CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-310

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 20-310

Nizoral A-D (ketoconazole shampoo), 1%

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION HFD-540

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-310

Nizoral A-D (ketoconazole shampoo), 1%

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 internal 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 Nizoral A-D (ketoconazole shampoo) 1%, Johnson & Johnson Consumer Products, Inc. has prepared an environmental assessment in accordance with 21 CFR 25.31a(b)(3) (attached)] which evaluates the potential environmental impacts of the manufacture, use and disposal of the product. The point sources of the manufacture of the drug substance is Johnson & Johnson Pharmaceutical ( ), Gurabo, Puerto Rico, and the finished product is a contract manufacturer and packager for Johnson & Johnson Consumer Products, Inc. The ingredients used to manufacture this product are not cited as hazardous and/or toxic air pollutants. The applicant's facilities operate in conformance with current Good Manufacturing Practices, and employ appropriate procedural and technological measures to control air, liquid, and solid emission waste streams. The drug's intended use is for "the control of flaking, scaling and itching associated with dandruff".

Insignificant quantities of either the drug substance or drug product are expected to enter the environment. Disposal will normally take place in landfills or by incineration.

Disposal of the drug product 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 subject and rejected or returned drug product will be disposed of at a licensed incineration facility or landfill. 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.

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.

Dec 22, 99

Prepared by Su C. Tso, Ph.D.
Chemist, HFD-540

Date

Concurred by W. H. DeCamp, Ph.D.
Supervisory Chemist, HFD-540

12/27/99
Date

Nancy Sager, Environmental Scientist
center for Drug Evaluation and Research

Date

Attachments: Environmental Assessment Report
Material Safety Data Sheet for Ketoconazole

cc: Original: NDA 20-310
HFD-540/SCTso
HFD-540/HBlatt
HFD-004/NSager
HFD-004/Docket File
HFD-019/FOI copy
FONSI file: NDA 20-310

FREEDOM OF INFORMATION

ENVIRONMENTAL ASSESSMENT

ENVIRONMENTAL ASSESSMENT
Format 21 CFR §25.31a (b)
NIZORAL-AD™ (ketoconazole 1% shampoo)

Item 1 **DATE:** November 11, 1992
AMENDED DATE: March 22, 1996

Item 2 **NAME OF APPLICANT**

Johnson & Johnson Consumer Products, Inc.

Item 3 **ADDRESS**

Grandview Road
Skillman, NJ 08558-9418

Johnson & Johnson CONSUMER PRODUCTS, INC.

Item 4 **DESCRIPTION OF PROPOSED ACTION**

This environmental assessment is prepared to provide for the manufacture of NIZORAL-AD ™ (ketoconazole 1% shampoo). The output is intended for the U.S. market. Ketoconazole 1% shampoo is a topical drug product, therefore, as indicated in CFR 21 §25.31a, items 7 through 11 and 15 are not provided for in this Environmental Assessment. The proposed indication for NIZORAL-AD ™ is the control of flaking, scaling and itching associated with dandruff.

Finished Drug Substance Manufacturing Location

The finished drug substance will be manufactured at:

Johnson & Johnson Pharmaceutical Partners
HC 02 Box 19250
Gurabo, Puerto Rico

Johnson & Johnson Pharmaceutical Partners is a wholly owned subsidiary of Janssen Pharmaceutica, Inc. and under the common ownership and control of JOHNSON & JOHNSON.

Johnson & Johnson Pharmaceutical Partners owns approximately 25 acres of property, dedicated for industrial use by the Puerto Rico Planning Board. The site is bounded on the west by State Road No. 933 and on the north by State Road No. 30. The facility has its primary access from State Road No. 933. This parcel is largely a flat area with Mamey Creek flowing at the lower elevation along its eastern and southeastern boundary.

Johnson & Johnson CONSUMER PRODUCTS, INC.

A subsoil investigation made by Jaca & Sierra (soil consulting engineers) found that the general subsoil showed favorable conditions for the development of the area as an industrial site. The underground aquifer consists of light brown, sandy clay and rock arrangements at the 40 foot level and broken, fractured rock at the 225 foot level. The water table is 40 feet or deeper. The thick layer of dense overburden provides excellent surface protection for the aquifer. Because of the small discharges anticipated with this drug substance there are no long term adverse effects anticipated from the operations of this plant.

