CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-310

ADMINISTRATIVE DOCUMENTS

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-310 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade (generic) name/dosage form: NIZORAL A-D (KETOCONAZOLE SHAMPOO) 1% Action: AP (AE) NA

Applicant JOHNSON & JOHNSON Therapeutic Class _____

Indication(s) previously approved _____
Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application ANTI-DANDRUFF SHAMPOO
(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
___ (1) Studies are ongoing,
___ (2) Protocols were submitted and approved.
___ (3) Protocols were submitted and are under review.
___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

5/7/97 _____
Signature of Preparer and Title (PM, CSO, MO, other)

5/15/97

cc: Orig (NDA/PLA # 20-310
HFD-540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

5/95

Dandruff is rare in the pediatric population.

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-310 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade (generic) name/dosage form: Ketoconazole Shampoo 1% Action: AP (AP) NA

Applicant Johnson & Johnson Therapeutic Class _____

Indication(s) previously approved _____

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application Anti dandruff shampoo

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing.
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Medical officer — 1/25/96

Signature of Preparer and Title (PM, CSO, MO, other) — Date

cc: Orig NDA/PLA # 20-310
HFD-540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

5/95

Product has low potential use as OTC antidandruff product.

Item 13 Patent Information On Any Patent Which Claims the Drug

1. U.S. Patent No. 4,335,125, issued June 15, 1982, claims the drug, ketoconazole.

2. U.S. Patent No. 4,942,162, issued July 17, 1990, claims a method of using ketoconazole to treat seborrheic dermatitis.

Sec. 5. So much of the unexpended balances of appropriations, allocations, or other funds (including funds available for the fiscal year ending June 30, 1950) for the use of the Bureau of Internal Revenue of the Treasury Department in the exercise of functions under the Oleomargarine Tax Act (26 U. S. C. 2300 subchapter A), as the Director of the Bureau of the Budget may determine, shall be transferred to the Federal Security Agency (Food and Drug Administration) for use in the enforcement of this Act.

Sec. 6. Nothing in this Act shall be construed as authorizing the possession, sale, or serving of colored oleomargarine or colored margarine in any State or Territory in contravention of the laws of such State or Territory.

Sec. 7. This Act shall become effective on July 1, 1950.

Approved March 16, 1950.

THE HUMPHREY-DURHAM ACT

Public Law 215 - 82d Congress
Chapter 578 - 1st Session
H. R. 3298

AN ACT

To amend sections 303 (c) and 503 (b) of the Federal Food, Drug, and Cosmetic Act, as amended.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That subsection (b) of section 503 of the Federal Food, Drug, and Cosmetic Act, as amended, is amended to read as follows:

Federal Food, Drug, and Cosmetic Act, amendments.
52 Stat. 1051.
21 U.S.C. § 353(b).

"(b) (1) A drug intended for use by man which—

"(A) is a habit-forming drug to which section 502 (d) applies; or

"(B) because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug; or

Conditions for dispensation of certain drugs.

"(C) is limited by an effective application under section 505 to use under the professional supervision of a practitioner licensed by law to administer such drug,

21 U.S.C. § 355.
65 Stat. 648.
65 Stat. 649.

shall be dispensed only (i) upon a written prescription of a practitioner licensed by law to administer such drug, or (ii) upon an oral prescription of such practitioner which is reduced promptly to writing and filed by the pharmacist, or (iii) by refilling any such written or oral prescription if such refilling is authorized by the prescriber either in the original prescription or by oral order which is reduced promptly to writing and filed by the pharmacist. The act of dispensing a drug contrary to the provisions of this paragraph shall be deemed to be an act which results in the drug being misbranded while held for sale.

