CENTER FOR DRUG EVALUATION AND RESEARCH

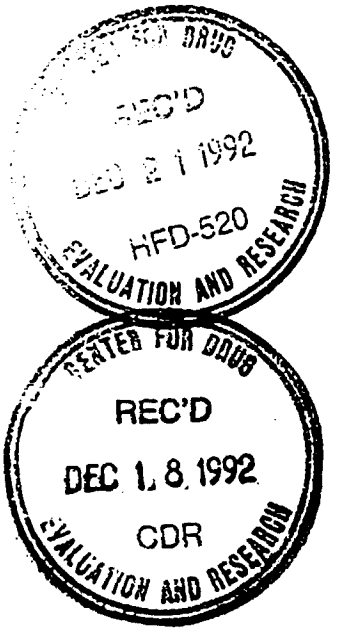
APPLICATION NUMBER: NDA 20-310

CORRESPONDENCE

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

NDA 20-310

December 18, 1992



NDA 20-310
Ketoconazole 1% Shampoo

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-520
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20857

Attention: Murray M. Lumpkin, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)

Gentlemen:

Pursuant to 21 CFR 314.50, enclosed please find an original New Drug Application, Number 20-310, for ketoconazole 1% shampoo.

Ketoconazole 1% shampoo is an anti-dandruff shampoo indicated for the control of flaking, scaling, and itching associated with dandruff, and is intended to be marketed as an over-the-counter product.

This submission consists of a total of thirty-nine archival volumes with the appropriate review copies. We are also providing two additional sets for the convenience of the reviewers.

If you have any comments or questions concerning this submission, please do not hesitate to contact Ms. Deborah L. Norby, Manager, Drug Regulatory Affairs at (908) 874-1434, fax number (908) 874-1118.

Sincerely yours,

Marjorie B. McTernan
Director, Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: June 30, 1992
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
12/18/92	
DIVISION ASSIGNED	**NDA/ANDA NO. ASS.**

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT
JOHNSON & JOHNSON Consumer Products, Inc.

DATE OF SUBMISSION

ADDRESS *(Number, Street, City, State and Zip Code)*
Grandview Road
Skillman, NJ 08558-9418

TELEPHONE NO *(Include Area Code)*
(908) 874-1337

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)*
20-310

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*
Ketoconazole (USP)

PROPRIETARY NAME *(If any)*
To be determined

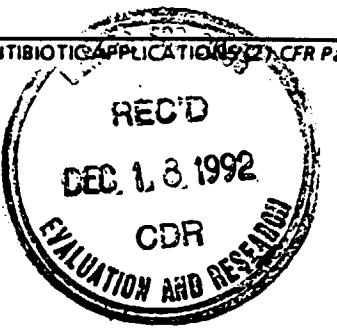
CODE NAME *(If any)*

CHEMICAL NAME
Piperazine, 1-acetyl-4-((2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl)methoxy)phenyl)-, cis-

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Topical	N/A	1%

PROPOSED INDICATIONS FOR USE
Controls the flaking, scaling, and itching associated with dandruff

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314 420)* REFERRED TO IN THIS APPLICATION:
see attached



INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION *(Check one)*

☐ PRESUBMISSION ☒ ORIGINAL APPLICATION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS *(Check one)*

☐ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☒ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*

CONTENTS OF APPLICATION	
This application contains the following items: *(Check all that apply)*	
X	1. Index
X	2. Summary (21 CFR 314.50 (c))
X	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
X	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
X	i. draft labeling *(4 copies)*
	ii. final printed labeling (12 copies)
X	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
X	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
X	8. Clinical data section (21 CFR 314.50 (d) (5))
X	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
X	10. Statistical section (21 CFR 314.50 (d) (6))
X	11. Case report tabulations (21 CFR 314.50 (f) (1))
X	12. Case reports forms (21 CFR 314.50 (f) (1))
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
X	15. OTHER *(Specify)* Drug Product Certification

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211
2. Labeling regulations in 21 CFR 201
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Marjorie B. McTernan Director, Regulatory Affairs	Marjorie B. McTernan	Dec 18, 1992
ADDRESS *(Street, City, State, Zip Code)* Grandview Road Skillman, NJ 08558		TELEPHONE NO. *(Include Area Code)* (908) 874-1337

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

ORIG AMENDMENT

February 25, 1994

General Correspondence:
Labeling

NDA 20-310
Ketoconazole 1% Shampoo

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-520
Document Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Murray M. Lumpkin, M.D., Director

Dear Dr. Lumpkin:

Reference is made to the recent telephone conversations between members of JOHNSON & JOHNSON Consumer Products, Inc. and Ms. Rosemary Cook of your staff concerning the labeling for NDA 20-310. In response to those conversations, attached is a copy of the proposed container label for which we considered recommendations made by the Joint Panel at FDA's Dermatologic Drugs Advisory Committee and Nonprescription Drug Advisory Committee Meeting, February 16, 1994.

At the Agency's request, we have changed as a tradename for ketoconazole 1% shampoo. It is our understanding that the Agency found the modifier to be unacceptable.

For your convenience, we have highlighted the new text and struck out the deleted text for the new proposed labeling.

If you have any questions or comments concerning this submission, please call me directly at (908) 874-1337.

Sincerely,

Marjorie B. McTernan
Director, Regulatory Affairs

4 copies submitted

cc: Rosemary Cook - Desk Copy
ls/file/a:corres4.ff

ORIGINAL

AMENDMENT

SL

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

FEDERAL EXPRESS

April 8, 1996

Jonathan Wilkin, MD, Director
Division of Dermatological and Dental Drug Products, HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Document Control Room # 12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 20-310
Ketoconazole 1% Shampoo
Safety Update
General Corespondence

Dear Dr. Wilkin:

Reference is made to NDA 20-310 March 22, 1996 submission (response to Approvable Letter) and to the April 19, 1993 submission (4-Month Safety Update).

Pursuant to 21 CFR 314.50 (d) (5) (vi) (b) we are submitting a safety update for NDA 20-310, ketoconazole 1% shampoo. This report contains updated safety information relevant to topical ketoconazole dating from April 1993 to the present. Preclinical safety is summarized in Attachment 1. There were no new preclinical studies conducted by J&J CPI on topical ketoconazole since the last safety update. A summary of published studies from our review of the literature constitutes this attachment.

There were no new clinical studies conducted since the last safety update. A summary of published clinical studies from our review of the literature is included in Attachment 2.

We have also included a Worldwide Safety Update prepared by Janssen Research Foundation International Pharmacovigilance Department dated May 1995, for the period April 1994 to April 1995. This report contains safety information on ketoconazole topical products: cream, emulsion, ointment and shampoo at both 1% and 2% concentrations. This information is included in Attachment 3.

With the exception of final printed labeling (due to be submitted by July 15, 1995), Johnson & Johnson Consumer Products, Inc. believes we have provided the agency with all information necessary for approval of NDA 20-310.

If you have any questions regarding this submission, please call me at (908) 874-1337. My fax number is (908) 874-1118.

Sincerely,

Marjorie B. McTernan
Director, Regulatory

submitted in triplicate

cc: H. Blatt, DDS (desk copies in duplicate)

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

June 21, 1995

Ms. Rosemary Cook
Food and Drug Administration
Division of Topical Drug Products

Telefax No. 301-594-6589

REF: NDA 20-310

Ms. Cook,

You telephoned our office on June 8, 1995 in regard to the above referenced NDA. In this conversation you requested copies of the certification of colorant FD&C Blue No. 1.

Per your request, attached are copies of the FDA Color Certification Branch certifications for the FD&C Blue No. 1 used in the manufacture of three batches of the subject drug product. Also attached are the vendor certificates for the same batches, a representative of which was submitted in the original NDA Volume 1.2, page 119.

I believe that this is adequate evidence that this material is truely a certified colorant.

I am providing this information to you via telefax per your request, and will submit the same by mail to the NDA.

Please contact me at (908) 874-1463 or Marjorie B. McTernan at (908) 874-1337 if there any further questions regarding this information.

Sincerely,

James A. Haviland
Manager, Regulatory Compliance

cc. M. B. McTernan

JANSSEN

• PHARMACEUTICA •
• RESEARCH FOUNDATION •

ORIGINAL

December 10, 1992

Murray Lumpkin, MD, Director
Division of Anti-Infective Drug Products/HFD-520
Document Control Room #12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA #19-927
Nizoral® (ketoconazole) 2% Shampoo
Cross-Reference Letter

Dear Dr. Lumpkin:

You are authorized to cross reference all sections of NDA #19-927 NIZORAL 2% Shampoo except Chemistry, Manufacturing and Controls, on behalf of J&J Consumer Products, Inc., Skillman, NJ 08558 for their New Drug Application for ketoconazole 1% shampoo. For Chemistry, Manufacturing and Controls information you are being authorized to refer to Janssen Research Foundation's original DMF for ketoconazole drug substance in a separate communication.

If you have any questions, please contact me at (609) 730-3065.

Sincerely,

Ruth Wasserman
Director/Regulatory Affairs

RW:ec

cc: NDA 19-927

O:\wpdocs\eileen\shampoo.niz\xrefltr.nda

JANSSEN AT WASHINGTON CROSSING
1125 TRENTON-HARBOURTON ROAD
POST OFFICE BOX 200
TITUSVILLE, NEW JERSEY 08560-0200

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

December 23, 1992

NDA 20-310
Ketoconazole 1% Shampoo

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-521
Room 12B05
5600 Fishers Lane
Rockville, Maryland 20857

Att: Rosemary Cook, Project Manager

Dear Ms. Cook:

Per your request enclosed please find two additional desk copies of Volume 1.1 for NDA 20-310 submitted December 18, 1992. This volume contains the Overall Summary for this application.

If you have any questions or comments concerning this material please contact me at (908) 874-1434.

Sincerely yours,

Deborah L. Norby

Deborah L. Norby
Manager, Regulatory Affairs

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

January 26, 1993

General Correspondence:
Chemistry

NDA 20-310
Ketoconazole 1% Shampoo

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-520
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20857

Att: Dr. Murray Lumpkin, M.D., Director
Division of Anti-Infective Drugs, HFD-520

Dear Dr. Lumpkin:

Reference is made to several telephone conversations (January 4, 1993 and January 8, 1993) with Dr. S. Tso, Chemistry Reviewer in the Division of Anti-Infective Drugs. Dr. Tso has requested the following information concerning the Chemistry, Manufacturing, and Controls section of NDA 20-310 for Ketoconazole 1% Shampoo.

FDA Request:

1. Has the sponsor established a trade name for the product? If not, what is the anticipated timing for selection of the trade name?

Response:

The official trade name has not been established as of yet.
JOHNSON & JOHNSON Consumer Products, Inc. is targeting the third quarter of 1993 for selection of the trade name.

FDA Request:

2. Please advise FDA as to the readiness of each of the three manufacturing sites (Belgium, Puerto Rico, and California) for an inspection.

Response:

Puerto Rico, manufacturer of ketoconazole drug substance, is currently ready for inspection by FDA. Only drug substance intermediates are manufactured in Belgium, as described in Janssen's DMF dated January 15, 1993. Janssen's Belgium facility was last inspected for chemical manufacturing in October 1990. It is Janssen's understanding, based on conversations with the Division of Field Inspections, International Programs and Technical Support Branch of FDA, that the next such inspection would occur sometime in 1994.

Please note that all questions pertaining to ketoconazole drug substance should be addressed to:

Maria A. Geigel
Director, Technical Regulatory Affairs
Janssen Research Foundation
1125 Trenton-Harbourton Road
Titusville, NJ 08560
Phone: (609) 730-3077
FAX: (609) 730-3091

Manufacturing of the drug product is conducted at They will be ready for inspection by the beginning of the second quarter of 1993. I indicated to Dr. Tso that the validation batches have not been run as of yet, but that we plan to notify the Los Angeles district office when they are definitively scheduled to be conducted. Dr. Tso requested that we also notify her.

FDA Request:

3. Please convert the year one and five production levels from fluid ounces to pounds, and extrapolate to determine the total amount of ketoconazole required to manufacture these volumes.

