CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-310

CHEMISTRY REVIEW(S)

JUN 9 1993

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-310 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 18/05/93

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	18-12-92	18-12-92	24-12-92
AMENDMENT/AC			

NAME & ADDRESS OF APPLICANT:
Johnson & Johnson Consumer Products, Inc.
Grandview Road
Skillman, NJ 08558-9418

DRUG PRODUCT NAME

Proprietary:	none
Nonproprietary/USAN:	Ketoconazole
Code Names/#'s:	R41,400 or Medic
Chemical Type:	3S
Therapeutic type:	Antifungal

ANDA Suitability Petition/DESI/Patent Status:

US Patent # 4,335,125, 6/15/82
US patent # 4,942,162, 7/17/90

PHARMACOLOGICAL CATEGORY/INDICATION:
Anti-fungal
Control the flaking, scaling, and itching associated with dandruff.

DOSAGE FORM:	Shampoo
STRENGTHS:	1%
ROUTE OF ADMINISTRATION:	Topical
DISPENSED:	_____ Rx __x__ OTC

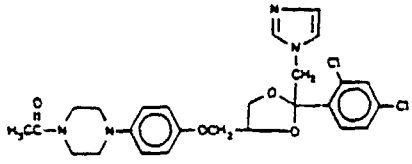
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Chemical Name - CAS, USP, USAN, INN

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

(2) (±)-cis-1-Acetyl-4-[*p*-[[2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolan-4-yl)methoxy]phenyl]piperazine

Structural formula:



Molecular formula: $C_{26}H_{28}Cl_2N_4O_4$

Molecular weight: 531.44

Compendial monograph, USP XXII, pg. 747

SUPPORTING DOCUMENTS:

Type of Document	Document No.	Subject	Document Holder	Date
IND		Ketoconazole		9/16/86
IND		Ketoconazole	J&J CPI	8/6/91
NDA		Nizoral		12/15/88
DMF - filed on 12/17/92	To be determined	Ketoconazole		12/17/92
DMF		Bottle		8/23/88
DMF		HDP Resin		N/A
DMF		Closure		7/3/89
DMF		Fragrance		N/A
DMF		Polypropylene Resin		N/A

RELATED DOCUMENTS (if applicable):

IND

IND
DMF

DMF

DMF

NDA 18-533, Nizoral (ketoconazole) Tablet, Janssen
NDA 19-297, Nizoral (ketoconazole) Shampoo, 2%

AMENDMENTS

NC, 1/26/93; NC, 2/10/93; NC, 4/19/93
NC, 5/3/93; NC, 5/4/93

REMARKS/COMMENTS:

Shampoo containing Ketoconazole has been marketed as both a prescription (2%) and over the counter shampoo (2% and 1%) in 69 countries, 33 of which also have an indication for seborrheic dermatitis of the scalp. In 1990, Nizoral, 2% ketoconazole shampoo (NDA 19-927, by Janssen) was approved in the US for prescription use for the reduction of scaling due to dandruff. Janssen does not currently market ketoconazole 1% shampoo in US or any foreign countries. Authorization letter dated 12/10/92 to NDA 19-927 is provided.

Janssen also market Nizoral (ketoconazole) 2% Cream, NDA 19-084, NDA 19-576, NDA 19-648; Nizoral (ketoconazole) Tablets, NDA 18-533. Nizoral (ketoconazole) 2% Shampoo, NDA 19-927, carries a 2 year expiration dating period.

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable from a chemistry standpoint. Specific deficiencies are listed
These deficiencies are summarized below:

1. DMF inadequate to support the manufacturing of bulk drug substance ketoconazole.

2. Other inadequacies are noted under the following sections: Composition, method of manufacturing, regulatory specifications and method, Container/closure manufacturer, Stability, Labeling, and Environmental Assessment.

