

This application contains the following items: (Check all that apply)		
1. Index		
2. Labeling (check one)	<input type="checkbox"/> Draft Labeling	<input type="checkbox"/> Final Printed Labeling
3. Summary (21 CFR 314.50 (c))		
4. Chemistry section		
A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)		
B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)		
C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)		
5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)		
6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)		
7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))		
8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)		
9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)		
10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)		
11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)		
12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)		
<input checked="" type="checkbox"/> 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. Establishment description (21 CFR Part 600, if applicable)		
16. Debarment certification (FD&C Act 306 (k)(1))		
17. Field copy certification (21 CFR 314.50 (k) (3))		
18. User Fee Cover Sheet (Form FDA 3397)		
19. OTHER (Specify) Response to		

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. 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.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Kathleen K. Wille</i>	TYPED NAME AND TITLE Kathleen K. Wille, Manager, Regulatory Affairs	DATE 6/15/00
ADDRESS (Street, City, State, and ZIP Code) 199 Grandview Road Skillman, NJ 08558	Telephone Number () 908 674-1625	

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.



Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: June 9, 2000. Number of Pages (including cover sheet) - 2
TO: Kathleen Wille, PhD, Manager, Regulatory Affairs
COMPANY: Johnson and Johnson
FAX #: 908-874-1118

MESSAGE: Re: NDA 21-108 Renova Cream, 0.02%

Please find request for information from clinical.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

cc: NDA 21-108
HFD 540 / DIV FILES
HFD 540 / Luke

1. Please provide all available follow-up information for patient #328, Study J89-024. This patient had facial cellulitis that was possibly therapy related and required hospitalization for IV antibiotics. The patient had post inflammatory hyperpigmentation. Did the hyperpigmentation eventually resolved?
2. Did any women enrolled in the study become pregnant? How many of those women were exposed to Renova 0.02%, and at what point in their pregnancy were they exposed?
3. Please provide information regarding the number of women of child-bearing age enrolled in studies supporting safety for Renova 0.02% and the number exposed to Renova 0.02%.

APPEARS THIS WAY
ON ORIGINAL

JUN 7 - 2000

Jonathan Wilkin, M.D.
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-540
Attn: DOCUMENT CONTROL ROOM N115
9201 Corporate Boulevard
Rockville, MD 20850

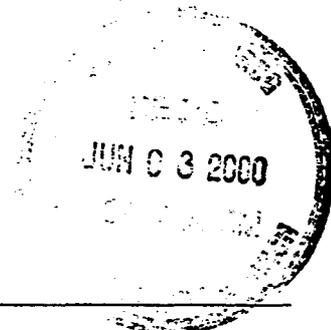
NDA 21-108

RENOVA®
(tretinoin emollient cream) 0.02%

FDA request for information:
Minor amendment
to a pending application

Attention: Olga Cintron, Project Manager

RENOVA® (tretinoin emollient cream) 0.02%



Dear Dr. Wilkin:

Reference This is in response to the telephone conference calls of 5/24/00 and 6/2/00 between FDA and Johnson & Johnson Consumer Companies, Inc. At the conclusion of the two calls, FDA requested that NDA 21-108 be amended with the following information:

- the marketing/regulatory history of _____
- information on the worldwide experience with _____ and
- details of the post hoc statistical analysis showing the comparability of the fragranced and unfragranced formulations of TEC II 0.05% in the cumulative irritation study K90-016.

Purpose of this submission This submission amends NDA 21-108 with the requested information on the fragrance. _____, which is the fragrance in the formulation under review.

Contents of this submission The marketing regulatory history and the worldwide experience of _____ are described below. The statistical analysis of K90-016 can be found attached.

Continued on next page

BEST POSSIBLE COPY

JUN 7 - 2000

**Marketing /
regulatory
history**

In the original RENOVA (tretinoin emollient cream) 0.05% NDA 19-963 (approved 12/29/85), _____ was present in the initially approved formulation at _____, which is 2 1/2 times higher than the level requested in the formulation under review in NDA 21-108 at _____

After approximately two years of marketing experience, the fragrance in RENOVA 0.05% was reduced from _____ to _____. Consumer feedback indicated that the product was too highly perfumed. The FDA was notified by an annual report, and the change was effective 2/28/98.