"(2) Any drug dispensed by filling or refilling a written or oral prescription of a practitioner licensed by law to administer such drug shall be exempt from the requirements of section 502, except paragraphs (a), (i) (2) and (3), (k), and (l), and the packaging requirements of paragraphs (g) and (h), if the drug bears a label containing the name and address of the dispenser, the serial number and date of the prescription or of its filling, the name of the prescriber, and, if stated in the prescription, the name of the patient, and the directions

Exemption from certain labeling requirements.
21 U.S.C. § 352.

for use and cautionary statements, if any, contained in such prescription. This exemption shall not apply to any drug dispensed in the course of the conduct of a business of dispensing drugs pursuant to diagnosis by mail, or to a drug dispensed in violation of paragraph (1) of this subsection.

Exemption from prescription requirements.

"(3) The Administrator may by regulation remove drugs subject to section 502 (d) and section 505 from the requirements of paragraph (1) of this subsection when such requirements are not necessary for the protection of the public health.

Drugs deemed to be misbranded.

"(4) A drug which is subject to paragraph (1) of this subsection shall be deemed to be misbranded if at any time prior to dispensing its label fails to bear the statement 'Caution: Federal law prohibits dispensing without prescription'. A drug to which paragraph (1) of this subsection does not apply shall be deemed to be misbranded if at any time prior to dispensing its label bears the caution statement quoted in the preceding sentence.

Compliance with narcotics or marihuana laws.

"(5) Nothing in this subsection shall be construed to relieve any person from any requirement prescribed by or under authority of law with respect to drugs now included or which may hereafter be included within the classifications stated in section 3220 of the Internal Revenue Code (26 U. S. C. 3220), or to marihuana as defined in section 3238 (b) of the Internal Revenue Code (26 U. S. C. 3238 (b))."

53 Stat. 382.
53 Stat. 387.

All 65 Stat. 649.

21 U.S.C. § 333.

SEC. 2. Subsection (c) of section 303 of the Federal Food, Drug, and Cosmetic Act, as amended, is amended by striking out the period at the end of clause (3) and inserting in lieu thereof a semicolon and the following: "or (4) for having violated section 301 (b), (c) or (k) by failure to comply with section 502 (f) in respect to an article received in interstate commerce to which neither section 503 (a) nor section 503 (b) (1) is applicable, if the delivery or proffered delivery was made in good faith and the labeling at the time thereof contained the same directions for use and warning statements as were contained in the labeling at the time of such receipt of such article."

Effective date.

SEC. 3. The provisions of this Act shall take effect six months after the date of its enactment.

Approved October 26, 1951.

THE AUREOMYCIN ACT OF 1953

Public Law 201 - 83d Congress
Chapter 334 - 1st Session
H. R. 5016

AN ACT

All 67 Stat. 389.

To amend sections 502 (1) and 507 of the Federal Food, Drug, and Cosmetic Act in order to identify the drug known as aureomycin by its chemical name, chlortetracycline.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That section 502 (1) of the Federal Food, Drug, and Cosmetic Act (21 U. S. C., sec. 352 (l)) is amended by striking out "aureomycin" and inserting in lieu thereof "chlortetracycline".

63 Stat. 409.

SEC. 2. (a) The heading of section 507 of such Act (21 U. S. C., sec. 357) is amended by striking out "AUREOMYCIN" and inserting in lieu thereof "CHLORTETRACYCLINE".

(b) The first sentence of subsection (a) of such section 507 is amended by striking out "aureomycin" and inserting in lieu thereof "chlortetracycline".

Approved August 5, 1953.

Consult #379 (HFD-540)

NIZORAL A-D Ketoconazole Shampoo 1%

Since Nizoral is already in use for the prescription ketoconazole products marketed by Janssen, including a 2% shampoo, the Committee considered the acceptability of the suffix "A-D" for the over-the-counter shampoo. The Committee is aware that the suffix "A-D" has been used in several different OTC products and, as such, has several different meanings: anti-diarrheal, arthritic dose, and now anti-dandruff. The Committee does not believe there is a significant potential for confusion in labeling an over-the-counter, topical, anti-dandruff product with the suffix "A-D".

The Committee has no reason to find the proposed name unacceptable.