Su C. Tso, ph.D.
Review Chemist

cc: Orig. NDA 20-310
HFD-520/Division File
HFD-520/SCTso/
HFD-520/Joshi
HFD-520/Cook
HFD-102/CKumkumian [#1 only]
HFD-520/Labib
HFD-520/Soprey
HFD-520/SUPERVISOR/WHDeCampi

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Ms. Yana Mille, Chair, (HFD-600) MPN II

FROM: Division of Anti-Infective Drug products HFD-520
Attention: Su C. Tao Phone 443-4300

DATE: 11/4/93

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Nizoral-DS or SEQUENZ NDA/~~ANDA#~~ 20-310

Company Name: Johnson + Johnson Consumer Products Inc

Established name, including dosage form: 1% Ketoconazole shampoo

Other trademarks by the same firm for companion products:
Nizoral, 2% Ketoconazole shampoo is currently marketed in US by Janssen

Indications for Use (may be a summary if proposed statement is lengthy):
Control the flaking, scaling + Etching associated with dandruff

Initial comments from the submitter: (concerns, observations, etc.)
This is an OTC product

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Oct. 93

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-310 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 2/1/94
Revised 3/9/94

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT AC	29-09-93	01-10-93	21-10-93
AMENDMENT BC	01-10-93	04-10-93	21-10-93
AMENDMENT BC	25-10-93	27-10-93	01-11-93
AMENDMENT BC	12-11-93	15-11-93	27-11-93
AMENDMENT BC	10-12-93	13-12-93	14-12-93

NAME & ADDRESS OF APPLICANT:

Johnson & Johnson Consumer Products, Inc.
Grandview Road
Skillman, NJ 08558-9418

DRUG PRODUCT NAME

Proprietary:	none
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Therapeutic type:	Antifungal

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US patent # 4,942,162, 7/17/90

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DISPENSED:	_____ Rx __x__ OTC

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Chemical Name - CAS, USP, USAN, INN

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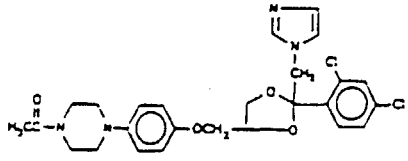
(2) (±)-cis-1-Acetyl-4-[*p*-[[2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolan-4-yl)methoxy]phenyl]piperazine

Structural formula:



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DMF - filed on 12/17/92		Ketoconazole		12/17/92
DMF		Bottle		8/23/88
DMF		HDP Resin		N/A
DMF		Closure		7/3/89
DMF		Fragrance		N/A
DMF		Polypropylene Resin		N/A

RELATED DOCUMENTS (if applicable):

Chemist's review #1, 5/18/93
Telephone conversation 10/21/93
DMF
DMF

REMARKS/COMMENTS:

Amendment AC dated 9/29/93 addresses the deficiencies cited from the chemist's review #1 of 5/18/93. Amendment BC dated 10/1/93 provides the method validation package. Amendment dated 10/25/93 provided post approval stability protocol. Amendment dated 11/12/93 provided additional copy for method validation and revised post approval stability protocol. Refer to Review Notes for details.

Facilities Updating requested on

EER 5404 (10/28/93).
EER 5830 (1/31/94)

Trade name consult (two) requested on 10/27/93.

Method validation requested on 11/22/93

EA acceptable, but FONSI can not be prepared without a trade name.

The expiry of the application will be 2 years, not 3 years as the sponsor requested.

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable. The reason for this conclusion are:

1. A lack of a statement from HFD-320 that the manufacturing facilities are in acceptable GMP compliance.

2. A lack of trade name for use in FONSI.

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. Certificateof analysis from manufacturer to demonstrate the presence of
   c. Commitment to control content of the excipient by the proposed method.

Su C. Tso, ph.D.
Review Chemist

cc: Orig. NDA 20-310
HFD-520/Division File
HFD-520/SCTso
HFD-520/Joshi
HFD-520/Cook
HFD-520/Bostwick
HFD-520/Soprey
HFD-520/SUPERVISOR/WHDeCamp

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-310 **CHEM.REVIEW #:** 3 **REVIEW DATE:** 3/12/94

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT BL	25-02-94	28-02-94	09-03-94
AMENDMENT NC	28-03-94	01-03-94	09-03-94

NAME & ADDRESS OF APPLICANT:

