.

PROFESSIONAL ACTIVITIES

Mr. Lesko is a member of the national and local sections of the American Industrial Hygiene Association and the American Society of Safety Engineers, and the Environmental Auditing Roundtable.

EDUCATION

Mr. Lesko holds a Bachelors degree in Biology from the Ramapo College of New Jersey and is currently pursuing a Masters degree in Environmental Science from the New Jersey Institute of Technology (expected graduation May, 1996).

CERTIFICATIONS AND LICENSES

Mr. Lesko also holds the designation of a Certified Safety Professional (CSP) from the American Society of Safety Engineers.

Joyce Ann Sinno, Ph.D.
Environmental/Occupational Toxicologist, HS&E

EMPLOYMENT

Dr. Sinno has been employed by Ciba Corporation since November 1990 as Environmental/ Occupational Toxicologist for the Pharmaceuticals Division. In addition to responsibilities associated with her position as Occupational Toxicologist, Dr. Sinno's environmental responsibilities include the preparation of Environmental Assessments for NDA and IND submissions. Dr. Sinno was previously employed by Pfizer Pharmaceuticals.

PROFESSIONAL ACTIVITIES

Dr. Sinno is a member of the Society of Environmental Toxicology and Chemistry (SETAC), the Mid-Atlantic Chapter of the Society of Toxicology (MASOT), and the American Industrial Hygiene Association (AIHA).

EDUCATION

Dr. Sinno holds a Bachelors degree and a Masters degree in Pharmaceutical Toxicology and a doctoral degree in Biochemical Toxicology from St. John's University College of Pharmacy and Allied Health Professions.

PUBLICATIONS

Biol. Trace Element Res. **20**: 153-160, 1989.