Response:

The first and fifth year production of ketoconazole 1% shampoo is projected to be pounds, respectively. Drug substance requirements to generate the final product are estimated to be pounds for year one and pounds in year five.

FDA Request:

4. Provide a summary paragraph which describes how the facility controls/regulates air and water discharge for the drug product, what permits has, when they were issued, when they expire, will they cover production of the drug product at the levels suggested in the year one and year five production levels, and will any additional licenses or permits be required. Dr. Tso also indicated similar information for the drug substance would be required for the Puerto Rico and Belgium facilities. However, she stated that for the Belgium facility it would be acceptable to obtain a Certificate of Compliance issued by the Belgian government.

Response:

As noted in the response to Question 2, issues relating to ketoconazole drug substance/DMF for this NDA will be handled by Janssen Research Foundation. The ketoconazole drug substance portion of the Environmental Assessment is expected to be completed in the first quarter of 1993 and submitted to the Agency for review.

The facility for the drug product is currently in compliance with EPA permits for air emissions and waste water discharge. Total air emissions and waste water discharge from the production of ketoconazole 1% shampoo are considered to be negligible. The South Coast Air Quality Management District has reviewed the current permit and indicated the production of ketoconazole 1% shampoo will fall within the parameters established of the original air emissions permit. Bulk product, packaged product deemed to be waste, and initial rinse water (*i.e.*, first 500 gal) from the production of ketoconazole 1% shampoo will not be discharged into the municipal waste stream until such time that the materials are determined to be non-hazardous. Bulk waste, packaged product, and initial rinse water will be handled as hazardous waste and be disposed at an appropriate facility. The following applicable permits are included in Addendum 1.

PERMIT DESCRIPTION	PERMIT NO.	TYPE OF INDUSTRY	ISSUED	EXPIRATION DATE
South Coast Air Quality Management District Permit to Operate Pre-mixing Tank 116	D11770	Manufactures Non-Hazardous Liquid and Creams (Cosmetic & Pharmaceuticals)	5/26/89	2/1/93
South Coast Air Quality Management District Permit to Operate Pre-mixing Tank 117	D11771	Manufactures Non-Hazardous Liquid and Creams (Cosmetic & Pharmaceuticals)	5/26/89	2/1/93
South Coast Air Quality Management District Permit to Operate Pre-mixing Tank 118	D11772	Manufactures Non-Hazardous Liquid and Creams (Cosmetic & Pharmaceuticals)	5/26/89	2/1/93
L.A. Sanitation District Wastewater Permit for Plant and Equipment Clean-Up	3164	Proprietary Medicine & Cosmetic Product	9/8/75	
L.A. Sanitation District Wastewater Permit for Accidental Spills	3163	Packaging & Warehousing	9/8/75	

If you have any comments or questions, please contact me at (908) 874-1434.

Sincerely yours,

Deborah L. Norby

Deborah L. Norby
Manager, Drug Regulatory Affairs

Submitted in triplicate

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

February 4, 1993

General Correspondence:
Chemistry

NDA 20-310
Ketoconazole 1% Shampoo

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-520
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20857

Att: Dr. Murray Lumpkin, M.D., Director
Division of Anti-Infective Drugs, HFD-520

Dear Dr. Lumpkin:

Reference is made to a telephone conversation February 4, 1993 with Rosemary Cook, Project Manager in the Division of Anti-Infective Drugs. Ms. Cook requested formulation data for the following:

- Ketoconazole 1% Shampoo (Formula 1760-156) which is the subject of this NDA;

- Ketoconazole 1% Shampoo (1116-77) early development formulation; and

- Nizoral 2% Shampoo (Janssen product).

This information is provided in Attachment 1, and additionally it can be found in Volume 1.7, page 00018 of the above referenced NDA.

If you have any comments or questions, please contact me at (908) 874-1434.

Sincerely yours,

Deborah L. Norby

Deborah L. Norby
Manager, Drug Regulatory Affairs

Submitted in triplicate
ls/file/NDACorres.2

ATTACHMENT 1.

Table 5: Composition of Shampoo Formulations

Composition of Shampoo Formulations (% w/w)			
	Ketoconazole 2% Shampoo NIZORAL Formula	Ketoconazole 1% Shampoo Formula 1116-77	Ketoconazole 1% Shampoo Formula 1760-156
Ketoconazole, USP			
Sodium Laureth Sulfate			
Sodium Cocoyl Sarcosinate			
Cocamide MEA			
Sodium Chloride U.S.P.			
Fragrance			
[redacted]			
Tetrasodium EDTA			
Quaternium-15			
Polyquaternium-7			
FD & C Blue No. 1			
[redacted]			
Glycol Distearate			
[redacted]			
Butylated Hydroxytoluene U.S.P.			
Sodium Hydroxide N.F.			
Hydrochloric Acid/Sodium Hydroxide q.s. to pH			
Purified Water U.S.P.			
	Nizoral 2% Shampoo	Early Development Formulation	Formulation Subject of NDA #20-310

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

February 10, 1993

NDA 20-310
Ketoconazole 1% Shampoo

General Correspondence:
Chemistry

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-520
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20857

Att: Dr. Murray Lumpkin, M.D., Director
Division of Anti-Infective Drugs, HFD-520

Dear Dr. Lumpkin:

Reference is made to a telephone conversation February 8, 1993 with Dr. S. Tso, Chemistry Reviewer in the Division of Anti-Infective Drugs. Dr. Tso has requested clarification of the quantitative composition of Ketoconazole 1% Shampoo, Formula No. 1760-156, provided in volume 1.2 (page 9) of the Chemistry, Manufacturing, and Controls section of NDA 20-310.

Accordingly, we are providing the attached table for reference and as an addition to volume 1.2 (page 9A). Per Dr. Tso's request, this table provides:

- the trade names of the ingredients;
- common names of the ingredients;
- percent solution (if ingredients are provided as such);
- % w/w according to manufacturing instructions;
- % w/w by individual chemical components.

Values for ingredients provided in our February 4, 1993 correspondence to FDA were calculated on a % w/w of the individual ingredient.

If you have any comments or questions, please contact me at (908) 874-1434.

Sincerely yours,

Deborah L. Norby

Deborah L. Norby
Manager, Drug Regulatory Affairs

Submitted in triplicate

ls/file/1so.2

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: June 30, 1992
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	**NDA/ANDA NO. ASS.**

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*

NAME OF APPLICANT
JOHNSON & JOHNSON Consumer Products, Inc.

DATE OF SUBMISSION
February 10, 1993

ADDRESS *(Number, Street, City, State and Zip Code)*
Grandview Road
Skillman, NJ 08558-9418

TELEPHONE NO *(Include Area Code)*
(908) 874-1434

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
20-310

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
Ketoconazole (USP)	to be determined

CODE NAME *(If any)*	CHEMICAL NAME
	Piperazine, 1-acetyl-4-((2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl)methoxy)phenyl)-, cis-

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Topical	N/A	1%

PROPOSED INDICATIONS FOR USE

Controls the flaking, scaling, and itching associated with dandruff

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION:

see attached

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION *(Check one)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☐ ORIGINAL APPLICATION ☐ RESUBMISSION General Correspondence: CHEMISTRY

PROPOSED MARKETING STATUS *(Check one)*

☐ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☒ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*

CONTENTS OF APPLICATION	
This application contains the following items: *(Check all that apply)*	
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	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. OTHER *(Specify)*

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211
2. Labeling regulations in 21 CFR 201
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Deborah L. Norby Manager, Regulatory Affairs	Deborah L. Norby	2/10/93
ADDRESS *(Street, City, State, Zip Code)*		**TELEPHONE NO.** *(Include Area Code)*
Grandview Road Skillman, NJ 08558		(908) 874-1434

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

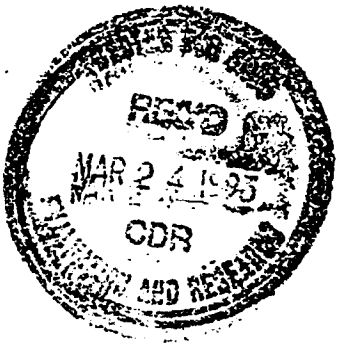
ORIGINAL

NEW CORRESPONDENCE

March 23, 1993

General Correspondence: Chemistry, Manufacturing and Controls, and Clinical

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-520
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20857



Attention: Murray M. Lumpkin, M.D., Director

Dear Dr. Lumpkin:

Reference is made to a telephone conversation on Tuesday, March 16, 1993 from Ms. Rosemary Cook, Project Manager, of your division. Ms. Cook requested that JOHNSON & JOHNSON Consumer Products Inc. identify the microbial preservatives in the ketoconazole 1% shampoo (NDA 20-310) intended for marketing.

The ketoconazole 1% shampoo, which is the subject of NDA 20-310, contains the preservative quaternium - 15 and a preservative potentiator, tetrasodium EDTA

Subsequently on Thursday, March 18, 1993, we received a telephone call from Dr. Ramzy Labib, also of your division. Dr. Labib requested information which explained the rationale for dividing the multi-center study, Protocol 16399.41B, into two geographical regions. In response, we refer you to the End-of-Phase-II meeting held on November 26, 1991 for this product.

At this meeting, the protocol for study number 16399.41B was presented, and several recommendations were made by members of the Division of Anti-Infective Drugs. During the discussion, it was noted that the planned sample size for Protocol

16399.41B was larger than required to show efficacy of the drug product. Although Dr. Lumpkin commented that the dose-ranging study, Protocol 16399.41, could be used as the second pivotal trial, it was discussed that the centers in Protocol 16399.41B could be divided into two distinct geographic regions. Subsequent to the meeting a decision was made to divide the centers into regions that would provide enough subjects to serve as two adequate and well-controlled trials. Furthermore, this design would allow the assessment of reproducibility of the results across geographic regions.

On January 10, 1992 IND was amended to provide for Protocol No. 16399.41B. The submission cover letter states that as per the November meeting's discussion, the six study sites would be divided into two different groups in order to provide the equivalent of two adequate and well-controlled studies. The division of the sites, specified in the protocol prior to study initiation, was done to attain diversity within each group. The sites were grouped as follows:

Group 1: Center 1, Dr. I. Kantor, New York
Center 3, Dr. D. Breneman, Ohio
Center 5, Dr. F. Dunlap, Arizona

Group 2: Center 2, Dr. C. McClellan, Indiana
Center 4, Dr. E. Jones, Ohio
Center 6, Dr. J. Hickman, Virginia

If you have any questions or comments concerning this submission, please do not hesitate to contact me at (908) 874-1434

Sincerely,

Deborah L. Norby

Deborah L. Norby

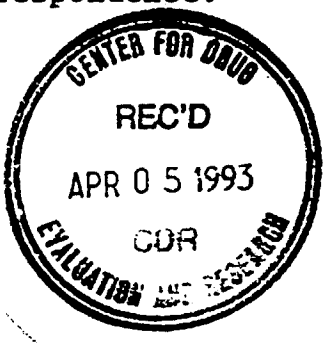
submitted in triplicate

ls/file/corres.Cook

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

April 2, 1993

General Correspondence:
Statistical



NDA 20-310
Ketoconazole 1% Shampoo

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-520
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20857

Attention: Murray M. Lumpkin, M.D., Director
Division of Anti-Infective Drug Products

Dear Dr. Lumpkin:

Reference is made to a telephone conversation on March 26, 1993 with Dr. Alaka Chakravarty in which five additional items were requested to assist her review of NDA 20-310, ketoconazole 1% shampoo.

Enclosed please find the following:

1. Format library to analyze the coded variables
   - Hard copy is provided in Appendix 1 and on floppy disk in the file called

2. MACRO libraries that have been used
   - These are contained on the enclosed floppy disk in a self-extracting file called

3. Any program/library accessed by "% include" statements
   - These are also contained in the file on the floppy disk.

4. A list of key variables used and their location/file name (data dictionary)
   - A hard copy is provided in Appendix 2. For each table in the NDA, this shows the data sets and the variables used.