Drug Product Manufacturing Location

The ketoconazole 1% shampoo will be manufactured at:

is located on a flat site in City of Vernon, an urban area of Los Angeles, CA. The site consists of a 240,000 sq. ft. stand alone commercially zoned manufacturing facility bounded on all sides by industrial or commercial development.

Drug Product Distribution Centers

The following commercial distribution centers are currently being used:

Johnson & Johnson CONSUMER PRODUCTS, INC.

Drug Product Disposal Facilities or Sites

Disposal of bulk drug product, bulk waste from processing, and returned, rejected or outdated finished products will be disposed by incineration or at an approved hazardous waste disposal facility in accordance with all local, state, and federal

requirements, until such time that the product or waste is determined to be non-hazardous. Waste determined by appropriate testing to be non-hazardous will be disposed of at an approved facility according to local, state, and federal environmental regulations.

All disposal sites are licensed by the EPA to dispose hazardous waste. Materials for disposal will be transported by an approved, licensed waste hauler from the source site.

Source: Production Site and Distribution Site #3

Disposal Site: The facility currently being used is:

Johnson & Johnson CONSUMER PRODUCTS, INC.

Source: Distribution Site # 1 and # 2

Disposition: The facility currently being used is:

In the home, 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.

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

a. Nomenclature:

i. **Generic name**: Ketoconazole, USP

ii. **Brand name**: None

iii. **Chemical name**: Piperazine, 1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-,cis-

b. Chemical Abstract Service (CAS) registration number:

65277-42-1

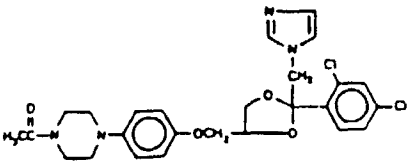
c. Molecular Formula:

$C_{26}H_{28}Cl_2N_4O_4$

d. Molecular Weight:

531.44

e. Structural formula:



f. Physical Description

Ketoconazole is a fine white to slightly beige powder.

g. Additives

Refer to Item 6

h. Impurities

Total Impurities %.

Johnson & Johnson CONSUMER PRODUCTS, INC.

Ketoconazole Release Specification

1. Appearance

Fine, almost white to slightly beige powder; free of any obvious foreign matter.

2. Infrared ID

The infrared spectrum shall exhibit absorption bands of the same pattern and placement as those exhibited by the standard, with no extraneous bands present, as determined by a qualified analyst.

3. Assay

%

4. Melting Range

148°C to 152°C

5. Specific Rotation

   Between -1° and +1°

6. UV Spectrum

   Sample exhibits same maxima and minima as those of a similarly prepared reference standard

7. Loss on Drying

   Not more than %

Johnson & Johnson CONSUMER PRODUCTS, INC.

8. Residue on Ignition

   Not more than %

9. Heavy Metals

   Not more than 20ppm

10. Chromatographic Purity

    Total impurities do not exceed %

11. Particle Size

    "Confidential"

Item 6 INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

Drug Substance

The drug substance ketoconazole, USP will be manufactured by Johnson & Johnson Pharmaceutical Partners, an affiliate of Janssen Pharmaceutica, Inc. and under the common ownership and control of JOHNSON & JOHNSON.

Drug Product

Johnson & Johnson CONSUMER PRODUCTS, INC.

All aspects of manufacture including production, packaging, labeling, and control of the drug product will be performed by in accordance with the production and test methods provided by Johnson & Johnson Consumer Products, Inc. as provided in this New Drug Application. Refer to Attachment # 1.

a. Substances Expected to be Emitted

No substances are expected to be emitted at levels other than low levels. These low level emissions are not likely to have a significant environmental impact.

b. Controls Exercised

The drug substance supplier has certified that the production of this material is in compliance with all emission requirements set forth in the facility environmental permits. Refer to Attachment No. 2.

No significant emissions are expected via air, or liquid waste streams from the manufacture of the drug product. The manufacturing controls include pre-weigh material handling in a semi-enclosed area which may be outfitted,as appropriate, with a dust collection system (bag filtered). The filtrate is disposed by appropriate means in accordance with all federal, state and local requirements.