**_____ in
RENOVA
0.02%**

Johnson & Johnson Consumer Companies, Inc. tested the unfragranced formulation of RENOVA 0.02% in the pivotal trials of NDA 21-108. Based on our knowledge of the product at the start of the phase III trials, _____ However, based on comments from consumer sensory evaluations, the unfragranced TEC II formulation was found to be cosmetically unacceptable; thus, the decision was made to request approval of the fragranced formulation of RENOVA 0.02% in NDA 21-108.

**Worldwide use
of _____**

J&J have an agreement with _____ for exclusive rights to _____ and it is the RENOVA fragrance.

RENOVA 0.05% is marketed in the following countries worldwide:

- Argentina, Australia, Belgium, Bolivia, Brazil, Canada, Chile, Colombia, Denmark, Ecuador, Finland, France, Germany, Greece, Ireland, Malaysia, Mexico, New Zealand, Norway, Paraguay, Peru, Philippines, Portugal, Russia, South Africa, Spain, Sweden, Thailand, United Kingdom, and Uruguay.

The formulation for RENOVA 0.05% was not changed outside of the US. and _____ is at _____ % ex-US.

_____ is not currently marketed in any other J&J consumer products.

Continued on next page

**APPEARS THIS WAY
ON ORIGINAL**

JUN 7 - 2000

K90-016

Study K90-016 was conducted to evaluate the cumulative irritation potential of

- TEC-II vehicle without fragrance,
- TEC-II 0.05% with fragrance,
- TEC-II 0.05% without fragrance,
- TEC-II 0.02% with fragrance, and
- TEC-II vehicle with fragrance.

A standard protocol to evaluate irritation potential, a cumulative irritation study yields ordinal results. To further evaluate the comparability of the fragranced and unfragranced formulations, an additional statistical analysis was performed post hoc and can be found in the attachment.

The additional analysis further demonstrates the comparable irritation potential of the fragranced and unfragranced formulations of TEC II.

Questions

Should you have any questions, please contact me.

Again, thank you for the opportunity to discuss this information request in the 6/2/00 conference call. The agency's input helped J&J provide the agency with the appropriate information promptly.

Directly	908-874-1625
FDA only phone number	908-874-1700
Fax	908-874-1118
e-mail	Kwille1@cpcus.jnj.com

Sincerely,



Kathleen K. Wille, Ph.D.
Manager, Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED:

July 27, 2000

DUE DATE:

August 13, 2000

OPDRA CONSULT #: 00-0196

TO:

Jonathan Wilkin, M.D.
 Director, Division of Dermatologic and Dental Drug Products
 HFD-540

THROUGH:

Olga Cintron, Project Manager
 HFD-540

PRODUCT NAME:

Renova
 (Tretinoin Emollient Cream) 0.02%

MANUFACTURER: Ortho Dermatological

NDA #: 21-108

SAFETY EVALUATOR: Carol Holquist, R.Ph.

SUMMARY: In response to a consult from the Division of Dermatologic and Dental Drug Products (HFD-540), OPDRA reviewed the proposed container labels and carton labeling of Renova, for possible interventions that may help minimize medication errors.

OPDRA RECOMMENDATION:

OPDRA recommends the Division request Ortho Dermatological to revise their labels and labeling accordingly. (See review)

[JS] 8/4/2000

Jerry Phillips, R.Ph.
 Associate Director for Medication Error Prevention
 Office of Post-Marketing Drug Risk Assessment
 Phone: (301) 827-3242
 Fax: (301) 480-8173

[JS] 8/4/00

Pete Honig, M.D.
 Director
 Office of Post-Marketing Drug Risk Assessment
 Center for Drug Evaluation and Research
 Food and Drug Administration

**APPEARS THIS WAY
 ON ORIGINAL**

**Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B-03
Center for Drug Evaluation and Research**

Labels and Labeling Safety Review

DATE OF REVIEW: August 2, 2000
NDA: 21-108
NAME OF DRUG: Renova (Tretinoin Emollient Cream) 0.02%
NDA HOLDER: Ortho Dermatological

I. INTRODUCTION

This consult is in response to a July 24, 2000, request from the Division of Dermatologic and Dental Drug Products (HFD-540), to review the container labels and carton labeling of Renova Cream for interventions that might minimize medication errors.