5. Consistent indexing scheme
   - To assist you we have provided a hard copy of the data set names in Appendix 3.
   - A cross-index showing every variable with a descriptive label in each data set is contained in Appendix 4.
   - A cross-index showing every variable and the data set where it is located is contained in Appendix 5.
   - A new Proc Contents with representative data for each data set is shown in Appendix 6. Please note that all variables and all data sets now have consistent and descriptive names. All datasets now have a variable 'product' with values 0.0 KETO, 0.3 KETO, 1.0 KETO or 2.0 KETO to identify the treatment groups. The values of the variables have not been changed.

For analysis, it is recommended using EFFI (% changes in dandruff), SUBJECT (all baseline data) or STAT (all clinical ratings with demographics).

The above noted documentation is from Protocol 16399.41, the dose-ranging study. We are preparing a similar packet of data for the large multi-center study, Protocol 16399.41B. We anticipate completion of data audit by Wednesday, April 7th, and will send it to your attention for delivery on Thursday, April 8th.

If you have any questions or comments concerning this submission, please do not hesitate to contact me at (908) 874-1434

Sincerely yours,

Deborah L Norby

Deborah L. Norby
Manager, Drug Regulatory Affairs

cc: Dr. Chakravarty att/w diskettes

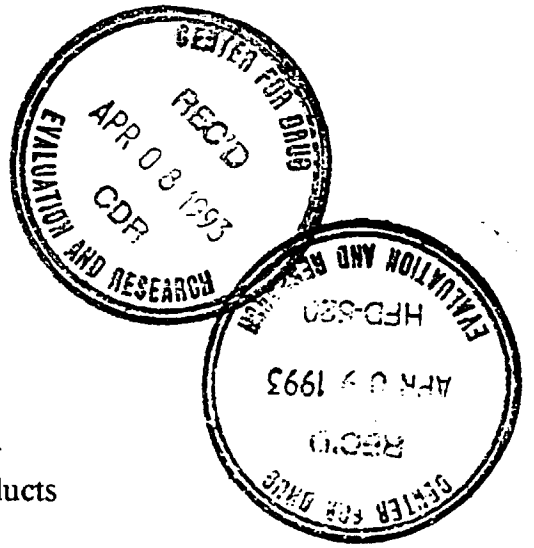
Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

NEW

DUPLICATE

April 7, 1993

General Correspondence:
Statistical



NDA 20-310
Ketoconazole 1% Shampoo

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-520
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20857

Attention: Murray M. Lumpkin, M.D., Director
Division of Anti-Infective Drug Products

Dear Dr. Lumpkin:

Reference is made to a telephone conversation on March 26, 1993 with Dr. Alaka Chakravarty in which five additional items were requested to assist her review of NDA 20-310, ketoconazole 1% shampoo. Reference is also made to a submission dated April 2, 1993 in response to Dr. Chakravarty's request. That submission contained information concerning Protocol 16399.41, the dose-ranging study. We are now submitting similar information which pertains to Protocol 16399.41B, the multi-center study. This represents the remainder of the information requested by Dr. Chakravarty.

Enclosed please find the following:

1. Format library to analyze the coded variables
   - Hard copy is provided in **Appendix 1** and on floppy disk in the self-extracting file called

2. MACRO libraries that have been used
   - These are contained on the enclosed floppy disk in a self-extracting file called

3. Any program/library accessed by "% include" statements
   - All programs used by Bio Pharm are contained in the file on the floppy disk.

4. A list of key variables used and their location/file name (data dictionary)
   - A hard copy is provided in **Appendix 2.** For each table in the NDA, this shows the data sets and the variables used.

5. Consistent indexing scheme
   - To assist you we have provided a hard copy of the data set names in **Appendix 3.**
   - A cross-index showing every dataset with a descriptive label for each variable is contained in **Appendix 4.** If you have a dataset name, use this index to find the names of the variables in that dataset.
   - A cross-index showing every variable and the data set where it is located is contained in **Appendix 5.** If you have a variable name, use this index to find out which dataset it came from.
   - A section of the training manual showing all data entry screens is contained in **Appendix 6.**
   - A new Proc Contents with representative data for each data set is shown in **Appendix 7.** Please note that all variables and all data sets now have consistent and descriptive names. All datasets now have a variable 'product' with values 0.0 KETO or 1.0 KETO to identify the treatment groups. We were unable to use "dose" globally because it refers to dose of concomitant medications for some datasets. The values of the variables have not been changed. The data value is missing if the person was screened but did not enter the protocol. Each dataset now contains the variable "subject" (some had a variable called "subject__"). The variable "study" identifies study sites 1 to 6.
   - The new data sets and labels are in the self-extracting file on the floppy disk.

If you have any questions or comments concerning this submission, please do not hesitate to contact me at (908) 874-1434

Sincerely yours,

Deborah L. Norby

Deborah L. Norby
Manager, Drug Regulatory Affairs

Submitted in duplicate
cc: Dr. Chakravarty att/w diskette

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

April 19, 1993

Four-Month Safety Update

NDA 20-310
Ketoconazole 1% Shampoo

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-520
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20857

Attention: Murray M. Lumpkin, M.D., Director

Dear Dr. Lumpkin:

Pursuant to 21 CFR 314.50(d)(5)(vi)(b) enclosed herewith please find the four month safety update for NDA 20-310, ketoconazole 1% shampoo. This report contains updated safety information relevant to the NDA. Included in the safety update we have provided you with worldwide data which integrates safety information from the J&J CPI ketoconazole 1% shampoo product with safety data from the use of ketoconazole 2% shampoo (Nizoral 2% shampoo), ketoconazole 1% shampoo (Nizoral 1% shampoo), and ketoconazole 2% cream (Nizoral 2% cream).

Reference is also made to a teleconference on February 11, 1993 between representatives of the Division of Anti-Infective Drugs and JOHNSON & JOHNSON Consumer Products, Inc. (J&J CPI) concerning NDA 20-310. During this discussion FDA requested that we provide information to justify the extrapolation of safety data from the Janssen Nizoral 2% shampoo to the ketoconazole 1% product, NDA 20-310.

Accordingly, the above noted information is provided in:

Appendix A: data to justify extrapolation of safety from the Janssen Nizoral 2% shampoo to ketoconazole 1% shampoo, NDA 20-310; and

Appendix B: Four Month Safety Update for NDA 20-310. This includes the worldwide safety data from other (Janssen Pharmaceutica) ketoconazole topical formulations.

Additionally, several other requests were made by the Agency for information concerning NDA 20-310. Responses to these are provided below.

FDA Request:
Does Janssen have any data on the no effect level of the oral dosage form on potential drug interactions leading to cardiac effects and liver toxicity?

Response:
J&J CPI has demonstrated in clinical studies that there is no detectable absorption (limit of detection ≥ to 5 ng/ml) of ketoconazole 1% shampoo. Dr. Yee, Associate Director, Safety Assessment, (Janssen Research Foundation) noted in the teleconference that Janssen US has not received any reports of drug interaction with Nizoral 2% shampoo.

No data are available from Janssen that specifically relate to the no effect level regarding potential drug interaction on cardiac or liver toxicity. However, we are providing you with the following related reports in Appendix C:

- Evaluation report entitled "The inhibition of the cytochrome P-450 mediated metabolism of drugs by ketoconazole is concentration-dependent: a scientific evaluation". Dr. Jos Heykants and Dr. Lavrijse, Department of Drug Metabolism & Pharmacokinetics, Janssen Research Foundation, B-2340 Beerse Belgium.

- Final Report entitled "Inhibition of the in vitro metabolism of astemizole and terfenadine in human liver microsomes by ketoconazole". Report number: R 41400/FK1125.

- Interim Report entitled "Inhibition of the in vitro metabolism of astemizole and terfenadine in human liver microsomes by itraconazole and ketoconazole". Report number: R 51211/FK1364

These studies show that ketoconazole at a concentration of μM (corresponding to about ng/ml) has no clinically relevant inhibition on the metabolism of tolbutamide, ethinylestradiol, cyclosporin, terfenadine, and astemizole in man. Therefore, topical application of ketoconazole will not provoke any clinically relevant interaction on the metabolism of concomitant drugs or steroid hormones.
Additionally, in Appendix C, we are providing you with a copy of a letter, from a leading hepatologist, Gordon Benson, submitted to NDA 19-084, Nizoral (ketoconazole) 2% Cream, on October 15, 1984. This letter addresses the issue of the potential for hepatotoxicity from ketoconazole in the Nizoral 2% cream. Dr. Benson states that in light of the fact that there is no evidence that the cream is absorbed to any significant degree, in his opinion it is unlikely that there would be any potential for liver injury.

FDA Request:
Provide the approved labeling for the non-US ketoconazole 1% shampoo preparations.

Response:
The Janssen ketoconazole 1% shampoo formulation is approved for marketing in Argentina, Columbia, Mexico, and Thailand. It is currently marketed in Argentina and Mexico. Approved labeling for Argentina and Thailand are provided in **Appendix D**. A package insert has been requested from Mexico but it is unavailable at this time. Upon receipt of the insert from Mexico it will be forwarded to the Agency. Janssen Pharmaceutica in Colombia submitted documentation for Nizoral shampoo 1% as an over the counter product, and therefore did not need to include a package insert.

FDA Request:
Please provide a justification for the use of a 1/100 dilution of the test material in the sensitization testing.

Response:
The sensitization tests submitted in NDA 20-310, Repeat Insult Patch and Phototoxicity/Photoallergy Tests, employed a 1/100 dilution of the J&J CPI ketoconazole 1% shampoo. Provided in **Appendix E** are statements and references from Dr. William P. Jordan, Lynne B. Harrison, Ph.D., and Dr. Lewis P. Stolman. Their letters clearly state that the 1/100 dilution is an approved industry-wide method for applying shampoos for sensitization testing.

FDA Request:
Please provide an overall compliance statement for both the nonclinical laboratory studies and the clinical studies.

Response:
Included in NDA 20-310, Volume 1.7, page 002, is a letter of cross-reference to the Preclinical Section of Janssen Research Foundation's NDA 19-927, Nizoral 2% (ketoconazole) shampoo. Contained within NDA 19-927, Volume 1.5, page 290, is an overall nonclinical compliance statement.

An overall clinical compliance statement can be found in NDA 20-310, Volume 1.9, pages 31-32.

Copies of these pages are provided in **Appendix F** for ease of the reviewer.

FDA Request:
Please provide an Environmental Assessment for the drug substance.

Response:
The drug substance, ketoconazole, is manufactured by Janssen. As noted during the teleconference, several discussions concerning the EA for the drug substance have taken place between J&J CPI, Janssen Research Foundation, and Dr. Tso, the chemistry reviewer. In a telephone conversation on March 19, 1993, between Dr. Tso and representatives of Janssen, it was indicated that Janssen Research Foundation would provide the EA for ketoconazole drug substance at the end of 1993.

FDA Request:
Please provide additional stability data to support the requested three year expiration date.

Response:
Provided in **Appendix G** are updated ketoconazole 1% shampoo stability data through the 39 week time point. These were generated from batches 0012P, 0022P, and 0032P in 11 oz. and 1 oz. size bottles. These batches are those which are presented in the original Chemistry, Manufacturing, and Controls section of the NDA. Additionally, two year data are provided for clinical batch 899-1374.

Stability updates will be provided as they become available.

If you have any questions or comments concerning this submission, please do not hesitate to contact me at (908) 874-1434.

Sincerely yours,

Deborah L. Norby
Manager, Drug Regulatory Affairs

submitted in duplicate

ls/file/Safety

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

NEW CORRESP

DUPLICATE

May 3, 1993
General Correspondance
Microbiology

NDA 20-310
Ketoconazole 1% Shampoo

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-520
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20857

Attention: Murray M. Lumpkin, M.D., Director
Division of Anti-Infective Drugs

Dear Dr. Lumpkin:

Reference is made to a telephone conversation on April 1, 1993, with Ms. Rosemary Cook, Project Manager, of your Division. Ms. Cook informed us that Dr. Soprey, the microbiology reviewer, would like JOHNSON & JOHNSON Consumer Products, Inc. to submit data from the preservative efficacy testing. We are providing the requested information in the following pages.