Bulk product waste, and rejected product are collected for disposal as described in section 4. Production vessel washdown of product residual with water will be disposed by direct discharge into the municipal waste treatment system.

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

The drug substance supplier has certified that the production of this material is in compliance with all emission requirements set forth in the facility environmental permits, and applicable local, state, and federal requirements.

The drug product contract manufacturer has certified that the production of this material is in compliance, or on an enforceable schedule to be in compliance with all emission requirements set forth in the facility environmental permits, and applicable local, state, and federal requirements.

The Material Safety Data Sheet (MSDS) for the drug substance is found in Attachment No. 4.

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

The drug substance supplier has certified that the increased production volume for this material will not effect the ability to ensure continued compliance with current emission requirements.

The drug product contract manufacturer has certified that the production of this product will not effect the ability to ensure continued compliance with current emission requirements. Release of small quantities of product into the municipal system is in compliance with current permits.

Johnson & Johnson
CONSUMER PRODUCTS, INC.

APPEARS THIS WAY
ON ORIGINAL

The manufacturing facility, operates under the following applicable permits:

PERMIT DESCRIPTION	PERMIT #	ISSUED	EXPIRATION DATE
South Coast Air Quality Management District Permit to operate Pre-mixing Tank 116	D89334	2/01/96	2/01/97*
South Coast Air Quality Management District Permit to operate Pre-mixing Tank 117	D89335	2/01/96	2/01/97*
South Coast Air Quality Management District Permit to operate Pre-mixing Tank 118	D89336	2/01/96	2/01/97*
L.A. Sanitation District Wastewater permit for plant and equipment clean-up	13995	5/23/95	**
L.A. Sanitation District Wastewater permit for accidental spills	13995	5/23/95	**

* Air Quality permits are renewed annually.

** Current permit does not bear a finite expiration date.

e. Introduction of substances into the environment

The calculated Maximum Expected Emitted Concentrations (MEEC) for ketoconazole 1% shampoo based on projected first and fifth year volumes of production are as follows:

Year 1	Wastewater Load Based On Bulk Weight	7801.8 lbs.
	Drum Disposal Based On Bulk Weight	5572.7 lbs.
	Wastewater Load Based On Limits Of Detection	0.2 ppm
	Drum Disposal Based On Limits Of Detection	5572.7 lbs.
Year 5	Wastewater Load Based On Bulk Weight	11951.7 lbs.
	Drum Disposal Based On Bulk Weight	8537.0 lbs.

Total wastewater loads are based on results from manufacturing runs. Analysis of ketoconazole following cleaning and sanitization of production equipment was not present above the detection limit of 0.2 ppm. All wastewater loads were based on a worst case scenario of 0.2 ppm ketoconazole and 175 pounds of waste per batch. These calculations of MEEC are based on the best engineering estimates of bulk material not packaged during production (approx. 1% of the total batch size).

Johnson & Johnson CONSUMER PRODUCTS, INC.

Drum disposal estimates are based on 125 pounds of waste removed from equipment. Note that all discharges to the atmosphere are anticipated to be within permit limits.

Packaging components are made of recyclable high density polyethylene (SPI #2) and polypropylene (SPI #5). Effects on the environment should be minimal as proposed packaging materials are recyclable by current technology.
Further information is available in the confidential Environment Assessment section #6.

Item 7 FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

N/A

Item 8 ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

N/A

Item 9 USE OF RESOURCES AND ENERGY

N/A

Johnson & Johnson CONSUMER PRODUCTS, INC.

Item 10 MITIGATION MEASURES

N/A

Item 11 ALTERNATIVES TO THE PROPOSED ACTION

N/A

Item 12 LIST OF PREPARERS

J. P. Reider Manager, Environmental Engineering

Item 13 CERTIFICATION

The undersigned, certifies that the information presented is true, accurate, and complete to the best of the knowledge of Johnson & Johnson Consumer Products, Inc.

J. Robert Reider 3/22/96

J.R. Reider
Manager, Environmental Engineering

Date

Item 14 REFERENCES

1. Environmental Impact Consideration 21 CFR §25 pages 203-223

Item 15 APPENDICES

N/A

Item 16 ATTACHMENTS

1. letter of commitment to manufacture in accordance with NDA #20-310.