CDER Labeling and Nomenclature Committee

_____, Chair 12/20/94

COMPLETED

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: MAR 10 1994

FROM: Office of OTC Drug Evaluation (HFD-800)
Through: Director, OODE

SUBJECT: Labeling Review of NDA 20-310 (Ketoconazole Shampoo 1%)

TO: Director
Division of Anti-Infective Drug Products (HFD-520)

We have reviewed the draft OTC labeling for shampoo (ketoconazole 1%) dated February 21, 1994, by the company and David Bostwick's draft labeling sent to us on March 7, 1994. We have the following comments:

1. The following revisions need to be made:

a. The words and the box around the Indication statement cannot be used at this time. These labeling items do not currently apply to NDA'd OTC drug products. The agency has only proposed such use; a final rule is still pending. The proposal does not authorize such use prior to a final rule.

b. It is our view that the company's statements about and must be deleted. We do not believe that the studies involved enough patients with to support such a statement. In addition, follow-up in the effectiveness trials was inadequate to demonstrate that subjects become

c. Under there is no need for the words after to begin with capital letters.

d. David Bostwick's draft inadvertently left out the warning We have reworded this statement in 2(c)(8) below.

e. We agree with David Bostwick's addition of the statement
However, this addition should be placed at the end of the Directions section instead of in the warnings section.

f. We believe some of the warning information needs to be stated in more detail, as follows:

The 2-4 week period is based on the joint advisory committee

recommendation made at its February 16, 1994 meeting.

g. The word to identify the inactive ingredients should be changed to

h. We recognize that the statements and are promotional and primarily related to the shampooing effect. Do we know that hair smells great (whatever that represents) after use or that hair is manageable, whatever that means? Were test subjects asked these questions? Without supporting evidence, these statements are inappropriate and need to be deleted.

2. The following revisions should be strongly considered:

a. The need for the standard OTC pregnancy-nursing warning in § 201.63 that reads:

We need to determine if we are sufficiently concerned about absorption to require this warning for a shampoo product. The subject was discussed at the joint advisory committee meeting on February 16, 1994. Although no vote was taken, the discussion favored having the statement in OTC labeling.

b. Are the inactive ingredients listed in descending order of prominence?

c. There are a number of items concerning that appear in the prescription product labeling that should be considered for the OTC product labeling:

(1) Prescription labeling says to
Add word to the OTC labeling.

(2) Prescription labeling says to
Add time
to the OTC labeling.

(3) We agree with David Bostwick's addition of following the word We suggest stating both and in this phrase.

(4) We agree with David Bostwick's addition of the words after the word

(5) We have some questions about the best wording to convey the message that David Bostwick has suggested be stated as

follows:

and
We are concerned that the last statement about not using more often than needed could be considered inconsistent with the statement to
The prescription labeling states:

The prescription labeling also states to

It seems like the key points to emphasize are to use regularly initially, with at least 3 days between shampooing, for up to 3 or 4 weeks, and then to use occasionally thereafter to maintain control. Unfortunately, intermittently and occasionally are not defined.

We may want to give OTC consumers some better guidance. The following is suggested:

We believe that the information about is more beneficial than stating to use twice a week, which does not provide a definitive schedule. The 3-4 days between use and the up to 8-weeks period are based on the clinical data submitted.

(6) The statement belongs under the section. We do not believe this statement needs to be in all capital letters nor the first statement under warnings. (See also (8) below.)

(7) We recommend that the warning be changed to read

(8) We recommend that the entire warnings section be organized in the following manner:

(9) The storage conditions need to be looked at by the chemist. The company has proposed The prescription labeling states to

Why the difference in temperatures? Also, it seems like the statement needs to be added per the prescription labeling.

3. The following items should be considered:

a. The prescription labeling states under information for patients that it has been reported that use of the shampoo resulted in removal of the curl from permanently waved hair. We believe the OTC labeling should provide consumers similar information.

b. We note that the prescription labeling states under directions to We question why this statement appears in the prescription labeling and whether it would be appropriate to include in the OTC labeling.

c. If a statement is allowed to remain in the labeling about prescription strength NIZORAL shampoo and the company is allowed to state that it is the company should be required to submit data to support this statement. We believe this reference to the prescription shampoo is inappropriate and should be deleted.