Additionally Ms. Cook inquired as to whether J&J CPI has conducted microbial limit testing, and if so, please provide the NDA reference. We refer you to Volume 1.3, page 058, page 2 of 7 of the Ketoconazole 1% Shampoo Product Specification. Section 2.6 entitled "Microbial Requirements TM7945" describes the microbial limit test that J&J CPI conducts for release of the product.

If you have any questions or comments concerning this submission, please do not hesitate to contact me at (908) 874-1434.

Sincerely yours,

Deborah L. Norby

Deborah L. Norby
Manager, Drug Regulatory Affairs

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

NEW CORRESP

May 4 1993
General Correspondence
Chemistry

NDA 20-310
Ketoconazole 1% Shampoo

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-520
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20857

Attention: Murray M. Lumpkin, M.D., Director
Division of Anti-Infective Drugs

Dear Dr. Lumpkin:

Reference is made to a telephone conversation on April 8, 1993, with Dr. S. Tso, of the Division of Anti-Infective Drugs. Dr. Tso requested clarification concerning the bottle resin used for the shampoo product. It was noted that the Package Material Specification (No. P1760, Vol. 1.3, Page 021) identifies the bottle resin as and on page 023 of the same specification it is identified as Provided in Attachment 1 are two letters from the maker of the resin, addressed to our bottle supplier, These letters state that had originally assigned the designation to the resin, upon commercialization of the product it was given the commercial product designation

Additionally, Dr. Tso inquired if the plastic container had been subjected to the USP extraction test protocol for plastic containers.

To our knowledge the final container has not been evaluated by the USP physicochemical test method (USP Chapter 661).
JOHNSON & JOHNSON Consumer Products Inc. is not aware of any USP test data generated by the component suppliers, however the contents of the suppliers' Drug Master Files are unknown to the applicant.

Volume 1.3 of NDA 20-310, page 053, contains a report of a package interaction study conducted under exaggerated conditions. Pieces of the bottle resin were placed in jars and subjected to varying temperatures for one month. The samples were than evaluated for

potency of ketoconazole. The results indicate that the potency of ketoconazole in the drug product remained unchanged from to °C after one month.

If you have any questions or comments concerning this submission, please do not hesitate to contact me at (908) 874-1434.

Sincerely yours,

Deborah L. Norby

Deborah L. Norby
Manager, Drug Regulatory Affairs

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

NDA ORIG AMENDMENT

DUPLICATE

BC

October 1, 1993

**General Correspondence:
Chemistry, Manufacturing and
Controls**

**NDA 20-310
Ketoconazole 1% Shampoo**

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-520
Document Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Murray M. Lumpkin, M.D., Director

Dear Dr. Lumpkin:

Reference is made to a telefax of March 16, 1993 and telephone call on May 27, 1993 from Dr. S. Tso, from the Division of Anti-Infective Drugs. In the telefax, JOHNSON & JOHNSON Consumer Products, Inc. was requested to submit information regarding samples for the methods validation package contained in NDA 20-310.

(Quaternium-15) has been added to the regulatory tests and to the methods validation package in response to the later telephone contact with Dr. Tso.

The actual samples requested are available at JOHNSON & JOHNSON Consumer Products, Inc., Grandview Road, Skillman, NJ. This is the site responsible for the analytical methods development.

The following lists the information requested, and the response to each item.

FDA Request:

1. Provide a list of all samples with lot number and sample size indicated.

   Drug product (at least two lots)
   Ketoconazole reference standard
   Control impurities R 53165 and R 39519
   (Quaternium-15)

Response:

A list of samples is provided in Attachment 1.

FDA Request:

2. Material Safety Data Sheets for all samples

Response:

Material Safety Data Sheets are provided for the drug product, drug substance, and preservative. Substitute MSDS for the control impurities has been provided by the supplier. Copies of the MSDSs are provided in Attachment 2.

FDA Request:

3. Composition of the drug product

Response:

Composition of the drug product, as presented in the original NDA (volume 1.2), is provided in Attachment 3.

FDA Request:

4. Regulatory specification of the drug product

Response:

The regulatory specification, as presented in the NDA (volume 1.3), is provided in Attachment 4.

FDA Request:

5. Certificates of analysis of all samples

Response:

Certificates of Analysis of all samples are provided in Attachment 5.

The Methods Validation section is amended to provide the methods evaluation report for the preservative, Quaternium-15. A complete Methods Validation section (volume 1.6) is appended to this package (Attachment 6).

In addition, copies of the Regulatory Test Methods as presented in NDA volume 1.4, are enclosed (Attachment 7).

If you have any comments or questions, please contact me at (908) 874-1337.

Sincerely yours,

Marjorie B. McTernan
Director, Regulatory Affairs

Submitted in triplicate

cc: Rosemary Cook - Desk Copy

ls/file/Tso.4

CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

October 25, 1993

General Correspondence:
Chemistry, Manufacturing and Controls

NDA 20-310
Ketoconazole 1% Shampoo

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-520
Document Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Murray M. Lumpkin, M.D., Director

Dear Dr. Lumpkin:

With regard to requests for information received via fax from Su C. Tso, PhD on October 21, 1993, we are submitting the following:

Request (1):

Regarding to method validation, which method, will be used as the regulatory stability indicating assay method for the drug product.

Response:

is the stability indicating assay method which will be used for the drug product. Reference is made to the following sections of Vol. 1.3: Section 3.2.6.2 **Regulatory Specifications and Test Methods**, page 000-00058, Spec. No. PR1760, page 2 of 7, Section 2.5 **% Ketoconazole** Section 3.2.7.3 **Additional Stability Studies**, page 000 00105 **Medic Stability Protocol.**

Request (2):

Please submit Post Approval Stability Protocol. The stability protocol supporting the NDA application is not adequate. For Post Approval Stability Protocol, please refer to the FDA's Guideline for Submitting Documentation of Human Drugs and Biologics.

Response:

Please refer to the attached submission of the revised Stability Study Protocol for MEDIC (Ketoconazole 1% Shampoo). This is the current revision of the protocol found in Volume 1.3, Section 3.2.7 **Stability** pages 000 00104, 000 00105, 000 00106 (revised 10/25/93).

If there are any questions regarding this submission, please contact me directly. My telephone number is (908) 874-1337.

Sincerely yours,

Marjorie B. McTernan
Director, Regulatory Affairs

Submitted in triplicate

cc: R. Cook (Desk Copy)
S.C. Tso (Desk Copy)

ls/file/mdc10

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

October 29, 1993

General Correspondence:
Clinical

NDA 20-310
Ketoconazole 1% Shampoo

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-520
Document Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Murray M. Lumpkin, M.D., Director

Dear Dr. Lumpkin

Reference is made to the teleconference on June 14, 1993 between Dr. R. Labib and Ms. R. Cook of your staff and personnel from JOHNSON & JOHNSON Consumer Products, Inc. The teleconference concerned the appropriate design for a cumulative irritation study that had been requested by Dr. Labib with Ketoconazole 1% Shampoo NDA 20-310. The protocol for this study was submitted to IND July 16, 1993, Serial No. 015. In response to Dr. Labib's request, enclosed as Attachment I is the final report for the study entitled "Study to Determine Irritation Potential of Ketoconazole 1% Shampoo" (CPI Protocol No. 16399.05). The study includes a 5-day pre-testing phase to develop dose range data a 21-day cumulative irritation testing phase, and a challenge phase following a rest period.

Also included in this amendment as Attachment II are results of the long-term safety and efficacy study for Ketoconazole 1% Shampoo (Protocol No. 16399.41A). The enclosed report entitled "An Evaluation of the Safety in Long-Term Use and Efficacy of an Anti-Dandruff Shampoo: An Extension to the 12-month Study", covers months 13 and 14.

If you have any questions or comments concerning this submission, please call me directly at (908) 874-1337.

Sincerely yours,

Marjorie B. McTernan
Director, Regulatory Affairs

Submitted in duplicate

cc: Rosemary Cook - Desk Copy
Dr. R. Labib - Desk Copy

ls/file/1:fdaclnsb

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

NDA ORIG AMENDMENT

ORIGINAL

November 8, 1993

VIA FEDERAL EXPRESS

General Correspondence:
Clinical

NDA 20-310
Ketoconazole 1% Shampoo

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-520
Document Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Murray M. Lumpkin, M.D., Director

Dear Dr. Lumpkin:

Reference is made to the recent telephone conversations between Mr. Fred Frullo of JOHNSON & JOHNSON Consumer Products, Inc. (J&JCPI) and Mr. David Bostwick (Clinical Reviewer) of you staff concerning NDA 20-310, Ketoconazole 1% Shampoo. Mr. Bostwick requested that J&JCPI prepare a gender analysis of efficacy data for Study 16399.41B. In response to Mr. Bostwick's request, enclosed are the following tables that contain an analysis of dandruff ratings by gender and geographic region that have been prepared according to Mr. Bostwick's specifications.

Table 1.1 and 1.2 show the mean clinical ratings by week of treatment, geographic region and sex of subject. Table 2 supplements this information by showing the means and sample sizes for the overall population.

Table 3(top portion) shows the distribution of the Investigators' global rating of efficacy at week 8 for females and males. Table 3 (bottom portion) shows the global ratings by sex and geographic region, as requested.

If you have any questions or comments concerning this submission, please call me directly at (908) 874-1337.

Sincerely yours,

Marjorie B. McTernan
Director, Regulatory Affairs

Submitted in duplicate

cc: Rosemary Cook
David Bostwick, Clinical Reviewer

ls/file/a:Bostwick.ff

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

NDA ORIG AMENDMENT
BC

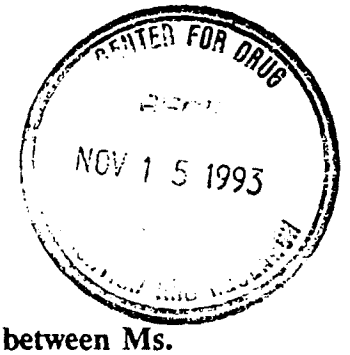
DUPLICATE

November 12, 1993

NDA 20-310
Ketoconazole 1% Shampoo

General Correspondence:
Chemistry, Manufacturing and Controls

Food & Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-520
Document Room 12B-30
5600 Fishers Lane
Rockville, MD 20857



Attn: Murray M. Lumpkin, M.D., Director

Dear Dr. Lumpkin:

Reference is made to the teleconference held on November 1, 1993 between Ms. Rosemary Cook (Project Manager) and Dr. Su Tso, (Reviewing Chemist) of the Agency and the following members of Johnson & Johnson Consumer Products, Inc.:

Fred Frullo, Manager, Drug Regulatory Affairs
James Haviland, Manager, Compliance Regulatory Affairs
Elvin Lukenbach, Manager, Product Development
Marjorie McTernan, Director, Regulatory Affairs
Mathews Nunes, Manager, Analytical Services

The teleconference was conducted to discuss chemistry issues for NDA 20-310, ketoconazole 1% shampoo. As a follow-up to that teleconference, below are addressed the specific points that were discussed:

- Method will be the stability indicating assay method which will be used for post-approval stability.

- Included in the Post-Approval Stability Protocol will be testing for preservative efficacy on the first three batches of the formulation to be marketed. Studies will be carried out past the expiration date. A copy of the stability protocol is attached (Attachment I) as requested by the Agency. The attached protocol (revised 11/93) supersedes all previously submitted stability protocols found in Volume 1.3, Section 3.2.7 Stability pages 000 00104, 000 00105 and 000 00106.

- Additional (updated) stability data is attached (Attachment II) that includes the 15-month test point. The attached stability data supersedes the data that was submitted in the original filing (Volume 1.3, Section 3.2.7 Stability pages 000 00069-000 00086).

- Included in Attachment III is a statistical evaluation of the stability data (Attachment II).