Johnson & Johnson CONSUMER PRODUCTS, INC.

2. Johnson & Johnson Pharmaceutical Partners statement of compliance with all local, district, and federal environmental regulations.

3. statement of compliance with all local, state and federal environmental regulations at the time of manufacture.

4. Material Safety Data Sheets

January 18, 1996

Marjorie B. McTeman
Director of Regulatory Affairs
JOHNSON & JOHNSON
CONSUMER PRODUCTS, INC.
Grandview Road
Skillman, NJ 08558

Johnson & Johnson
CONSUMER PRODUCTS, INC.

Dear Marjorie:

certifies that the methods, facilities, and controls used for the manufacture, packaging, labeling, analysis, and storage of Ketaconazole 1% Shampoo conforms with NDA (#20-310), the Good Manufacturing Practices as set forth in 21CFR210-211, Regulation of Food and Drug Administration, as well as all other applicable Federal, State, and local government regulations.

Sincerely,

Chief Executive Officer

000 10134

STATEMENT OF COMPLIANCE

Johnson & Johnson Pharmaceutical Partners has been engaged in the manufacture of the drug substance ketoconazole at its facilities in Gurabo, Puerto Rico for the past 12 years.

The anticipated supply volumes for the subject drug product, ketoconazole 1% shampoo, will not cause an increase in the qualitative composition of emission from this facility.

Johnson & Johnson CONSUMER PRODUCTS, INC.

Johnson & Johnson Pharmaceutical Partners is currently in compliance with, all emission requirements set forth in permits, applicable to the production of ketoconazole drug substance at its facilities in Gurabo, Puerto Rico. This facility is in compliance with all emission requirements set forth in applicable federal, state and local statutes and regulations.

The production volumes to support this application (NDA 20-310) are not expected to effect the ability to ensure continued compliance with the above requirements.

John Ortiz
Director
Quality Assurance & Regulatory Affairs

Juan Merced
Environmental & Safety Manager

January 18, 1996

Marjorie B. McTernan
Directory of Regulatory Affairs
JOHNSON & JOHNSON
CONSUMER PRODUCTS, INC.
Grandview Road
Skillman, NJ 08558

Johnson & Johnson
CONSUMER PRODUCTS, INC.

Dear Marjorie:

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 Ketaconazole 1% Shampoo at its facility as well as emission requirements set forth in applicable Federal, State, and local statutes and regulations in the production of Ketaconazole 1% Shampoo at its facility

Sincerely,

Chief Executive Officer

000 10136

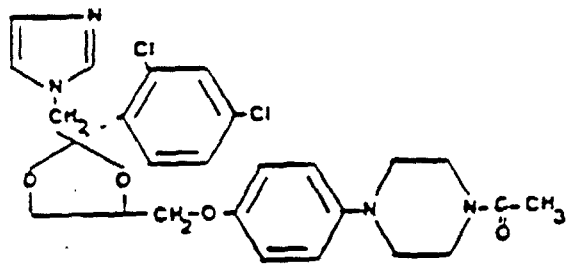
JANSSEN PHARMACEUTICA

SAFETY SERVICES

SAFETY INFORMATION PHARMACEUTICALS	VIF 005	PAGE 1
PRODUCT NAME: KETOCONAZOLE	R 41400-b	DATE April 1986
	REPLACES: Nov. 1984	

CAS No. : 65277-42-1 $C_{26}H_{28}Cl_2N_4O_4$

EINECS No. :



I ACTIVITY AND SYMPTOMS UPON INCIDENTAL OVERDOSAGE

Activity : orally active fungicide

Incidental overdosage: mild effects on gastrointestinal tract.

II PERSONAL MEANS OF PROTECTION

RESPIRATION: approved dust mask Dräger Combitox,or Airstream anti-dust helmet, gas mask with filtertype A St or Kolloidfilter 910 o compressed-air mask or -hood. No disposable mask.

EYES: goggles.

SKIN: gloves, closed working clothes.

000 10137

Johnson & Johnson CONSUMER PRODUCTS, INC.