We would allow the statement We believe the word antifungal should be included because it informs consumers that the product contains an antifungal ingredient and may assist in OTC product selection.

We would be glad to discuss any of our comments with your staff, as necessary.

Debra Bowen, M.D.
Director, Medical Review Staff

Gerald M. Rachanow, P.D., J.D.
Deputy Director
Monograph Review Staff

cc: NDA 20-310
HFD-800:Weintraub
HFD-810:PRD-N/Reading
HFD-811:Rachanow
HFD-830:Bowen
R/D:GRachanow:je:3/9/94
Revised:GRachanow/DBowen/WGilbertson/MWeintraub/vjm/3-9-94
Revised:GRachanow/jee/3-10-94
F/T:GRachanow/jee/3-10-94
Doc:a:\label
Rachanow - Disk 8 3-10-94

Memorandum of a Telephone Conversation

Date: 1/4/~~92~~93 WJ

NDA: 20-310

Between: Ms. Debrorah L. Norby
Regulatory Affairs
Tel (908) 874-1434
Fax (908) 874-1118

And: Su C. Tso, Ph.D.
HFD 520

Subject: Supplemental Information

Ms. Debrorah Norby was contacted by phone. I spoke to Ms. Norby and Mr. Steve Townsend on the speaker phone:

1. Trade name of the drug product
Not available yet. She will check with marketing Dept. and get back to me.

2. Yearly production volume of the drug product in lb or Kg, and the required drug substance in lb/yr will be provided

4. For the manufacturing of drug product at
I asked them to provide a description of air emission control equipment, wastewater management, the source of wastewater and where is it been discharge. Give air and wastewater discharge permits #, issuer, and expiration date.

5. With regard to the GMP inspection of manufacturing facilities, they will let me know when these facilities will be for Pre-approval GMP inspection.

6. There is no EA for the manufacturing of KETOCONAZOLE at DMF was submitted on 12/17/92 for the facility. EA should be included in the DMF. The DMF has been received but no DMF no. is assigned yet.

Amendment 1/26/93

Memorandum of a Telephone Conversation

Date: 3/12/93

NDA: 20-310

Between: Ms. Debrorah L. Norby
Regulatory Affairs
Tel (908) 874-1434
Fax (908) 874-1118

And: Su C. Tso, Ph.D.
HFD 520
(301) 443-4300

Subject: Supplemental Information

I called Ms. Debrorah Norby Today. I asked her that the environmental permits presented in amendment dated 1/26/93 are expired. The air emission permits are under renew, but the waster water discharge permits were dated 1975. There is no expiration dates indicated on the permits, what are the current status of these permits. She told me that they are working on the permit renew.

I also requested her to submit additional stability data for the pre-production batches (one year at room temperature) as soon as they are available. She told me the form will do so.

In the pH determination by TM 7130, pg. 223 vol 1.4, How the sample is dilute. What is temperature of measurement? I told her that the method should be specific for the drug product. The firm promise to look into the method.

I remind the firm again that all formulations should be based on dry weight of the ingredient. When solution is used, concentration of the solution must be clearly indicated. Chemical Name of the ingredients should be used in the formulation, trade name may be included for reference.

Memorandum of a Telephone Conversation

Date: 3/16/93

NDA: 20-310

Between: Ms. Debrorah L. Norby
Regulatory Affairs
Tel (908) 874-1434
Fax (908) 874-1118

And: Su C. Tso, Ph.D.
HFD 520
(301) 443-4300

Subject: Method Validation

For method validation, please prepared the followings, and submitted to the agency as an amendment to the method validation package. Do not send sample. Samples will be pickup by investigator from Los Angeles District Office.

1. A list of all samples with lot #, sample size indicated.

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

2. MSDS sheets of all samples

3. Composition of the drug product

4. Regulatory specification of the drug product.

5. Certificates of analysis of all Samples

SCT

Memorandum of a Telephone Conversation

Date: 10/21/93

NDA: 20-310

Between: Ms. Debrorah L. Norby
Regulatory Affairs
Tel (908) 874-1434
Fax (908) 874-1118

And: Su C. Tso, Ph.D.
HFD 520

Subject: amethod Validation and Post Approval Stability Protocol

Ms. Debrorah Norby was contacted by phone, but could not reach her. so I request the following information by fax.