BACKGROUND

Renova was approved on December 29, 1995, under NDA 19-963 as a 0.05% topical cream. NDA 21-108 was submitted on August 31, 1999, for a new formulation and strength of the cream with the same active ingredient. The Division requested OPDRA review the proposed name, Renova, for this new application. On March 5, 2000, OPDRA forwarded the Division an e-mail in which we stated "OPDRA has no objections and encourages the firms proposal to utilize the same name, Renova, for a new strength of the same active ingredient".

PRODUCT INFORMATION

Renova is indicated as an adjunctive agent for use in the mitigation (palliation) of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin. The cream will be available in a 2 gram physician sample size and 40 gram tube.

**APPEARS THIS WAY
ON ORIGINAL**

II. RISK ASSESSMENT

In the review of the container labels and carton labeling of Renova, OPDRA has attempted to focus on safety issues relating to possible medication errors. OPDRA has reviewed the current labels and labeling and has identified a few areas of possible improvement, which might minimize potential user error (see below).

A. CONTAINER LABELS (2 g and 40 g)

- 1. The drug name and strength should have the greatest prominence on the labels and labeling. We suggest increasing the prominence of the product strength.**
- 2. We recommend differentiating the two product strengths (0.05% and 0.02%), with the use of boxing, contrasting colors or some other means.**

B. CARTON LABELING (1 x 40 g)

- 1. See above comments.**
- 2. We recommend relocating the "Rx only" statement to the principal display panel.**
- 3. We note the firm has included the statements "New Strength" and "New Formula". These statements should only be utilized for a period not to exceed six months.**

**APPEARS THIS WAY
ON ORIGINAL**

III. RECOMMENDATIONS

OPDRA recommends the above labeling revisions, which might lead, to safer use of the product.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Carol Holquist at (301) 827-3244.

[/S/] 8/2/00

Carol Holquist, RPh
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

[/S/]

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

**APPEARS THIS WAY
ON ORIGINAL**

CC: NDA 21-108
HFD-540; Division Files/Olga Cintron, Project Manager
HFD-540; Jonathan Wilkin, Division Director
HFD-400; Jerry Phillips, Associate Director, OPDRA

Electronic only cc:

HFD-002; Murray Lumpkin, Deputy Center Director for Review Management
HFD-400; Peter Honig, Director, OPDRA
HFD-430; Patrick Guinn, Project Manager, OPDRA
HFD-400; Sammie Beam, Project Manager, OPDRA

\\CDFDA\OPDRA\OPDRA00\HOLQUIST\00-0196RENOVA.DOC

**APPEARS THIS WAY
ON ORIGINAL**



Memorandum

Date 18 July, 2000

From William C. Timmer, Ph.D.; HFD-540

Subject Labeling Changes to NDA 21-108, RENOVA®, 0.02%
Addendum to NDA 21-108 Chemistry Review #1, dated 30-MAY-00

To Wilson H. DeCamp, Ph.D.

JUL 18 2000

At the NDA 21-108 labeling meeting on 13-JUL-00, it was noted that the sponsors's proposed label was not consistent with the USP. In particular, the USP indicates that the inactives should be stated in alphabetical order.

Accordingly, the purpose of this memo is to make a post-labeling meeting correction to label of NDA 20-108. The correction, attached, now lists the inactives in alphabetical order.

In addition, the following information should be communicated to the sponsor regarding the tube and carton artwork:

The artwork is acceptable; however, the storage statement on the carton must be changed to be consistent with the FDA-approved storage statement in the label.

[/S/]

William C. Timmer, Ph.D.

Original NDA 21-108

HFD-540/Division File
HFD-540/DD/JWilkin
HFD-540/Chem/WCTimmer
HFD-540/ChemTL/WHDeCamp
HFD-540/PM/OCintron

[/S/] 7/13/2000 ✓

File Name: nda21108_fnl_lbl_memo.doc



NDA ORIG AMENDMENT JUL 17 2000

Jonathan Wilkin, M.D.
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-540
Attn: DOCUMENT CONTROL ROOM N115
9201 Corporate Boulevard
Rockville, MD 20850

NDA 21-108

RENOVA®
(tretinoin emollient cream) 0.02%

Amendment to a pending
application

Attention: Olga Cintron, Project Manager

RENOVA® (tretinoin emollient cream) 0.02%

[/S/]

Dear Dr. Wilkin:

Purpose of this submission The purpose of this amendment is to provide additional information requested by the medical reviewer on July 14, 2000.