III TOXIC EFFECTS

III-1 ACUTE TOXICITY IN EXPERIMENTAL ANIMALS

ORALLY: rat(m) LD_{50}: 287 mg/kg — mouse(m) LD_{50}: 786 mg/kg

rat(f) LD_{50}: 166 mg/kg — mouse(f) LD_{50}: 618 mg/kg

dog(m) LD_{50}: 937 mg/kg

dog(f) LD_{50}: 640 mg/kg

SKIN: not known

EYES: not known

INHALATION: not known

III-2 SUBACUTE TOXICITY IN EXPERIMENTAL ANIMALS

Irrespective of the duration of the treatment (in rat 3 and 6 months and in dog 6 and 12 months), neither the rat nor the dog, treated with doses up to 10 mg/kg bodyweight, showed any differences with the controls.

III-3 GENOTOXICITY

STRUCTURAL ANALYSIS:

Non-mutagenic in mammals

AMES TEST: non-mutagenic in Salmonella typhimurium

III-4 ECOTOXICOLOGICAL CHARACTERISTICS			
ACUTE TOXICITY FISH:	species:		
	TLm 96	mg/l	not known
ACUTE TOXICITY DAPHNIA:	LC_{50}	mg/l	not known
	N.E.L.	mg/l	
ACUTE TOXICITY ALGAE:	EC_{50}	mg/l	not known
	N.E.L.	mg/l	
DECOMPOSABILITY:	BOD	mg/l	
	COD	mg/l	$\frac{BOD}{COD}$ not known

IV FIRST AID	
ORALLY:	Rinse the mouth thoroughly with water. Notify the medical service a physician.
SKIN:	After each contact, wash the skin thoroughly with water and soap.
EYES:	Rinse the eyes thoroughly with running water for 10-15 minutes. Ke the eyelids open and turn the eyes in all directions during rinsir Notify the medical service or a physician.
INHALATION:	Remove the victim from the hazard zone and take him into th fresh air. Apply artificial respiration and, if necessary, heart massage upon breathing difficulties or respiratory arrest. Administer oxygen. Keep the victim warm and quiet. Immediately notify the medical service or a physician.

Johnson & Johnson CONSUMER PRODUCTS, INC.

MEDICATION:

- Specific antidote: NONE.
- Upon oral intake a gastric lavage with aqueous potassium permanganate (20 mg/100 ml) may be performed. Then administer a purgative (30 g sodium sulfate in 250 ml water).

Johnson & Johnson CONSUMER PRODUCTS, INC.

SAFETY INFORMATION PHARMACEUTICALS	VIF 005	PAGE 5
PRODUCT NAME: KETOCONAZOLE	R 41400-b	DATE April 1986
	REPLACES: March 1985	

IV PHYSICAL-CHEMICAL CHARACTERISTICS

APPEARANCE: white powder

MELTING POINT: MELTING RANGE: 148-152°C	BOILING POINT: inappl. BOILING RANGE: inappl.	MOLECULAR WEIGHT: 531.44
RELATIVE DENSITY inapplicable	VAPOUR TENSION: inappl.	VAPOUR DENSITY (air=1) inappl.
SURFACE TENSION: inapplicable	SOLUBILITY IN WATER: 10mg/l 20°C	SOLUBILITY IN FATS: 78 mg/100ml Fettsimulans MB 307
STABILITY dep. on pH 1 N HCl: not stable 1 N NaOH: not stable	DISTRIBUTION COEFFICIENT: OCTANOL/H_2O: logP= 3.73	AZEOTROPE: inappl.
pH SATURATED SOLUTION: 6.5	Solubility in solvents g/100 ml methanol : 11.3 ethanol : 1.86 2-propanol : 1.00	chloroform : 48.7 acetone : 1.35 toluene : 0.8

VI FIRE AND EXPLOSION HAZARD

FLASH POINT : inapplicable	AUTOIGNITION TEMP.: 520°C	EXPLOSION LIMIT: L.E.L. $\langle$ 15g/m^3
FLAMMABILITY: fire class: r.t.: 1 ; 100°C: 2	EXPLOSION HAZARD: not known	OXIDATIVE PROPERTIES not known

UNUSUAL FIRE AND EXPLOSION HAZARD:

[x] dust explosion class 1 [x] sensitive to shock class 1 [X] ignition class 1 [ ] temperature [ ] othe

VII FIRE CONTROL

[x] water [X] halones [X] powder [X] CO_2 [ ] sand [ ] foam

[ ] other

Johnson & Johnson CONSUMER PRODUCTS, INC.