- Stability studies include the following information that was requested by Dr. Tso:

    1) Packaging information including the package size
    2) Lot number
    3) Manufacturing date
    4) Expiration date
    5) Initial Values and Finished Drug Product Specification Limits

- Included in Attachment IV are two additional copies of the Methods Validation Package (Volume 1.6) that was requested by Dr. Tso.

If you have any questions or comments, please call me directly at (908) 874-1337.

Marjorie B. McTernan
Director, Regulatory Affairs

cc: Rosemary Cook - Desk Copy
Dr. Su Tso - Desk Copy

Submitted in duplicate
a:\telecon11-1

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

NDA CORRESPONDENCE
BC

ATTACHMENT 1

December 10, 1993

General Correspondence:
Chemistry, Manufacturing & Controls

NDA 20-310
Ketoconazole 1% Shampoo

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-520
Document Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Murray M. Lumpkin, M.D., Director

Dear Dr. Lumpkin:

Reference is made to the telephone conversation on December 6, 1993 between Mr. Fred Frullo of JOHNSON & JOHNSON Consumer Products, Inc. (J&J CPI) and Ms. Rosemary Cook of your staff concerning NDA 20-310, Ketoconazole 1% Shampoo. In response to that conversation, enclosed are the following documents that Ms. Cook had requested:

Attachment I: FOI copy of the Environmental Assessment (EA) for Ketoconazole 1% Shampoo. The attached EA is identical to what was submitted in the original NDA dated December 18, 1992 with the exception of proprietary trade secret information being blocked out.

Attachment II: Material Safety Data Sheets (MSDS) for Ketoconazole Raw Material. The attached MSDS is identical to what was submitted in the original NDA dated December 18, 1992.

It is our understanding that the above information is proprietary trade secret until NDA 20-310 is approved and will not be released until after approval.

If you have any questions or comments concerning this submission, please call me directly at (908) 874-1337.

Sincerely yours,

Marjorie B. McTernan
Director, Regulatory Affairs

Submitted in duplicate

cc: Rosemary Cook
ls/file/a:Cook.ff

Johnson & Johnson
CONSUMER PRODUCTS, INC.

SKILLMAN, NJ 08558-9418

ORIGINAL

January 20, 1994

General Correspondence:
Clinical

NDA 20-310
Ketoconazole 1% Shampoo

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-520
Document Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Murray M. Lumpkin, M.D., Director

Dear Dr. Lumpkin:

Reference is made to the recent telephone conversations between members of JOHNSON & JOHNSON Consumer Products, Inc. (J&J CPI) and Mr. David Bostwick, Medical Reviewer of the Agency concerning the Four-Month Safety Update for NDA 20-310, Ketoconazole 1% Shampoo that was submitted to the Agency on April 19, 1993. Mr. Bostwick requested clarification of terminology for two tables in response to a request from Dr. Lillian Gavrilovich, Acting Director.

In response to the request, listed below is the additional information that was requested by Dr. Gavrilovich.

FDA Request:

What were the three Side Effects under the heading "Body as a Whole General Disorder" on page 34 of Table 10?

J&J CPI Response:

Two female subjects reported that their hair straightened (lost permanent wave) after using NIZORAL® Ketoconazole 2% Shampoo.

One female subject had her permanent wave "not take" after using NIZORAL Ketoconazole 2% Shampoo.

FDA Request:

What does Vision Abnormal mean under the heading "Vision Disorders" on page 40 of Table 12?

J&J CPI Response:

One subject reported that his/her vision decreased while using NIZORAL Ketoconazole 2% Shampoo.

I hope that this clarifies the comments that Dr. Gavrilovich had concerning the four-month Safety Update.

If you have any further questions or comments, please call me directly at (908) 874-1337.

Sincerely,

Marjorie B. McTernan
Director, Regulatory Affairs

cc: Rosemary Cook
David Bostwick

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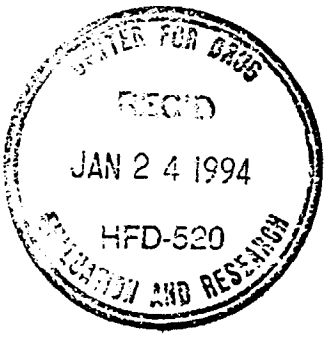
Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

January 21, 1994

General Correspondence:
Chemistry, Manufacturing & Controls

NDA 20-310
Ketoconazole 1% Shampoo



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-520
Document Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Murray M. Lumpkin, M.D., Director

Dear Dr. Lumpkin:

Reference is made to the recent telephone conversations between members of JOHNSON & JOHNSON Consumer Products, Inc. and Ms. Rosemary Cook of your staff concerning NDA 20-310, Ketoconazole 1% Shampoo. In response to these conversations, enclosed is an FOI copy of the Environmental Assessment (EA) for Ketoconazole 1% Shampoo. Please note that this is a revised copy and supersedes the copy that was submitted to the Agency on December 10, 1993.

It is our understanding that the above information is Proprietary Trade Secret and will not be released until NDA 20-310 is approved.

If you have any questions or comments concerning this submission, please call me directly at (908) 874-1337.

Sincerely,

Marjorie B. McTernan
Director, Regulatory Affairs

submitted in triplicate

cc: Rosemary Cook - Desk Copy

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Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

January 31, 1994

General Correspondence:
Advisory Committee Meeting

NDA 20-310
Ketoconazole 1% Shampoo

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-520
Document Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Murray M. Lumpkin, M.D., Director

Dear Dr. Lumpkin:

In preparation for the upcoming Dermatologic Drugs Advisory Committee meeting that is scheduled for February 16, 1994, enclosed are 10 copies of the Briefing Package that has been prepared at the Agency's request. Included in the Briefing Package is a brief overview of the Ketoconazole 1% Shampoo NDA.

If you have any questions prior to the meeting, please call me directly at (908) 874-1337.

Sincerely,

Fred J. Fuller / for

Marjorie B. McTernan
Director, Regulatory Affairs

4 copies submitted

cc: Rosemary Cook - 10 Desk Copies

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Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

ORIGINAL

February 25, 1994

General Correspondence:
Labeling

NDA 20-310
Ketoconazole 1% Shampoo

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-520
Document Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Murray M. Lumpkin, M.D., Director

Dear Dr. Lumpkin:

Reference is made to the recent telephone conversations between members of JOHNSON & JOHNSON Consumer Products, Inc. and Ms. Rosemary Cook of your staff concerning the labeling for NDA 20-310. In response to those conversations, attached is a copy of the proposed container label for which we considered recommendations made by the Joint Panel at FDA's Dermatologic Drugs Advisory Committee and Nonprescription Drug Advisory Committee Meeting, February 16, 1994.

At the Agency's request, we have changed as a tradename for ketoconazole 1% shampoo. It is our understanding that the Agency found the modifier to be unacceptable.

For your convenience, we have highlighted the new text and struck out the deleted text for the new proposed labeling.

If you have any questions or comments concerning this submission, please call me directly at (908) 874-1337.

Sincerely,

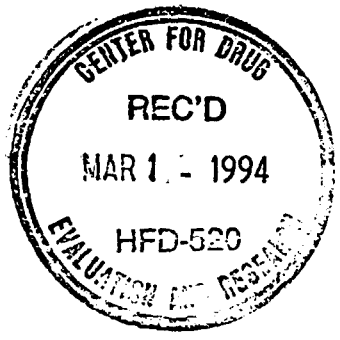
Marjorie B. McTernan
Director, Regulatory Affairs

4 copies submitted

cc: Rosemary Cook - Desk Copy
ls/file/a:corres4.ff

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

February 28, 1994



NDA 20-310
Ketoconazole 1% Shampoo

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-520
Document Room B-30
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Murray M. Lumpkin, M.D., Director

Dear Dr. Lumpkin:

Reference is made to the recent inspection by FDA's Los Angeles District Office of , the manufacturing and testing site for ketoconazole 1% shampoo. For your information, attached is the FDA 483 that was issued by the Los Angeles District office along with response to each observation. It should be noted that the investigators, Ms. Omotunde O. Osunsanmi, (CSO) and Mr. Mihaly S. Ligmond (chemist) did not find any deficiencies at during their inspection that would preclude approval of NDA 20-310. Mr. Mihaly S. Ligmond who inspected on January 11-12, 1994 reviewed all chemistry data including data concerning clinical supplies.

If you have any questions or comments concerning this submission, please call me directly at (908) 874-1337.

Sincerely,

Marjorie B. McTernan
Director, Regulatory Affairs

Submitted in duplicate

cc: Rosemary Cook - Desk Copy

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Johnson & Johnson
CONSUMER PRODUCTS, INC.

SKILLMAN, NJ 08558-9418

March 11, 1994

NDA 20-310
Ketoconazole 1% Shampoo

General Correspondence:
Proposed Labeling

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anti-Infective Drugs, HFD-520
Document Room B-30
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Murray M. Lumpkin, M.D., Director

Dear Dr. Lumpkin:

Reference is made to the recent telephone conversation between Mr. Fred Frullo of JOHNSON & JOHNSON Consumer Products, Inc. and Ms. Rosemary Cook of your staff concerning NDA 20-310, Ketoconazole 1% Shampoo. In response to that conversation, enclosed is a diskette containing the proposed container label for Ketoconazole 1% Shampoo which is identical to what was submitted to the Agency on February 25, 1994.

If you have any questions or comments concerning this submission, please call me directly at (908) 874-1337.

Sincerely,

Fred J. Frullo / for

Marjorie B. McTernan
Director, Regulatory Affairs

Submitted in duplicate

cc: Rosemary Cook - Desk Copy with Diskette

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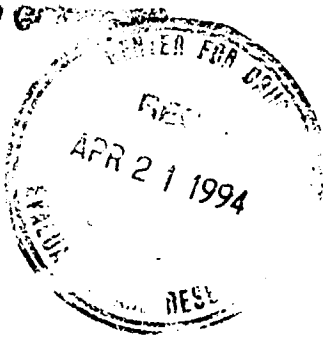
Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

DUPLICATE



April 13, 1994

NDA 20-310
Ketoconazole 1% Shampoo

General Correspondence:
Meeting Request

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Topical Drug Products, HFD-540
Document Room 3-30
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Jonathan K. Wilkin M.D., Director

Dear Dr. Wilkin:

Reference is made to the Agency's letter dated December 6, 1993 concerning NDA 20-310 Ketoconazole 1% Shampoo which extended the user fee due date 90 days to March 18, 1994.

At this time JOHNSON & JOHNSON Consumer Products, Inc. requests to meet with the Agency to discuss the current status of NDA 20-310, including any issues the Agency may have. It is our understanding that Dr. Wiley Chambers, Supervisory Medical Officer, has concerns regarding the appropriateness of the 1% concentration.

We wish, if possible, to have the following FDA personnel available at the meeting:

FDA Personnel

Murray Lumpkin, MD, Acting Director, Center for Drug Evaluation and Research

Johnathan K. Wilkin, MD, Division Director, Topical Drug Products

Ramzy Labib, MD/David Bostwick, Medical Review Officers

Michael Weintraub, MD, Director, Office of Over-the-Counter Drug Evaluation

Wiley Chambers, MD, Supervisory Medical Officer

We are requesting to meet with the Agency as soon as possible, and in any event, no later than May 6, 1994. It is our understanding that no FDA action will take place prior to this meeting. We will be furnishing to you a formal agenda in the very near future.

If you have any questions, please call me directly at (908) 874-1337.

Sincerely,

Marjorie B. McTernan
Director, Regulatory Affairs

Submitted in duplicate

cc: Rosemary Cook
Sandy Childs

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Johnson & Johnson
CONSUMER PRODUCTS, INC.

SKILLMAN, NJ 08558-9418

June 28, 1994

NDA 20-310
Ketoconazole 1% Shampoo

Jonathan Wilkin, MD, Director
Division of Topical Drug Products, HFD-540
Document Control Room #12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Jonathan K. Wilkin, MD, Director

Dear Dr. Wilkin:

Reference is made to the recent telephone conversation between Mr. Fred Frullo of JOHNSON & JOHNSON Consumer Products, Inc. and Ms. Rosemary Cook of your staff concerning NDA 20-310, Ketoconazole 1% Shampoo. In response to that conversation, enclosed is a copy of the letter that we received from FDA's Los Angeles District Office recommending approval of The pre-approval inspection was conducted at during the period January 11 through February 1, 1994 and covered the manufacture and control process for ketoconazole 1% shampoo.