Contents of this submission In this submission, you will find:

- Form FDA 3454 for clinical trial J89-045
- A discussion of the relationship of the _____ dosing system and the instructions to use a "pea-sized" amount.

Financial Disclosure Johnson & Johnson Consumer Companies, Inc. is providing Form FDA 3454, a certification for the investigators of clinical study J89-045 to supplement the statement found in Volume 1.1, page 019 00001. This attests to the absence of financial interests and arrangements, as described in 21CFR54.

All clinical studies submitted in NDA 21-108 concluded prior to the end of 1994; this was well before implementation of the financial disclosure rule.

BEST POSSIBLE COPY

ORIGINAL

JUL 17 2000

Dosing

The medical reviewer requested more information describing the relationship between 0.25 grams and a "pea-sized" amount. because the clinical trials utilized a dosing system that delivered approximately 0.25 grams of material per use, and the instructions in the package insert state that a "pea-sized" amount should be used.

[

Questions

Should you have any questions, please contact me.

Directly	908-874-1625
Fax	908-874-1118

Sincerely,



Kathleen K. Wille, Ph.D.
Manager, Regulatory Affairs

BEST POSSIBLE COPY

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

100 Cintron

Food and Drug Administration
Rockville MD 20857

JUL 12 2000

[]

Dear _____

Between November 22 and 25, 1999, Mr. Fernando Chavez, representing the Food and Drug Administration (FDA), met with you and your staff to review your conduct of a clinical study (protocol # J89-024) of the investigational drug Renova (tretinoin emollient cream 0.02%), performed for R. W Johnson Pharmaceutical Research Institute. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Chavez during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me by letter at the address given below.

Sincerely yours,

[/S/]

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

APPEARS THIS WAY
ON ORIGINAL

FEI: 2082661

Field Classification: NAI

Headquarters Classification:

1) NAI

2) VAI-no response required

3) VAI-response requested

cc:

HFA-224

HFD-540 Review Div. Dir.

HFD-540/ MO/Luke

HFD-540/ PM/Cintron

HFD-540/Doc. Rm. NDA # 21-108

HFD-45 r/f

HFD-47 c/r/s GCP file# 10107

HFD-47/Carreras

HFD-47/Currier

HFR-PA250/Kozick

HFR-PA2565/Koller

HFR-PA2540/Chavez

Edited: AEH

Final:mgk 7/12/00

**APPEARS THIS WAY
ON ORIGINAL**

Note to Rev. Div. M.O.

This investigator enrolled 60 subjects in the study. Fifty-three subjects completed the study. The field investigator examined 20 records. Data audit did not reveal any significant discrepancies and/or deficiencies in the conduct of the study. The data collected from this site appears acceptable.

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELEPHONE CONVERSATION

DATE: May 23, 2000.

DRUG: Renova (tretinoin emollient cream), 0.02%

NDA: 21-108

SPONSOR: Dr. Judit Nyirady
Dr. Kathleen Wille, Manager, Regulatory Affairs
Johnson and Johnson Consumer Companies, Inc.

FDA: Dr. Marty Okun, Clinical Team Leader, DDDDP, HFD-540
Dr. Markham Luke, Medical Officer, DDDDP, HFD-540
Olga Cintron, Project Manager, DDDDP, HFD-540

Subject: Request for Information

/S/ 4/14/00

The Sponsor was contacted to request additional information with the intent to address the Agency's concerns regarding the use of the fragrance on the Renova 0.02% formulation. The Agency indicated that the Phase 3 studies J89-024, J89-025, and J89-045 were conducted using the unperfumed drug product. Study K90-016 compared irritation of the perfumed and unperfumed TEC II, 0.05% with what appeared to be a slight increase in irritation from the perfumed formulation. No data was available comparing the TEC II 0.025% perfumed and unperfumed formulations. Information is needed to assess the safety vs. benefit of addition of fragrance to the formulation used in Phase 3 testing. Any relative decrease in safety due to addition of fragrance needs to be weighed against the potential benefit of adding fragrance.