Johnson & Johnson Consumer Products, Inc.
Grandview Road
Skillman, NJ 08558-9418

DRUG PRODUCT NAME

Proprietary:	none
Nonproprietary/USAN:	Ketoconazole
Code Names/#'s:	R41,400 or Medic
Chemical Type:	3
Therapeutic type:	Antifungal

ANDA Suitability Petition/DESI/Patent Status:

US Patent # 4,335,125, 6/15/82
US patent # 4,942,162, 7/17/90

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DISPENSED:	_____ **Rx** __x__ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Chemical Name - CAS, USP, USAN, INN

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(2) (±)-cis-1-Acetyl-4-[*p*-[[2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolan-4-yl)methoxy]phenyl]piperazine

RELATED DOCUMENTS (if applicable):

Chemist's review #1, 5/18/93
Chemist's review #2, 2/1/94, revised 3/9/94

REMARKS/COMMENTS:

Amendment dated 2/25/94 provides drafted labeling with trade name as Rosemary Cook has agreed to submit this proposed trade name to Labeling Committee for final approval. **The proposed labeling is acceptable in term of storage temperature. However under other ingredients,**

1. **the words should be added after**

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

A expiry of 2 years can be granted on the basis of the stability data.

EER 4122 was filed on 2/5/93, the facilities were in GMP compliance as of 3/25/93. EER 5404 was filed for final update on 10/28/93, and EER 5830 was filed to add additional inspection site at J&J analytical laboratory at Skillman, NJ.

With respect to EER 5404, Los angeles District inspected the manufacturing facility at FDA form 483 was issued to J&J on 2/1/94 by inspector Ms. Omotunde O. Osunsanmi. Amendment dated 2/28/94 was submitted by J&J to address the deficiencies itemized in the form 483. This amendment provided the firm's response to the 10 citations of Form 483 with a copy of the form 483 included. The citations are GMP issues, it will be reviewed by the District and HFD 320. With respect to EER 5930, the compliance status is unknown. At this time, we are awaiting answer from Compliance Department, therefore **the application is not approvable on the ground of GMP compliance.**

We are still waiting for the firm's response to the #3 deficiency cited in the chemist's review # 2. However this deficiency is not the reason for withholding approval. The response to this deficiency can be a phase IV commitment.

EA is acceptable. FONSI will be prepared for approval as soon as the trade name obtained the final approval from the Labeling Committee.

CONCLUSIONS & RECOMMENDATIONS:

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.

Su C. Tso, Ph.D.
Review Chemist

cc: Orig. NDA 20-310
HFD-520/Division File
HFD-520/SCTso
HFD-520/Joshi
HFD-520/Cook
HFD-520/Bostwick
HFD-520/Soprey
HFD-520/SUPERVISOR/WHDeCamp

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-310 **CHEM.REVIEW #:** 4 **REVIEW DATE:** 3/22/94

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Final update			

NAME & ADDRESS OF APPLICANT:

Johnson & Johnson Consumer Products, Inc.
Grandview Road
Skillman, NJ 08558-9418

DRUG PRODUCT NAME

Proprietary:	none
Nonproprietary/USAN:	Ketoconazole
Code Names/#'s:	R41,400 or Medic
Chemical Type:	3
Therapeutic type:	Antifungal

ANDA Suitability Petition/DESI/Patent Status:

US Patent # 4,335,125, 6/15/82
US patent # 4,942,162, 7/17/90

PHARMACOLOGICAL CATEGORY/INDICATION:

Anti-fungal
Control the flaking, scaling, and itching associated with dandruff.

DOSAGE FORM:	Shampoo
STRENGTHS:	1%
ROUTE OF ADMINISTRATION:	Topical
DISPENSED:	_____ Rx __x__ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

RELATED DOCUMENTS (if applicable):

Chemist's review #1, 5/18/93
Chemist's review #2, 2/1/94, revised 3/9/94
Chemist's review #3, 3/12/94
Memo, 3/16/94

REMARKS/COMMENTS:

All facilities are in GMP compliance as of 3/14/94.

The Labeling Committee has determined that is not acceptable as the trade name.

EA is acceptable, no environmental impact found. FONSI will be prepared for approval as soon as the an acceptable trade name is provided.