SAFETY INFORMATION PHARMACEUTICALS	VIF 005	PAGE 6
PRODUCT NAME: KETOCONAZOLE	R 41400-b	DATE April 1986
	REPLACES: June 1985	

VIII REACTIVITY AND STORAGE

STABILITY: Stable at room temperature. No exothermic reaction at 315°C (Dyn. test). No exothermic reaction up to 270°C (Isoth. test). No exothermic reaction up to 145°C (Dyn.test under air suply). No exothermic reaction at 135°C-8h (Isoth.test under air supply). Qualitatively stable up to 135°C-8h (TLC-controle)

AVOID CONTACT WITH: acids, oxidants, strong bases

DECOMPOSITION PRODUCTS: not known

COMBUSTION PRODUCTS: nitrous oxides, hydrogen chloride

RISK OF POLYMERIZATION: not known

RISK OF STATICAL ACCUMULATION : ground CONDUCTIVENESS: not known

CONDITIONS TO BE AVOIDED

[ ] heat [X] open fire [X] sparks [X] ignition sources [ ] other

IX CLEARANCE OF SPILLED PRODUCT

Upon rupture or spillage, carefully collect and scoop up spilled product and store it in a closed container for destruction.
Always wear closed working clothes, gloves, goggles and an approved dust mask when cleaning up spilled product.

X STORAGE AND TRANSPORTATION INSTRUCTIONS

HAZARD SYMBOLS		ADR-RID	class: —	VN No.: —
			symbol: —	

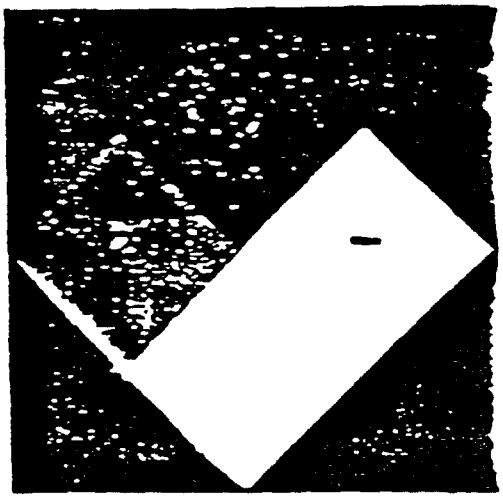
NATURE OF THE SPECIAL HAZARDS: Harmful if swallowed.
SAFETY RECOMMENDATIONS: After contact with skin, wash immediately with plenty of water and soap. Incase of insufficient ventilation, wear suitable respiratory equipment.

Johnson & Johnson CONSUMER PRODUCTS, INC.

SAFETY INFORMATION PHARMACEUTICALS	VIF 005	PAGE 7
PRODUCT NAME: KETOCONAZOLE	R 41400-b	DATE April 1986
	REPLACES: June 1985	

Johnson & Johnson
CONSUMER PRODUCTS, INC.

HAZARD RATING



XI SUMMARY

The substance is a white powder and an orally active fungicide. The substance can be absorbed in the body by inhalation and ingestion. Upon incidental overdosage there are mild effects on the gastrointestinal tract. Upon intoxication, immediately notify the medical service or a physician. Always wear gloves, goggles, closed working clothes and suitable respirator equipment when handling the substance. Upon rupture or spillage, carefully collect and scoop up the spilled product and store it in a closed container for destruction.

Rinse the containers and adjuvants used with a suitable solvent before transfer to the washing room.

XII REFERENCES

(1) VIF 005 dd. 02.80.
(2) ARAB Art. 723 bis.
(3) List of active Janssen R-compounds dd. 30 May 1984.
(4) Safety Services Janssen Pharmaceutica.
(5) Chemical Quality Control Janssen Pharmaceutica.
(6) P.C.-CHAR 82-7 dd. 29th March 1982.
(7) Histology Dept. Janssen Pharmaceutica.
(8) Medical Dept. Janssen Pharmaceutica.
(9) P.C.-Results 84-51.
(10) Chem. Dev. Lab. therm. risks: n° 1984/041B.