The following information was requested from the Sponsor to address this issue:

The Sponsor should submit an explanation for the use of the perfumed formulation

formulation, the Sponsor should provide a compelling argument for the use of the perfumed formulation and that there is no safety concern that will affect the public health. Such may be evidenced by: a literature search, an analysis of the significance of the Phase 1 cumulative irritation study (K90-016), and a sense of the worldwide use of the fragrance.

The Sponsor understood the issue at hand. The Sponsor indicated that they will work to address the above mentioned issues.

The conversation ended amicably.

cc:

NDA 21-108

HFD-540/Div Files

HFD-540/Luke (concurrence 6/13/00)

HFD-540/Okun (concurrence 6/14/00)

HFD/540/Wilkin

HFD/540/Decamp

HFD-540/Timmer

HFD-540/Nostrandt

HFD-540/Jacobs

HFD-880/Ghosh

HFD-880/Bashaw

HFD-725/Thomson

HFD-725/Al-Osh

HFD-540/Cintron

**APPEARS THIS WAY
ON ORIGINAL**

AMENDMENT

Bm

APR 27 2000



Jonathan Wilkin, M.D.
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-540
Attn: DOCUMENT CONTROL ROOM N115
9201 Corporate Boulevard
Rockville, MD 20850

NDA 21-108

RENOVA®
(tretinoin emollient cream) 0.02%

FDA request for information:
Minor amendment
to a pending application

Attention: Olga Cintron, Project Manager

RENOVA® (tretinoin emollient cream) 0.02%

Dear Dr. Wilkin;

Reference

This is in reference to our telephone conference call of April 13, 2000. The agency requested an additional analysis of the clinical signs for the controlled clinical studies J89-024, J89-025, J89-045, K90-011, and L91-026.

In addition, we reference the sponsor fax of April 18, 2000 and the two FDA faxes of April 20, 2000, one clarifying the requested data analysis, the other requesting clinical information.

Requested analysis

For the modified intent-to-treat population, exclude patients who had a baseline value=0 (none) or 1 in the intent-to-treat population. Generate for both populations p-values (two-sided) for analysis of change from baseline to double-blind endpoint using ANOVA (row mean score) stratified by investigator. Display 95% confidence intervals on the difference in treatment group mean changes from baseline. Use Holm's modified Bonferroni to adjust for multiple comparisons. The agency agreed that submission of this information by April 28, 2000 would not extend the review period.

**Clinical
information
request**

The agency asked J&J the following questions in the fax of April 20, 2000:

- 1) Please provide further information regarding the proposed indication of _____ to explain why this is a drug product indication.
- 2) The Sponsor is referred to 21CFR201.57(c) regarding approved indication appropriate for labeling and should address the relevance of _____ in this regard.
- 3) Any literature or textbook reference to _____ would be appreciated, specifically addressing incidence, and current treatment.
- 4) The Sponsor should indicate how it proposes to address labeling so as to diminish any possible confusion between _____

**Contents of this
submission**

This submission provides the requested analyses and supportive documentation. The results for study L91-026 are presented in separate tables to emphasize the difference in study population; study L91-026 was conducted in non-Caucasians.

Holm's adjusted p-values are presented. They were adjusted within each study to take into account the six simultaneous comparisons of the clinical signs; thus, they represent an extremely conservative test.

The clinical information request is addressed below.

**Response to
clinical
information
request**

The term _____ is a well-recognized descriptive term for one of the primary clinical signs of photodamage. Refer to the references included in this submission that define _____ and detail its current treatment. Subjects with _____ present with a _____ tint to their skin on the photo exposed areas accompanied by other clinical signs of photodamage like fine _____ wrinkles, mottled hyperpigmentation, tactile roughness, and laxity.

**APPEARS THIS WAY
ON ORIGINAL**

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Questions

Should you have any questions, please contact me.