Please note that this letter was officially submitted to NDA 20-310 May 9, 1994.

If you have any questions or comments concerning this submission, please call me directly at (908) 874-1337.

Sincerely,

Fred J. Frullo /for

Marjorie B. McTernan
Director, Regulatory Affairs

cc: Rosemary Cook

Submitted in duplicate

SCHERING-PLOUGH
CONSUMER PRODUCTS WORLDWIDE
SKILLMAN, NJ 08558-9418

ORIGINAL

July 14, 1994

NDA 20-310
Ketoconazole 1% Shampoo

General Correspondence:
Chemistry, Manufacturing & Controls

Jonathan Wilkin, MD, Director
Division of Topical Drug Products, HFD-540
Document Control Room #12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Jonathan K. Wilkin, MD, Director

Dear Dr. Wilkin:

Reference is made to our pending New Drug Application, 20-310 for Ketoconazole 1% Shampoo.

Attached is additional (updated) stability that includes the 24 month test point. This stability data supersedes the data that was submitted to the Agency on November 12, 1993 and supports an expiration date of two years.

If you have any questions or comments concerning this submission, please call me directly at (908) 874-1337.

Sincerely,

Fred J. Fruth / for

Marjorie B. McTernan
Director, Regulatory Affairs

Submitted in triplicate

cc: Rosemary Cook - Desk Copy

ls/file/corres10

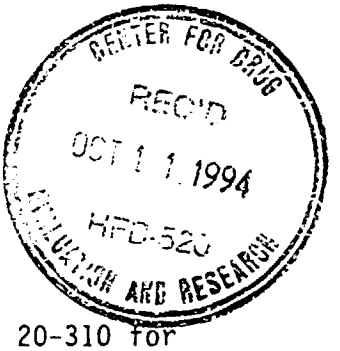
Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

October 6, 1994

NDA 20-310
Ketoconazole 1% Shampoo

General Correspondence:
Chemistry, Manufacturing & Controls

Division of Topical Drug Products, HFD-540
Document Control Room #12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Attention: Jonathan K. Wilkin, MD, Director

Dear Dr. Wilkin:

Reference is made to our pending New Drug Application 20-310 for Ketoconazole 1% Shampoo.

Enclosed is the 27-month stability report which supersedes the 24-month report (See *Stability Report).* Also enclosed is a report of the identification of Decomposition Product One (See *Degradation Product).*

Reference is also made to the telephone conversation on August 29, 1994 with Rosemary Cook of your staff concerning the status of the above-mentioned NDA. In response to that conversation, below are listed the Division's chemistry comments along with our response.

Comment:

Stability data has only been submitted for 1 and 11 oz. sizes, while intermediate container sizes are proposed for marketing.

Response:

The one fluid ounce and 11 fluid ounce bottle sizes were selected for Pre-Production stability as these are the smallest and largest size containers proposed for marketing. As such these sizes present the maximum and minimum package/product surface interfaces.

The extremes of the package/product interface represent the maximum environments for potential degradation due to oxidation or reduction pathways. As such these sizes present the extreme conditions for stability study.

The primary package for the proposed intermediate sizes are composed of

identical materials as the bottles used in these studies. Thus no additional questions arise regarding product-package reaction.

Additional stability data will be available on the intermediate container sizes from the process validation studies and post-approval stability studies.

Comment:

Investigate the reason for observed off-specification value for viscosity which was reported at the 24-month stability interval.

Response:

The Pre-Production Stability studies have demonstrated consistent increases in viscosity. These increases are not unexpected. However, the increase has exceeded the manufacturing specification limits for some lots.

The 27 month stability has demonstrated approximately a cps increase in viscosity among the three stability batches. This increase in viscosity can be attributed to the effect of pH on the viscosity building agent, in the formula. The capacity to build viscosity changes with pH of the system.[1] The maximum viscosity building of is reached at pH 5 (cps) in this formula.

Stability data demonstrate the pH changes slightly over time. Due to the characteristics of this change in pH has resulted in the increased product viscosity.[2]

The purpose of formulating to this viscosity range for the product is primarily for aesthetic reasons for the ease of dispensing and application through the hair and scalp during shampooing. Therefore, relatively slight increases in viscosity will not affect the functionality of this product.

The viscosity range for the manufacturing specification was originally established at cps[3] based on preliminary data from early research batches. The specification range will be revised to reflect the viscosity data generated in the Pre-Production Stability studies.

Comment:

The stability protocol should be revised to include monitoring of degradation products.

Response:

The Pre-Production Stability studies (current report enclosed) includes the monitoring of degradation products. Also enclosed is the report of

the identification of Decomposition Product One.

The Post-Approval Stability Protocol does not include monitoring of degradation products. This protocol was discussed previously with the Reviewing Chemist and revised accordingly.

These changes included addition of the preservative assay and alteration of the sampling intervals as requested. The revised protocol was provided to the Agency on November 12, 1993. We believe that these changes were adequate and fulfill the requirements of the Agency.

Comment:

The specifications for BHT should be revised to reflect real-time data.

Response:

The current product specification specifies the concentration of "at time of release". As noted in correspondence of September 29, 1993, this preservative functions as a formaldehyde donor and its concentrations are expected to diminish with time while maintaining adequate preservation. Thus the stability program was intended to correlate the concentration of with the preservative efficacy to determine the minimum acceptable concentration. The stability data demonstrates that the product continues to be adequately preserved. A tentative minimum concentration of % has been proposed based upon the 24-month data. Upon further evaluation of this data a minimum concentration of the preservative will be specified.

The specification for BHT will be revised to provide the manufacturing control ("at time of release") limit, which is the current specification limit. Stability data demonstrate that BHT remains effective at levels below the release levels. That is, no apparent changes consistent with oxidative reactions have been observed in the stability program although concentrations of BHT have decreased.

Comment:

Revisions to the stability protocol and product specification should be provided to the FDA when available.

Response:

No further revision to the stability protocol is anticipated at this time. The Reviewing Chemist did request changes to the Post-Approval Stability Protocol which were incorporated and provided to the Agency on November 12, 1993. These changes included addition of the preservative assay and alteration of the sampling intervals.

The product specification will be provided with the addition of the

lower limit for the preservative, and revision of the viscosity limit.

Comment:

FDA's Nomenclature Committee finds the proposed brand name to be unacceptable for the following reasons:

1. *If a physician were to write the name on a pad there is concern that it could be mistaken to mean of NIZORAL 2% shampoo.*

2. *The Nomenclature Committee has concern with allowing the same name for Rx and OTC drug products.*

Response:

In order to address the concerns expressed by FDA's Nomenclature Committee, Johnson & Johnson Consumer Products, Inc. has decided to use the name NIZORAL A-D as the brand name for ketoconazole 1% shampoo. We feel that the modifier A-D (anti-dandruff) more accurately describes the product and both the physician and consumer are less likely to be confused and mistake this product for the NIZORAL 2% product. In the past when Rx to OTC switches have been approved by the Agency, a number of sponsors have retained the brand name and differentiated the Rx from the OTC product by adding a modifier. Examples of these are Imodium® (Rx) and Imodium® A-D (OTC); Tavist-® (Rx) and Tavist-1® (OTC); Motrin® (Rx) and Motrin® IB (OTC); Monistat (Rx) and Monistat® 7 (OTC).

If you have any questions or comments concerning this submission, please call me directly at (908) 874-1337.

Sincerely,

Marjorie McTiernan /FF

Marjorie B. McTernan
Director, Regulatory Affairs

submitted in triplicate

cc: Rosemary Cook - Desk Copy
Dr. Su Tso

ls/file/corres11

1. NDA #20-310, Volume 1.5, page 00046, Product Development Summary.

2. NDA #20-310, Volume 1.5, pages 00067-000668, 00084, Product Development Summary.

3. NDA #20-310, Volume 1.3, page 00058, Product Specification.

JANSSEN
• PHARMACEUTICA •
• RESEARCH FOUNDATION •

ORIGINAL

DOUGLAS N. DOBAK
VICE PRESIDENT
REGULATORY AFFAIRS

October 7, 1994

Jonathan Wilkin, M.D.
Division of Topical Drug Products/HFD-540
Document Control Room 12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Wilkin:

Please refer to NDA #19-927 and to your letter of March 4, 1994 concerning the prescription status of Janssen Pharmaceutica's Nizoral® (ketoconazole) 2% shampoo. We also refer to our July 19, 1994 meeting with you and Dr. M. Weintraub regarding the status of NDA #20-310 which represents the OTC use of a 1% Nizoral® (ketoconazole) shampoo, and our objective is to keep the prescription product on the market. We wish to take this opportunity to respond to the aforementioned FDA letter based on our previous discussions and current understanding of the regulatory status of pending NDA #20-310.

It is now very evident that we must differentiate both products by their respective labeling in order to gain approval of the 1% OTC shampoo product. In order to do so, Janssen has expressed its preference to keep our 2% prescription product on the market with both the current anti-dandruff claim and a new indication to satisfy the regulatory labeling requirements. Although the Division felt that this approach might be acceptable in satisfying the Humphrey-Durham amendments, we have not received a formal confirmation of this request.

After a review of clinical trials literature and unpublished foreign studies conducted with the 2% prescription shampoo, we are prepared to file a Supplemental New Drug Application to include a new indication for tinea versicolor. For your review, we are providing background information from these foreign studies which may support use of a single dose of Nizoral® 2% shampoo for the treatment of tinea versicolor (see attachment). The data in the Supplemental NDA will consist of clinical trial information from these foreign studies, revised labeling, and reviews of the product's safety and efficacy for this new indication. We are currently ascertaining the availability of case report forms and study reports.

JANSSEN AT WASHINGTON CROSSING
1125 TRENTON-HARBOURTON ROAD
POST OFFICE BOX 200
TITUSVILLE, NEW JERSEY 08560-0200

In summary, we are asking that the Agency provide us with confirmation that our 2% prescription product can keep its current anti-dandruff indication with the addition of a tinea versicolor indication. Further, the acceptability of a Supplemental New Drug Application for expanding the indication also requires agreement. Lastly, we conclude from our discussion that if all of the above tasks are completed, the FDA will also approve the pending 1% OTC shampoo product (NDA 20-310).

We sincerely wish to make both products available now that the pertinent issues have been clearly identified. We feel that an acceptable approach has been defined which needs FDA's final concurrence. We look forward to your response. If you have any questions, please contact me at 609-730-3058 or Ruth Wasserman at 609-730-3065.

Sincerely,

Douglas N. Dobak
Vice President
Regulatory Affairs

DND/snr

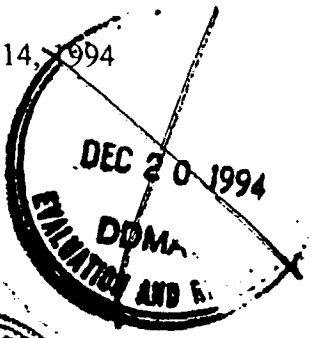
cc: Wiley Chambers, M.D. - HFD 540
James Bilstad, M.D. - HFD 500

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

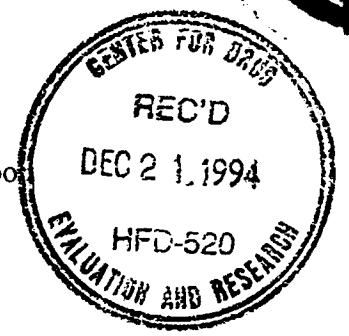
ORIGINAL

NEW CORRESPONDENCE

December 14, 1994



Jonathan Wilkin, MD, Director
Division of Topical Drug Products, HFD-540
Document Control Room #12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Subject: NDA 19-927 and NDA 20-310
Ketoconazole 2% and 1% Shampoo
Meeting Minutes

Dear Dr. Wilkin:

Reference is made to the teleconference held on December 8, 1994 between JOHNSON & JOHNSON Consumer Products, Inc. (J&J CPI), Janssen Pharmaceutica Inc. (Janssen) and members of the Agency. The teleconference was held to discuss the approvability of NDA 20-310. Below are listed the highlights of the teleconference:

- FDA restated their position that if Janssen continued to market the 2% product (NDA 19-927) with the anti-dandruff indication, J&J CPI's pending 1% product (NDA 20-310) would have to either be withdrawn by J&J CPI or the FDA would reject it with a non-approvable letter.