Label should contains the words

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable. However FONSI can not be prepared until the firm provides an acceptable trade name.

Su C. Tso, Ph.D.
Review Chemist 3/30/94

cc: Orig. NDA 20-310
HFD-520/Division File
HFD-520/SCTso
HFD-520/Joshi
HFD-520/Cook
HFD-520/Bostwick
HFD-520/Soprey
HFD-520/SUPERVISOR/WHDeCamp

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-310 **CHEM.REVIEW #:** 5 **REVIEW DATE:** 5/22/94 16

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE

Method validation by Philadelphia District Laboratory

NAME & ADDRESS OF APPLICANT:

Johnson & Johnson Consumer Products, Inc.
Grandview Road
Skillman, NJ 08558-9418

DRUG PRODUCT NAME

Proprietary:	none
Nonproprietary/USAN:	Ketoconazole
Code Names/#'s:	R41,400 or Medic
Chemical Type:	3
Therapeutic type:	Antifungal

ANDA Suitability Petition/DESI/Patent Status:

US Patent # 4,335,125, 6/15/82
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PHARMACOLOGICAL CATEGORY/INDICATION:

Anti-fungal
Control the flaking, scaling, and itching associated with dandruff.

DOSAGE FORM:	Shampoo
STRENGTHS:	1%
ROUTE OF ADMINISTRATION:	Topical
DISPENSED:	_____ Rx __x__ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

RELATED DOCUMENTS (if applicable):

Chemist's review #1, 5/18/93
Chemist's review #2, 2/1/94, revised 3/9/94
Chemist's review #3, 3/12/94
Chemist's review #4, 3/22/94

REMARKS/COMMENTS:

Method validation package sent to Newark District Office on 3/23/94. Mathod validation was completed by Philadelphia District Laboratory. Based on the laboratory report of 4/6/94, the methodology submitted to the NDA is suitable for regulatory purpose.

CONCLUSIONS & RECOMMENDATIONS:

The methodology is adequate for the manufacture & control of the NDA drug product.

Su C. Tso, Ph.D.
Review Chemist

May 16, 1994

cc: Orig. NDA 20-310
~~HFD-520/Division File~~
HFD-520/SCTso
HFD-520/Joshi
HFD-520/Cook
HFD-520/Bostwick
HFD-520/Soprey
HFD-520/SUPERVISOR/WHDeCamp

OCT 14 1994

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-310 **CHEM.REVIEW #:** 6 **REVIEW DATE:** 8/19/94

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	7/14/94	7/15/94	7/20/94

NAME & ADDRESS OF APPLICANT:

Johnson & Johnson Consumer Products, Inc.
Grandview Road
Skillman, NJ 08558-9418

DRUG PRODUCT NAME

Proprietary:	none
Nonproprietary/USAN:	Ketoconazole
Code Names/#'s:	R41,400 or Medic
Chemical Type:	3
Therapeutic type:	Antifungal

ANDA Suitability Petition/DESI/Patent Status:

US Patent # 4,335,125, 6/15/82
US patent # 4,942,162, 7/17/90

PHARMACOLOGICAL CATEGORY/INDICATION:

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STRENGTHS:	1%
ROUTE OF ADMINISTRATION:	Topical
DISPENSED:	_____ Rx __x__ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

RELATED DOCUMENTS (if applicable):

Chemist's review #1, 5/18/93
Chemist's review #2, 2/1/94, revised 3/9/94
Chemist's review #3, 3/12/94
Chemist's review #4, 3/22/94
Chemist's review #5 5/22/94

REMARKS/COMMENTS:

This amendment updates the stability to support expiry of 24 months.

CONCLUSIONS & RECOMMENDATIONS:

The application is not approval, However the only reason for this conclusion is a lack of statement from Compliance (HFD-324) that the manufacturing facility at is in acceptable GMP compliance.

However, CSO should notify the sponsor to :

1. Investigate the reason for viscosity change for batch 0022P and report the result of investigation.
2. Submit:

   a. Revised stability specifications for and according to real time data.

   b. Revised stability protocol adding control of impurities (known and unknown structure). Limit the total impurities to area% of ketoconazole.

   c. Revised stability protocol and stability specifications in an amendment.