Directly	908-874-1625
FDA only phone number	908-874-1700
Fax	908-874-1118
e-mail	Kwille1@cpcus.jnj.com

Sincerely,



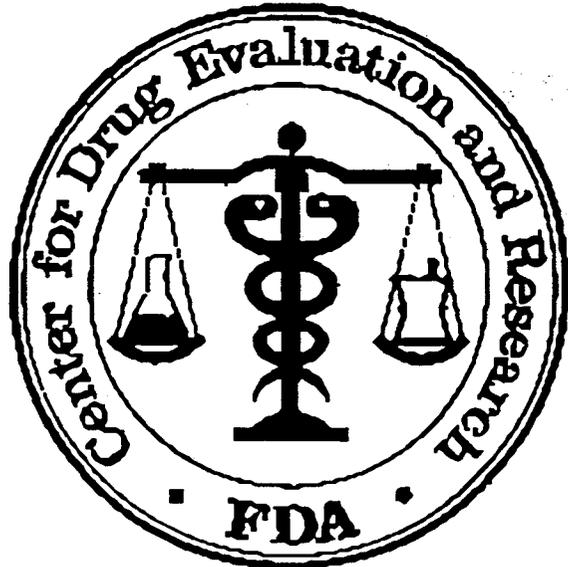
Kathleen K. Wille, Ph.D.
Manager, Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

FOOD AND DRUG ADMINISTRATION
DIVISION OF DERMATOLOGIC AND
DENTAL DRUG PRODUCTS
HFD-540
9201 CORPORATE BLVD.
ROCKVILLE, MARYLAND 20850

DATE: 4/20/06



TO:

Name Arthur Wilkin
Fax No. 908 874-1118
Phone No. _____
Location J+S

FROM:

Name MARY JEAN KOZMA-FORNARO
Fax No. 301 827-2075/2091
Phone No. 301 827-2020

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copy, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

Comments:

NDA 21108
① Clarification of multiple comparison method
② Clinical Information Request

NDA 21108
HFD 540 21108
HFD 5401 Clinical
" 1 Lake
1 Thomson

Clinical Request for Information:

- 1) Please provide further information regarding the proposed indication of _____ to explain why this is a drug product indication.
 - 2) The Sponsor is referred to 21 CFR 201.57 (c) regarding approved indications appropriate for labeling and should address the relevance of _____ in this regard.
 - 3) Any literature or textbook references to _____ would be appreciated, specifically addressing incidence, and current treatment.
 - 4) The Sponsor should indicate how it proposes to address labeling so as to diminish any possible confusion between : _____
-

Clarification of Fax 4/20/00 on multiple comparisons of each study:

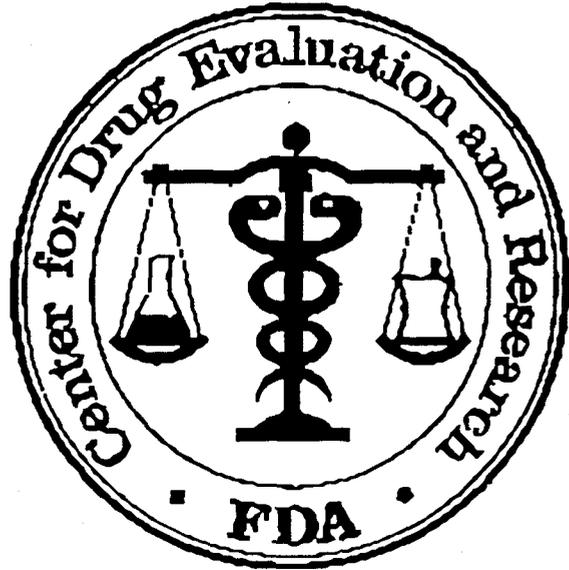
Please use Holm's modified Bonferroni (i.e. starting with small p-values)

**APPEARS THIS WAY
ON ORIGINAL**

Olya

FOOD AND DRUG ADMINISTRATION
DIVISION OF DERMATOLOGIC AND
DENTAL DRUG PRODUCTS
HFD-540
9201 CORPORATE BLVD.
ROCKVILLE, MARYLAND 20850

DATE: *4/20/00*



TO:

Name *Kathleen Wile*

Fax No. *908 874-1118*

Phone No. _____

Location *J+J*

FROM:

Name MARY JEAN KOZMA-FORNARO

Fax No. 301 827-2075/2091

Phone No. 301 827-2020

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copy, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

Comments:

*NDA 21108
Response to fax of 4/18/00*

[*/S/*]

CC: *NDA 21108
HFD540 DIV FILE
HFD540 / CENTRAL
HFD540 / Thomson
HFD540 / Alask*

NDA 21-108 Renova (tretinoin emollient cream) 0.02%

Reference Fax of 4/18/00 with sponsor interpretation of medical and statistical request of 4/13/00.