- J&J CPI and Janssen presented a proposal to the Agency that would keep the 2% Rx product on the market and also free up the approvability of the 1% OTC product. Janssen does not plan to withdraw their 2% Rx NDA and would commit to submitting additional data (supplement) to NDA 19-927 for an indication of tinea versicolor and delete the current anti-dandruff indication once the supplement is approved.

- FDA will discuss this proposal internally and will get back to both J&J CPI and Janssen once they have internal agreement.

- Upon notification by FDA that the aforementioned proposal has been accepted, Janssen will submit, in writing, its commitment to withdraw the dandruff claim in NDA 19-927 upon approval of a tinea versicolor claim.

- Upon approval of Janssen's commitment letter, FDA will release an approvable letter for NDA 20-310.

- Once the dandruff claim has been removed from NDA 19-927, NDA 20-310 will be eligible for approval.

If you have any questions concerning the above, please contact Marjorie McTernan at (908) 874-1337.

Sincerely,

Fred J. Fuller / for

Marjorie B. McTernan
Director, Regulatory Affairs

submitted in triplicate

cc: Rosemary Cook - Desk Copy
Wiley Chambers, MD - Desk Copy

ls/file/corres.13

JANSSEN • PHARMACEUTICA • RESEARCH FOUNDATION •

DOUGLAS N. DOBAK
VICE PRESIDENT
REGULATORY AFFAIRS

DUPLICATE

December 15, 1994

Jonathan Wilkin, MD, Director
Division of Topical Drug Products/HFD-540
Document Control Room #12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 19-927
NIZORAL® (ketoconazole) 2% shampoo
COMMITMENT CONFIRMATION

Dear Dr. Wilkin:

Please refer to NDA 19-927 and to the telephone conference of December 8, 1994 between Janssen Pharmaceutica, Johnson & Johnson, CPI and Wiley Chamber, MD, Rosemary Cook, CSO, and you. That phone call was held to discuss the pending approval of ketoconazole 1% shampoo NDA 20-310 and the continued marketing of our Nizoral (ketoconazole) 2% shampoo NDA 19-927 by prescription only for the treatment of dandruff.

At this time Janssen reiterates our committment made during that phone conference to file a supplement to the Nizoral (ketoconazole) 2% shampoo NDA 19-927, for the treatment of tinea versicolor. Once the tinea versicolor supplement has been approved, Janssen will withdraw the claim for dandruff. Concurrently, Johnson & Johnson, CPI's pending NDA for ketoconazole 1% shampoo NDA 20-310 will be approved for the treatment of dandruff.

The commitment made by Janssen in this letter, however, is based on the understanding that FDA is taking approvable action on J&J, CPI's NDA 20-310 prior to Janssen filing the tinea versicolor supplement to NDA 19-927.

A copy of this letter has been sent to NDA 20-310. If you have any questions regarding this letter, please call me at (609) 730-3058.

Sincerely,

Douglas N. Dobak
Vice President, Regulatory Affairs

DND/snr
cc: NDA 20-310
Rosemary Cook, CSO - desk copy via FAX
Wiley Chambers, MD - desk copy

JANSSEN AT WASHINGTON CROSSING
1125 TRENTON-HARBOURTON ROAD
POST OFFICE BOX 200
TITUSVILLE, NEW JERSEY 08560-0200

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

December 19, 1994

Jonathan Wilkin, MD, Director
Division of Topical Drug Products, HFD-540
Document Control Room #12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 20-310
Ketoconazole 1% Shampoo

Dear Dr. Wilkin:

As a result of the teleconference that was held on December 8, 1994, Janssen has sent a letter (copy attached) to their NDA (19-927) with a commitment to submit additional data (supplement) for an indication of tinea versicolor and deleting the current anti-dandruff indication once the supplement is approved.

We understand that the approval of our NDA (20-310) in contingent on the approval of the Janssen supplemental application that has been described above. It is also our understanding that there are no major obstacles that will lead to Johnson & Johnson Consumer Products, Inc. now receiving an "Approvable" letter for NDA 20-310.

If you have any questions concerning the above, please contact either Fred Frullo at (908) 874-1361 or myself at (908) 874-1337.

Sincerely,

Fred J. Frullo /for

Marjorie B. McTernan
Director, Drug Regulatory Affairs

submitted in triplicate

cc: Rosemary Cook - Desk Copy
Wiley Chambers, MD - Desk Copy

ls/file/corres.14

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

RC

DUPLICATE January 6, 1995

Jonathan Wilkin, MD, Director
Division of Topical Drug Products, HFD-540
Document Control Room #12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 20-310
Ketoconazole 1% Shampoo
General Correspondence:
Chemistry, Manufacturing and Controls

Dear Dr. Wilkin:

Reference is made to our pending New Drug Application 20-310 for Ketoconazole 1% Shampoo. Reference is also made to the teleconference on December 27, 1994 with Dr. Wilson DeCamp and Ms. Rosemary Cook. The teleconference was in response to our submission dated October 6, 1994 which included 27-month stability data. Below are listed the four minor chemistry issues that were identified by the Division along with our response:

Comment 1:

The package specification for the 4 fluid ounce bottle has not been provided to the reviewer.

Response:

A copy of the package specification is found in **Attachment 1**.

This packaging specification revision was previously submitted to HFD-520 September 29, 1993. This specification provides the composition and reference for the engineering drawings of all proposed container/closure systems. Actual drawings of two sizes appear in the body of the specification as exemplars. The container profile of all sizes is similar and differ only in bottle capacity.

In addition, initial stability results, both accelerated and controlled room temperature, for product packaged in 1, 4, and 7 fluid ounce sizes are found in **Attachment 2**. Attachment 2 contains a tabular presentation of

the data, and statistical reports of both the validation batches and the 27-month stability batches. The validation data are from recent validation trials and have not been previously submitted.

The attached reports and tables demonstrate that the stability profile of product packaged in intermediate size containers is the same as the profiles established for the largest (11 fl.oz.) and smallest (1 fl. oz.) containers.

Comment 2:

The product specification should be revised for to reflect real-time data.

Response:

Section 2.6 of the attached specification **(Attachment 3)** reflects the changes proposed for that appeared in the October 6, 1994 submission. The specification range for has been revised with the addition of the expected range "during shelf-life".

As noted in the October 6, 1994 submission, this range was established based upon confirmation of adequate preservation at the 24-month stability interval. A copy of the microbiology report is found in **Attachment 4.**

Comment 3:

The product specification should be revised for BHT to reflect real-time data.

Response:

Section 3.3 of the attached specification **(Attachment 3)** reflects the changes proposed for BHT that appeared in the October 6, 1994 submission. The specification range for BHT has been revised with the addition of the phrase The assay range has not been altered.

Comment 4:

The product specification should be revised for Viscosity to reflect real-time data.

Response:

Section 2.3 of the attached specification **(Attachment 3)** reflects the changes proposed for Viscosity that appeared in the October 6, 1994 submission. The specification range for Viscosity has been revised with the addition of the expected range "during shelf-life".

As noted in the 24-month stability report the viscosity of this product demonstrates a consistent increase with time. This relatively slight increase in viscosity does not adversely impact the delivery or performance of this product.

We feel this submission has addressed all remaining chemistry issues that the Agency has raised and will now lead to Johnson & Johnson Consumer Products, Inc. receiving an "Approvable Letter" for NDA 20-310.

If you have any questions or comments concerning this submission, please call me directly at (908) 874-1361.

Sincerely yours,

Fred J. Frullo

Fred J. Frullo
Manager, Drug Regulatory Affairs

submitted in triplicate

cc: Rosemary Cook
Dr. Wilson DeCamp
Dr. Su Tso

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

BC

trip

January 31, 1995

Jonathan Wilkin, MD, Director
Division of Topical Drug Products, HFD-540
Document Control Room #12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 20-310
Ketoconazole 1% Shampoo
General Correspondence:
Chemistry, Manufacturing and Controls

Dear Dr. Wilkin:

Reference is made to our pending New Drug Application 20-310 for Ketoconazole 1% Shampoo. Reference is also made to the teleconference on January 18, 1995 with Dr. Wilson DeCamp and Dr. Su Tso. The teleconference was in response to our submission dated January 6, 1995.

Below are listed the two issues that were identified along with our response:

Comment 1:

The stability data for the 4 fluid ounce bottle which was submitted in the January 6 correspondence did not include EDTA and BHT data. Please provide available data.

Response:

The submitted stability data was generated from process validation batches. And, indeed the properties evaluated do demonstrate a stability profile similar to that reported for the 1 and 11 fl oz packages from the pre-approval stability batches. However, neither BHT or EDTA were analyzed since the process validation protocol did not require evaluation of the non-regulatory tests.

Initial stability results for product packaged in 1, 4, and 7 fluid ounce sizes were submitted to help substantiate the rationale previously presented regarding stability in the intermediate size packages. That is, the stability profile demonstrated by the largest (11 fl oz) and smallest (1 fl oz) package sizes represent the extremes in package to product interactions, and should be predictive of the profiles for intermediate package sizes. Refer to correspondence of October 6, 1994.

BHT and EDTA assays will be added to all remaining sampling intervals for the validation batch stability studies.

Comment 2:

Lower limits for EDTA and BHT during shelf-life should be established.

Response:

The product specification has been revised to reflect changes to the BHT specification **(Attachment 1)**.

The specification range for BHT has been revised to indicate and Section 3.3 of the attached specification reflect these changes.

Development studies indicate that BHT provides antioxidant activity as low as % in this formula.

The stability data generated to date indicate that EDTA is stable. Therefore no change is proposed in the specification range for EDTA during the shelf-life. Section 3.2 of the attached specification remains unchanged.

Comment 3:

The Post-Approval Stability Protocol should be revised to include BHT and EDTA, rather than Fill Weight.

Response:

The Post-Approval Stability Protocol has been revised with the addition of BHT and EDTA analyses. The protocol is found in **(Attachment 2)**.

We believe that the above issues have been adequately addressed by this submission. If you have any questions or comments concerning this response, please call me directly at (908) 874-1361.

Sincerely yours,

Fred J. Frullo

Fred J. Frullo
Manager, Drug Regulatory Affairs

submitted in triplicate

cc: Rosemary Cook
Dr. Wilson DeCamp
Dr. Su Tso

ls/file/corres.16

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

ORIGINAL

BL

Attachment 1

March 8, 1995

Jonathan Wilkin, MD, Director
Division of Topical Drug Products, HFD-540
Document Control Room #12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

7/11/95

Re: **NDA 20-310**
Ketoconazole 1% Shampoo
General Correspondence:
Chemistry, Manufacturing and Controls

Dear Dr. Wilkin:

Reference is made to our pending New Drug Application 20-310 for Ketoconazole 1% Shampoo. Reference is also made to the telephone conversation on February 21, 1995 between Mr. Fred Frullo of JOHNSON & JOHNSON Consumer Products, Inc. and Dr. Su Tso of the Agency. As a result of that conversation, included in this submission are the following attachments:

Attachment 1 - Draft Container Label
Originally submitted to the Agency on February 25, 1994. The brandname has been revised from to NIZORAL-AD™ at the Agency's request.

Attachment 2 - Environmental Assessment (EA)
The attached EA has been revised and reformatted at the request of Dr. Benson. This copy supersedes the EA dated November 11, 1992.

Attachment 3 - FOI Copy of the Environmental Assessment (EA)
The attached EA has been reformatted at the request of Dr. Benson. It was originally submitted to the Agency on January 21, 1994. This EA supersedes the January 21, 1994 submission and should be treated as a Proprietary Trade Secret and should not be released until NDA 20-310 is approved.