1. Regarding to method validation, which method, TM 7790 or TM 4055 will be used a the regulatory stability indicating assay method for the drug product. Amendment 11/12/93 10/1/93

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. 10/25/93 11/12/93

Call me if you have questions. You may fax me a copy of the proposed stability protocol for a comment prior to the formal submission.

NDA 20-310

Rosemary:

I do not know the new Regulatory Officer of J&J.
Please communicate the following to J&J immediately:

In amendment dated 9/29/93, response to question #2 about the inconsistency in composition, the firm indicated that the

The firm also showed was presented in placebo 1 and placebo 2 at 0.0221% without any being added (attachment 2 Table I). My question is **Which excipient contains** Please provide evidence by submitting manufacturer's certificate of analysis. Commitment should be made to analyze content of this excipient before use of this excipient.

Also the trade name is not acceptable to CEDER Labeling and Nomenclature Committee. I have sent you a copy of the letter, consult # 258. I was not notified of any other trade name proposal. Therefore FONSI will be delayed until an acceptble trade name is received by lthis reviewer. If J&J already proposed a new trade name, would you clear it with CEDER Committee and let me know

Su C. Tso
Chemist, HFD-520
3/7/94

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: March 16, 1994

To: file

From: Wilson H. De Camp, Ph.D.
Supervisory Chemist, HFD-540

Subject: Supervisor's Addendum, NDA 20-310, Chemist's Review #3

The original review, dated March 12, 1994, stated the reviewer's conclusions and recommendations as follows:

> The application is not approvable. The reason for this conclusion is a lack of statement from Compliance, HFD 320, that the manufacturing and control facilities are in acceptable GMP compliance.

A final update of GMP compliance status was signed March 14 and received March 15, indicating that all facilities were acceptable. The reviewer's conclusion should be reversed, with the proviso that an approval action must be taken on or before May 13, 1994.

With regard to the reviewer's other technical comments on the labeling, they should stand as stated as follows:

1. the words should be added after

2. the location of the expiration date and lot No. should be imprinted on the label.

With regard to the outstanding deficiency #3 from Chemist's Review #2, the chemist's comment was as follows:

3. Minor chemistry deficiency - inconsistency in the compositions of in shampoo formulation and the specification in stability protocol. CSO is to inform the applicant to provide:
   a. The excipient that contains
   b. Certificate of analysis from manufacturer to demonstrate the presence of and
   c. Commitment to control content of the excipient by the proposed method.

The applicant submitted an example at my request, and also submitted copies of the relevant CTFA listing and the Material Safety Data Sheet. This ingredient appears to be supplied as a dry powder that is at least 94% pure quaternium-15. In the September 29, 1993, submission to the NDA, the applicant stated that the high test results for could be attributed to

This assertion should be supported by data.

The commitment described above should be communicated to the applicant using the following paragraph:

> We note from your submission of September 29, 1993, that you are aware of
>
> As a post-approval commitment, the following studies are to be done, with the results being reported to FDA within 6 months of the date of the approval letter:
>
> 1. Any other components of the drug product that contain quaternium-15 are to be identified;
> 2. If the certificate(s) of analysis for these component(s) declare an amount of quaternium-15, they are to be submitted; otherwise, the component is to be assayed for quaternium-15 using the analytical method approved in the NDA; and
> 3. A specification and test method will be proposed to be applied to this component if the supplier does not declare the amount of quaternium-15.