Primary Analysis:

- For the modified intent-to-treat population, exclude patients who had a baseline value=0 (none) or 1 in the ITT population. Generate for both ITT and MITT populations p-values (two sided) for analysis of change from baseline to Double-Blind Endpoint using ANOVA (row mean score) stratified by investigator. Display 95% confidence intervals on the difference in treatment group mean changes from baseline.
- Adjust for multiple comparisons within each study.
- We did not request any of the "secondary analyses".
- April 28, 2000 submission is fine. No extension of clock.

**APPEARS THIS WAY
ON ORIGINAL**

APR 4 2000

Jonathan Wilkin, M.D.
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-540
Attn: DOCUMENT CONTROL ROOM N115
9201 Corporate Boulevard
Rockville, MD 20850

NDA 21-108

RENOVA®
(tretinoin emollient cream) 0.02%

FDA request for information:
Electronic file of labeling

Attention: Olga Cintron, Project Manager

RENOVA® (tretinoin emollient cream) 0.02%



Dear Dr. Wilkin;

Purpose of this submission

On April 3, 2000, Johnson & Johnson Consumer Companies, Inc. received a request from the agency for an electronic file of the labeling submitted in NDA 21-108. With this submission, we are providing you with a copy of the labeling contained in that NDA.

Targeted action date

Johnson & Johnson Consumer Companies, Inc. would like to work interactively with the agency so that the labeling can be finalized on the tentative action date and an approval letter could be issued. As we enter into discussions on the labeling, we would like to understand the agency's position as thoroughly as possible, so that we can productively address any concerns. We will make ourselves available for a conference call or a meeting at your earliest convenience.

Enclosures

Enclosed you will find a diskette containing a Microsoft Word copy of the labeling in submitted in the NDA.

Continued on next page

**APPEARS THIS WAY
ON ORIGINAL**

ORIGINAL

APR 4 2000

Questions

Should you have any questions, please contact me.

Directly	908-874-1625
FDA only phone number	908-874-1700
Fax	908-874-1118
e-mail	Kwille1@cpcus.jnj.com

Sincerely,



Kathleen K. Wille, Ph.D.
Manager, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

HFD-540
Cintron

Food and Drug Administration
Rockville MD 20857

MAR 31 2000

[]

Dear _____

Between December 7 and 13, 1999, Ms. Stephanie E. Hubbard, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol # J89-025) of the investigational drug Renova (tretinoin emollient cream 0.02%) performed for R. W. Johnson Pharmaceutical Research Institute. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Ms. Hubbard discussed with you her inspectional observations which included: a) subject # 225 was enrolled despite the use of anti-depressants; b) not performing pregnancy test on subjects # 241 and #260 prior to enrollment; and c) visit schedule deviations were observed for subjects 204, 241, and 259. We acknowledge your responses and your promise to make corrections/changes in your procedures to ensure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Hubbard during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301)594-1032.

Sincerely,

[/s/]

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

APPEARS THIS WAY
ON ORIGINAL

CFN: _____

Field Classification: NAI

Headquarters Classification:

1) NAI

2) VAI-no response required

3) VAI-response requested

Deficiencies noted:

inadequate consent form

inadequate drug accountability records

failure to adhere to protocol

inadequate records

failure to report ADRS in the case report form

Other (specify)

cc:

HFA-224

HFD-540 Review Div. Dir.