Attachment 4 - Material Data Sheet (MSDS) for Ketoconazole

NDA 20-310
Ketoconazole 1% Shampoo
March 8, 1995

If you have any questions or comments concerning this submission, please call me directly at (908) 874-1361.

Sincerely yours,

Fred J. Frullo

Fred J. Frullo
Manager, Drug Regulatory Affairs

submitted in triplicate

cc: Rosemary Cook (1 copy)
Dr. Su Tso (2 copies)

ls/file/corres.16

Attachment I

Attachment II

Attachment III

CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

ORIGINAL

June 21, 1995

Jonathon Wilkin, MD, Director
Division of Topical Drug Products, HFD-540
Document Control Room No. 12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: **NDA 20-310**
Nizoral A-D™ (Ketoconazole 1% Shampoo)
General Correspondence:
Chemistry, Manufacturing Controls

Dear Dr. Wilkin:

Reference is made to our pending New Drug Application 20-310 for NIZORAL A-D™ (ketoconazole 1% shampoo). Reference is also made to the telephone conversation of June 8, 1995 between Ms. Rosemary Cook of the Agency and Mr. James Haviland of Johnson & Johnson Consumer Products, Inc.

Ms. Cook requested copies of the color certification for the colorant in the drug product.

Attached are certificates representing three batches of FD&C Blue No. 1 used in the production of stability batches. Certificates from both the colorant supplier and the FDA Color Certification Branch are provided.

Note that the original NDA submission provided an exemplar of the supplier's certification (See Volume 1.2, page 119).

Please call me if you have any questions or comments concerning this submission. I may be reached by telephone at (908)874-1463.

Sincerely,

James A. Haviland
Manager, Regulatory Compliance

submitted in triplicate

cc: Rosemary Cook
Dr. Wilson DeCamp (cover letter only)
Dr. Su Tso (2 copies)
Archival Copy

Johnson & Johnson
CONSUMER PRODUCTS WORLDWIDE
SKILLMAN, NJ 08558-9418

VIA FEDERAL EXPRESS

FEB 1 1996

January 2, 1996

Jonathan Wilkin, MD, Director
Division of Topical Drug Products, HFD-540
Document Control Room #12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

BC
NDA GRIG ATTACHMENT

Re: NDA 20-310
Ketoconazole 1% Shampoo
General Correspondence
Chemistry, Manufacturing and Controls

Dear Dr. Wilkin:

Reference is made to our pending New Drug Application 20-310 for ketoconazole 1% shampoo. Reference is also made to the teleconference of December 21, 1995 between Marjorie McTernan of Johnson & Johnson CPWW and Ms. Rosemary Cook, Mr. Hal Blatt and Kevin Darryl White of the Agency. As requested by Ms. Cook the following is attached:

Attachment 1- 1/2/96 Revision to the FOI Copy of the Environmental Assessment (EA).

The attached has been revised to include Item 6. Introduction of Substances into the Environment. This copy supercedes the the EA submitted on March 8, 1995.

Desk copies of this have been sent to Hal Blatt and Rosemary Cook.

If there are any questions related to this submission, please notify me directly at (908) 874-1337.

Sincerely,

Marjorie B. McTernan
Director, Regulatory Affairs

i:ea.doc

ORIGINAL

Johnson & Johnson

CONSUMER PRODUCTS, INC.

SKILLMAN, NJ 08558-9418

March 18, 1996

VIA CERTIFIED MAIL

Jonathan Wilkin, MD, Director
Division of Dermatological and Dental Drug Products HFD-540
Document Control Room # 12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: **IND 28, 988**
Ketoconazole 2 % Shampoo
General Correspondence
Serial Number 044

Dear Dr. Wilkin:

Reference is made to the letter of authorization submitted by Douglas N. Dobak on May 26, 1995 (IND . The study entitled " A Double-Blind Placebo-Controlled Study of Ketoconazole 2 % Shampoo in the Treatment of Pityriasis Versicolor " Protocol No 19075.1 has been completed. J&J CPI has completed the assigned responsibilities for monitoring the conduct and progress of the clinical investigation .

The responsibility for communication with FDA on any issues regarding this study is being transferred back to Janssen, Pharmaceutica. Donna Castro-Ohye and Tracie Averill will be responsible for all future communication on this study.

If you have any questions regarding this reassignment of responsibilities, please contact :

Donna Castro-Ohye
Director, Regulatory Affairs
Janssen Pharmaceutica Research Foundation
1125 Trenton-Harbourton Road
Post Office Box 200
Titusville, New Jersey 08560-0200
(609) 730-3396

Sincerely,

Marjorie B. McTernan
Director, Regulatory Affairs

enclosure

ORIGINAL

BC

NDA ORIG AMENDMENT

March 22, 1996

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products, HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Document Control Room # 12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

REVIEWS COMPLETED
LETTER MEMO
OSE/DMETS INITIALS DATE

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 26 1996
HFD

Re: **NDA 20-310**
Ketoconazole 1 % Shampoo
Amendment to Chemistry, Manufacturing and Controls (FOI-EA)
General Correspondence

Johnson & Johnson CONSUMER PRODUCTS, INC.

Dear Dr. Wilkin:

Reference is made to the approvable letter for NDA 20-310 (ketoconazole 1% shampoo) dated March 14, 1996 received via fax on March 15 (Attachment 1); the March 21, 1996 teleconference between FDA, represented by Hal Blatt, DDS and Nancy Sager; and J&J CPI, represented by James Haviland and Marjorie McTernan regarding additional information requested for Items 5 and 6 of the FOI Environmental Assessment (Attachment 2).

With regard to the submissions requested before the application may be approved, our response is as follows:

FDA REQUEST: *Item 1.*
"Sixteen copies of the final printed labeling (FPL) for the drug product that are identical to the enclosed revised version of the draft labeling. Ten copies of the FPL should be individually mounted on heavy-weight paper or similar material.

Should additional information relating to the safety or effectiveness of this drug become available, revision of the FPL may be required.

RESPONSE: **Sixteen copies of the final printed labeling will be submitted as soon as it is available, estimated to be by July 15, 1996.**

FDA REQUEST: *Item 2.*
A safety update that includes all safety information you now have regarding your new drug, as required by the provisions of 21CFR 314.50(d)(5)(vi)(b).

RESPONSE: **The safety update will be submitted on April 8, 1996.**

FDA REQUEST: *Item 3.*
An Environmental Assessment (EA) suitable for release under the Freedom of Information Act(FOI) to be revised as follows:

A. The information included in the format items 5a. through 5g. of the confidential EA dated March 8, 1995 should be incorporated into the FOI EA. Format item 5.h. (impurities) should be listed but can be identified as "confidential".

B. No information was included in the FOI EA dated March 14, 1995 for format item 6. In general the following information should be included in the EA for both the drug product and the drug substance manufacturing sites, although some of the specific information may be classified as confidential;

I. For the bulk drug production site include:

a. Substances Expected to be Emitted
b. Controls exercised
c. Citation Statement of Compliance with the Applicable Emission Requirements
d. Discussion of the Effect of Approval on Compliance with Current Emission Requirements
e. Expected Introduction Concentrations (estimate of maximum yearly market volume for abbreviated EA's)

II. For the drug product manufacturing site, some information to fulfill the requirements of format item 6 has been provided in the confidential EA. but there may be a discussion included in the FOI EA. The following is suggested:

a. *For 6. a and 6. e., a reference to the information in the confidential EA. submitted March 8, 1995 is acceptable.*

b. *For 6.b, 6.c, and 6.d, information should be included in FOI EA. (this should include, but not limited to the previously submitted certifications and permitting information).*

RESPONSE: **With regard to Item 3 A, as noted in the minutes of the March 21 teleconference (Attachment 2) at the direction of Nancy Sager, we are submitting a certification from the manufacturer of the drug substance (ketoconazole , USP) to the FOI EA (Attachment 3).**

With regard to Item 3 B, we are submitting revised copies of both the confidential EA and the FOI EA incorporating the format and information requested. These supersede the submissions of March 8, 1995 and January 2, 1996 (Attachment 4).

FDA REQUEST: *Item 4.*
A commitment to compete the following as Phase 4 requests:

RESPONSE: **With regard to Phase IV request 4 A, this commitment was made in previous submissions of November 12, 1993 and January 31, 1995 (Attachment 5). We are reconfirming this commitment.**

With regard to 4 B, in the submission dated September 29, 1993 we explained that

test method. We can confirm that the only excipient material containing The raw material specification and certificate of analysis submitted in the original December 18, 1992 NDA identified both the identity and the amount of We reconfirm this in a resubmission of both the raw material specification for (Attachment 6).

FDA REQUEST: *Item 5.*

The copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

RESPONSE: **Copies of introductory promotional material will be submitted for review to the Division of Drug Marketing, Advertising and Communications when they become available.**

We note your comments regarding a satisfactory inspection of the manufacturing facility. This facility was inspected by the Los Angeles District Office in February 1996. The inspector (Mark Balboni) reported that there were no deficiencies to merit a change in the previous recommendation for approval to manufacture ketoconazole shampoo under NDA 20-310.

We also acknowledge your statement that approval of NDA 20-310 is contingent on submission of modified labeling for the 2% shampoo to distinguish both drug products from each other consistent with FD&C Act Sec. 503 (b). This labeling submission will be made by Janssen Pharmaceutica.

If you have any questions on any information in this submission, please contact me at (908) 874-1337.

Sincerely,

Marjorie B. McTeman
Director, Regulatory Affairs

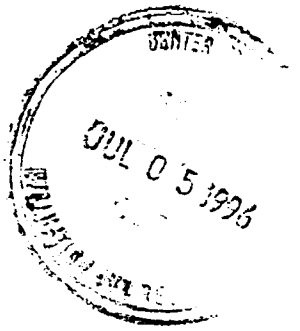
attachments

submitted in triplicate

cc: H. Blatt (5 desk copies)

Johnson & Johnson
CONSUMER PRODUCTS, INC.
SKILLMAN, NJ 08558-9418

1687
7/22/96



VIA FEDERAL EXPRESS

July 3, 1996

Jonathan Wilkin, MD, Director
Division of Dermatological and Dental Drug Products, HFD 540
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Central Document Room, Park Bldg. Rm. 214
Food and Drug Administration
14240 Parklawn
Rockville, Maryland 20852

Re: NDA 20-310
Ketoconazole 1% Shampoo
General Correspondence

Dear Dr. Wilkin:

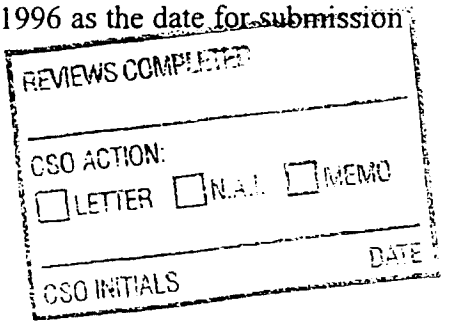
Reference is made to the approvable letter for NDA 20-310 (ketoconazole 1% shampoo) dated March 14, 1996 and the March 22, 1996 response letter.

With regard to Item 1:

"Sixteen copies of the final printed labeling (FPL) for the drug product that are identical to the enclosed revised version of the draft labeling. Ten copies of the FPL should be individually mounted on heavy-weight paper or similar material.

Should additional information relating to the safety or effectiveness of this drug become available, revision of the FPL may be required".

The March 22 response to this request estimated July 15, 1996 as the date for submission of Final Printed Labeling (FPL).



Johnson & Johnson Consumer Products, Inc. plans to have another J&J affiliate distribute this product after approval of the NDA. Due to additional insights for market positioning and trade dress, the Final Printed Labeling (FPL) will not be available for submission until the end of October, 1996.

If you have any questions on any information in this submission, please contact me at (908) 874-1337.

Sincerely,

Marjorie B. McTernan
Director, Regualtory Affairs

attachment

submitted in triplicate

cc: H. Blatt (desk copy)