3. Clarify the container size which is to be marketed and provide container/closure description for any new size that is not included in the original application.

4. Provide trade name as soon as possible.

Su C. Tso, Ph.D.
Review Chemist

cc: Orig. NDA 20-310
HFD-540/Division File
HFD-540/SCTso
HFD-540/Bostwick
HFD-540/Joshi
HFD-540/Soprey
HFD-540/Cook
HFD-540/SUPERVISOR/WHDeCamp

5.1

MAR 10 1995

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: **20-310** CHEM.REVIEW #: 7 REVIEW DATE: 3/7/95

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	10/6/94	10/25/94	11/12/94
Amendment	1/6/95	1/9/95	1/18/95
Amendment	1/31/95	2/6/95	2/10/95
Amendment	2/27/95	2/28/95	3/6/95

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Chemist's review #1, 5/18/93
Chemist's review #2, 2/1/94, revised 3/9/94
Chemist's review #3, 3/12/94
Chemist's review #4, 3/22/94
Chemist's review #5, 5/22/94
Chemist's Review #6, 8/19/94
FDA phone: 1/18/95

REMARKS/COMMENTS:

These amendments are the response to the deficiencies from review #6 which were communicated to the sponsor by Rosemary Cook on 8/29/94 by phone.

Trade name "Nizoral A-D" acceptable.

FONSI drafted and submitted to Dr. Vincent on 1/20/95

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from a chemistry standpoint. The recommended expiry will be two years. However the approval letter should be issued after a satisfactory GMP inspection of the manufacturing facility at

In addition, the following should be submitted:

1. Revised EA document in accordance with 21 CFR 25.31a(b)(3),

2. Bottle label should be modified by deleting the word before FD&C Blue No. 1 and adding under Inactive Ingredients.

3. FD&C Blue No 1 is listed as color requiring certificate under 21 CFR 74. A certificate is therefore required.

Su C. Tso, Ph.D.
Review Chemist March 7, 1995

cc: Orig. NDA 20-310
HFD-540/Division File
HFD-540/SCTso
HFD-540/Alum
HFD-540/Cook
HFD-520/Bostwick
HFD-520/Soprey
HFD-540/SUPERVISOR/WHDeCamp 3/9/95

3/10/95

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-310 **CHEM.REVIEW #:** 8 **REVIEW DATE:** 6/21/95

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	3/8/95		
Amendment	3/15/95		
Amendment	3/21/95		

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Chemist's review #3, 3/12/94
Chemist's review #4, 3/22/94
Chemist's review #5, 5/22/94
Chemist's Review #6, 8/19/94
Chemist's review #7, 3/7/95
Enironmental Assessment Review #3, 3/21/95

REMARKS/COMMENTS:

1. Revised EA document in accordance with 21 CFR 25.31a(b)(3) was provided in amendment dated 3/8/95 & 3/15/95. These document was reviewed in EA review #3 dated 3/21/95. This updated EA review and the related memo are included with this report. The EA remains acceptable. FONSI package has been forwarded to Dr. P. Vincent for approval.

2. As requested, bottle label was modified by deleting the word before FD&C Blue No. 1 and adding under Inactive Ingredients. An example of this label is attached in the EA report of 3/21/95.

3. FD&C Blue No 1 is listed as color requiring certificate under 21 CFR 74, A certificate is therefore required. The firm provided the certificate in amendment of 6/21/95 (FDA lots AF5047, 4/26/90; AF8980, 5/28/91; & AF8687, 5/2/91).