Analytical methods validation has been requested and is in progress. The standard paragraph concerning their continuing efforts in this area should be incorporated into the letter.

cc: Orig: NDA 20-310
HFD-540
HFD-540/Bostwick
HFD-540/Alam
HFD-541/Cook
HFD-520/Soprey
HFD-540/Tso
init. by SUPVCHEM
wd:3/16/94

Consult #379 (HFD-540)

NIZORAL A-D Ketoconazole Shampoo 1%

Since Nizoral is already in use for the prescription ketoconazole products marketed by Janssen, including a 2% shampoo, the Committee considered the acceptability of the suffix "A-D" for the over-the-counter shampoo. The Committee is aware that the suffix "A-D" has been used in several different OTC products and, as such, has several different meanings: anti-diarrheal, arthritic dose, and now anti-dandruff. The Committee does not believe there is a significant potential for confusion in labeling an over-the-counter, topical, anti-dandruff product with the suffix "A-D".

The Committee has no reason to find the proposed name unacceptable.

CDER Labeling and Nomenclature Committee

_____, Chair 12/20/94

COMPLETED

RECORD OF 45 DAY CONFERENCE

DATE: February 5, 1993

PARTICIPANTS FROM FDA:

M. Lumpkin, M.D., Division Director
S. Alpert, M.D., Group Leader
R. Labib, M.D., Medical Officer
R. Osterberg, Ph.D., Supervisory Pharmacologist
S. Joshi, Ph.D., Pharmacologist
W. De Camp, Ph.D., Supervisory Chemist
S. Tso, Ph.D., Chemist
A. Sheldon, Ph.D., Supervisory Microbiologist
P. Soprey, Ph.D., Microbiologist
R. Harkins, Ph.D., Supervisory Mathematical Statistician
S. Lam, Ph.D., Section Head, Biopharmaceutics
F. Ajayi, Ph.D., Biopharmaceutics
J. Bona, Supervisor, Project Management Staff
M. R. Cook, Project Manager

SUBJECT: ketoconazole shampoo, 1% NDA 20-310

OBJECTIVE: To determine the fileability of NDA 20-310

The meeting was convened to determine the adequacy of NDA 20-310 for filing. All sections of the New Drug Application (NDA) were evaluated in terms of the general content and format requirements.

From a preliminary evaluation of the general content and format, as well as the chemistry, manufacturing, and controls, nonclinical pharmacology and toxicology, human pharmacokinetics and bioavailability, and statistical sections of the application, it was recommended that NDA 20-310 be filed.

However, a decision would be forthcoming regarding the adequacy of the clinical data section for filing. Specifically, there were concerns regarding the absence of irritation testing using exaggerated doses and the lack of safety data to support the marketing of this new drug as an over-the-counter (OTC) product.

In addition, the need for the following was cited:

1. A statement that all nonclinical laboratory studies were conducted in compliance with Part 58 or a statement why a study was not conducted in compliance with those requirements.

2. A statement that all clinical trials were conducted in accordance with the IRB/Declaration of Helsinki provisions of the CFR.

3. Information in the environmental assessment with regard to the manufacture of the bulk drug substance, ketoconzole, at

4. Additional stability data to support the proposed expiration dating period of 3 years.

5. Information regarding the foreign marketing of the ketoconazole shampoo, 1% formulation. Samples of foreign labeling should also be submitted.

6. Submission of a complete Microbiology technical section. Data from preservative effectiveness testing should be included in the Microbiology section.

7. Submission of all clinical safety and efficacy data in diskette format for statistical review.

8. Patient profile listing by center (including all enrolled subjects, date of enrollment and disposition) and adverse event listings by center and time of occurrence relative to enrollment date submitted in diskette format for statistical review.

With regard to the labeling for the new drug product, a concern was expressed by S. Joshi, Pharmacologist regarding the designation of a Pregnancy Category classification for an OTC product.

It was concluded that a teleconference would be conducted with the applicant, Johnson & Johnson Consumer Products Inc. to convey the concerns specified above.