4. With regard to the facilities:

was inspected in 3/94, the facility was acceptable. However an recommendation of withhold of approval was advised based on an inspection on 7/4/94. A warning letter was issued to On May 30, 1995, HFD-324 has informed us that the facility is now acceptable. Compliance statement is attached.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from a chemistry standpoint. The recommended expiry will be two years. **THE APPROVAL ACTION MUST BE TAKEN ON OR BEFORE 7/30/95.**

Su C. Tso, Ph.D.
Review Chemist

cc: Orig. NDA 20-310
HFD-540/Division File
HFD-540/SCTso
HFD-540/Alum
HFD-540/Cook
HFD-520/Bostwick
HFD-520/Soprey
HFD-540/SUPERVISOR/WHDeCamp 6/28/95

6/28/95

NDA #: 20-310 CHEM.REVIEW #: 9 REVIEW DATE: 4/29/97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT/BC	3/22/96	3/28/96	3/28/96
AMENDMENT/AL	11/14/96	11/1/96	11/21/96
AMENDMENT/WA	4/4/97	4/8/97	4/10/97
AMENDMENT/BL	4/18/97	4/21/97	4/28/97

NAME & ADDRESS OF APPLICANT: Johnson & Johnson Consumer Products, Inc.
Skillman, NJ 08558-9418

DRUG PRODUCT NAME

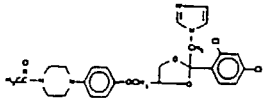
Proprietary: Nizoral A-D
Nonproprietary/USAN:
ketoconazole shampoo
Code Names/#'s: R41,400
Chem.Type/Ther.Class: 3 S

ANDA Suitability Petition/DESI/Patent Status:
N/A

PHARMACOL.CATEGORY/INDICATION: Antifungal Agent

DOSAGE FORM: Solution
STRENGTHS: 1%
ROUTE OF ADMINISTRATION: Topical
DISPENSED: x Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:



Molecular formula: $C_{26}H_{28}Cl_2N_4O_4$
Molecular weight: 531.44

Chemical Name - CAS, USP, USAN, INN
(1) Piperazine, 1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-, cis-

SUPPORTING DOCUMENTS: See Chemist Review #1

RELATED DOCUMENTS (if applicable): See previous Chemist Reviews dated 5/18/93, 3/9/94, 3/12/94, 3/22/94, 5/16/94, 8/19/94, 3/7/95 and 6/21/95. Also, see Agency's approvable letter dated 3/13/96.

REMARKS/COMMENTS:

The applicant responded on 3/22/96 and 11/14/96 to the Agency's approvable letter dated 3/13/96, whereby information on FPL and the remaining EA deficiencies were addressed. This information was reviewed and the following comments are made:

Labeling: Acceptable

The 11/14/96 amendment contains 16 copies of FPL as requested in our 3/22/96 letter. However, the labeling was found not identical as submitted in draft as follows:

Amendment (4/18/97)- FPL was submitted, incorporating the changes stated above. Acceptable.

EA: Acceptable

The original environmental assessment was reviewed and found not acceptable. Our approvable of 3/13/96 conveyed the remaining EA deficiencies. Therefore, the applicant's amendment dated 3/22/96 corrected the remaining EA deficiencies. The EA was reviewed and found acceptable (see EA #4 review dated 4/22/97 and FONSI). Sent to Nancy Sager on 4/22/97 for concurrence. The FONSI was signed by Nancy Sager on 4/25/97.

EER: Acceptable

An EER update (FUR) was requested 4/24/97 via EES. EES memo dated 4/25/97 reported the firms acceptable.

Phase 4 Commitment (4 B): Acceptable

CONCLUSIONS & RECOMMENDATIONS:

The New Drug Application is approved from a manufacturing and controls standpoint.

EER: EES memo dated 4/25/97 reported EER acceptable (see FUR dated 4/24/97).

MV: Philadelphia District Laboratory completed MV; laboratory report dated 4/6/94 found methods suitable for regulatory purposes. Sent to NDA (see Chemist Review #5 dated 5/16/94).

EA: Found acceptable and a FONSI was drafted on 4/22/97; sent to Nancy Sager on 4/22/97 for concurrence. The FONSI was signed by Nancy Sager on 4/25/97.

Labeling: The labeling was found acceptable from a technical standpoint. (See above Comments)

5/8/97

Ernest G. Pappas
Review Chemist

cc: Orig. NDA 20-310
HFD-540/Division File
HFD-540/Pappas
HFD-540/Huene
HFD-540/Nostrandt
HFD-540/Srinivasan
HFD-520/King
HFD-540/Blay
R/D Init by: SUPERVISOR 5/8/97

5/15/97