Maria Rossana R. Cook
Project Manager, HFD-521

cc:
Orig NDA 20-310
HFD-520
HFD-520/DIV DIR/Lumpkin
HFD-520/MO SUPV/Alpert
HFD-520/MO/Labib
HFD-520/PHARM SUPV/Osterberg
HFD-520/PHARM/Joshi
HFD-520/CHEM SUPV/De Camp
HFD-520/CHEM/Tso
HFD-520/MICRO SUPV/Sheldon
HFD-520/MICRO/Soprey
HFD-714/BIOMETRICS/Harkins
HFD-714/BIOMETRICS/Turney
HFD-426/BIOPHARM/Ajayi
HFD-426/BIOPHARM/Lam
HFD-521/PROJ MGR SUPV/Bona
HFD-521/PROJ MGR/Cook

45 days meeting notes

NDA 20-310

For item #5:

The environmental assessment contain no information on the manufacturing of bulk drug substance, ketoconazole, at There is no EA in the the DMF submitted on January 27, 1993. Sponsor commits to provide the required EA by the end of March for review. This is acceptable.

For item 10:

Stability data provided in the application does not justify the requested expiration dating period of 3 years. However based on the experience with the marketed Nizoral (ketoconazole), 2% Shampoo and the stability data provided in the application, a two years's expiration dating period may be granted. Therefore, this is acceptable.

Conclusion:

The NDA is filable on a chemistry, manufacturing, and control standpoint.

2/3/93

2/2/93

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

JOHNSON & JOHNSON Consumer Products, Inc. hereby certifies that as the sponsor of New Drug Application 20-310 for ketoconazole 1% shampoo, has not and will not use in any capacity, the services of any person debarred under subsections (a) or (b) [section 306 (a) or (b)], in connection with such application.

Marjorie B. McTernan
Director, Regulatory Affairs

NDA 20-310

Marjorie B. McTernan
Director, Regulatory Affairs
Johnson & Johnson Consumer Products, Inc.
Grandview Road
Skillman, NJ 08558-9418

DEC 6 1993

Dear Ms. McTernan:

We acknowledge receipt on November 1, 1993, of your amendment dated October 29, 1993, to your new drug application (NDA) for ketoconazole shampoo, 1%.

We consider this to be a major amendment received by the Agency within three months of the user fee due date. Therefore, the user fee clock is extended three months. The new user fee due date is **March 18, 1994.**

Should you have any questions concerning this application, please contact Ms. Maria Rossana R. Cook, Project Manager, at 301-443-0257.

Sincerely yours,

Murray M. Lumpkin, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Orig NDA 20-310
HFD-520
HFD-520/ACTG DIV DIR/Gavrilovich
HFD-520/MO/Bostwick
HFD-520/PHARM/Joshi
HFD-520/PHARM SUPV/Osterberg
HFD-520/CHEM/Tso
HFD-520/CHEM SUPV/De Camp
HFD-520/MICRO/Soprey
HFD-520/MICRO SUPV/Sheldon
HFD-426/BIOPHARM/Ajayi
HFD-426/BIOPHARM SUPV/Pelsor
HFD-713/STAT/Sobhan
HFD-713/STAT SUPV/Harkins
HFD-521/PROJ MGR/Cook

Concurrences:
HFD-520/MO SUPV/Chambers MMC 12/6/93

REVIEW EXTENSION

MMC 12-03-93

MML 12/6/93

NDA 19-927

Ruth Wasserman
Director, Regulatory Affairs
Janssen
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

MAR 4 1994

Dear Ms. Wasserman:

Reference is made to your New Drug Application for Nizoral Shampoo (ketoconazole shampoo), 2%.

At a recent public Advisory Committee meeting, data on ketoconazole shampoo, 2% were discussed. Questions regarding the necessity for the product to remain a prescription only product were raised. In order to determine compliance of this product with Section 503(b) of the Federal Food, Drug, and Cosmetic Act (the Act), the Food and Drug Administration requests that you submit within the next 30 days a justification to support the continued marketing of this product by prescription only.

Failure to respond may result in a determination that the product is misbranded under Section 503(b) of the Act.

Should you have any questions concerning this application, please contact Ms. Maria Rossana R. Cook, Project Manager, at 301-443-0257.

Sincerely yours,

3/4/94

Murray M. Lumpkin, M.D.
Deputy Director for Review Management
Center for Drug Evaluation and Research