HFD-540/ MO/Luke

HFD-540/ PM/Cintron

HFD-540/Doc. Rm. NDA # 21-108

HFD-45 r/f

HFD-47 c/r/s GCP file# 9953

HFD-47/Carreras/Currier

HFR-SE150/Kline

HFR-SE150/Todd

HFR-SE150/Hubbard

**APPEARS THIS WAY
ON ORIGINAL**

O:\JAC\21-108. _____

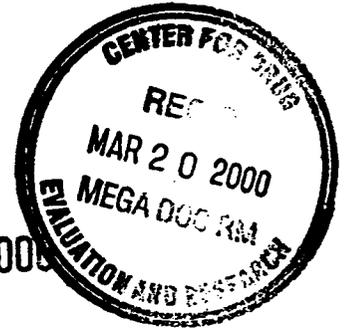
r/d:1/7/00

f/c:mb:3/31/00

Note to Rev. Div. M.O.

This investigator enrolled 60 subjects in the study. Fifty-six subjects completed the study. Four subjects were lost to follow up. The D.O. investigator examined 8 subject records. Data audit did not reveal any significant discrepancies and/or deficiencies in the conduct of the study. The data collected from this site appears acceptable.

Johnson & Johnson
CONSUMER COMPANIES, INC.



MAR 17 2000

Jonathan Wilkin, M.D.
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-540
Attn: DOCUMENT CONTROL ROOM N115
9201 Corporate Boulevard
Rockville, MD 20850

NDA 21-108

RENOVA®
(tretinoin emollient cream) 0.02%

FDA request for information:
Minor amendment
to a pending application

Attention: Olga Cintron, Project Manager

NDA ORIG [unclear]

RENOVA® (tretinoin emollient cream) 0.02%

[/S/]

Dear Dr. Wilkin;

Reference:

This is in reference to a request for information from the medical officer dated February 7, 2000. The items requested were:

- An electronic copy of the Integrated Summary of Safety Data (Volume 1.73) ✓
- To integrate the safety data from the studies J89-022, J89-023, and J89-033 (submitted as an amendment October 25, 1999) with those in the original NDA.
- An electronic copy of the Clinical Data/Statistical Analysis section (Volume 1.2), and ✓
- An electronic copy of the summaries of each of the studies submitted to this NDA.

On February 29, 2000 all requested items were submitted to the Agency with the exception of the amendment integrating the safety data from the studies J89-022, J89-023, and J89-033. ✓

BEST POSSIBLE COPY

ORIGINAL

MAR 17 2000

Purpose of this submission

This submission provides an amendment to Item 8, Volume 1.73 of the NDA, integrating the safety information from the studies submitted with the October 25, 1999 amendment. This amendment is based on a new pool of patients, summarizing the patients' safety data obtained from studies J89-022, J89-023, and J89-033.

Contents of this submission

Enclosed you will find an amendment to the Integrated Summary of Safety that summarizes the safety data obtained from studies J89-022, J89-023, and J89-033.

In addition, the studies J89-035 and K90-010 are discussed briefly for completeness and to ensure full disclosure. J89-035 was a discontinued study in non-Caucasians; biopsies, which were previously thought lost, have been recovered and read. The histology results were unremarkable and did not reveal any safety concerns. K90-010 was a regression study in which no active treatment was administered.

Because these provide safety data for a concentration of a formulation for which we have not requested market approval, the Benefit/Risk Summary (Item 3) will not change. J&J has also reviewed the draft labeling submitted with the original application, and we propose no changes to the draft labeling (Item 2) based upon the safety information obtained from these studies.

Electronic files

Enclosed you will find a diskette with an electronic copy of this amendment to the Integrated Summary of Safety.

Questions

Should you have any questions, please contact me.

Directly	908-874-1625
FDA only phone number	908-874-1700
Fax	908-874-1118
e-mail	Kwille1@cpcus.jnj.com

Sincerely,



Kathleen K. Wille, Ph.D.
Manager, Regulatory Affairs

BEST POSSIBLE COPY

FEB 29 2000

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-540
Attn: DOCUMENT CONTROL ROOM N115
9201 Corporate Boulevard
Rockville, MD 20850

NDA 21-108

RENOVA®
(tretinoin emollient cream) 0.02%

FDA request for information:
Minor amendment
to a pending application

Attention: Olga Cintron, Project Manager

RENOVA® (tretinoin emollient cream) 0.02%

[S/]

Dear Dr. Wilkin:

Reference:

This is in reference to a request for information from the medical officer dated February 7, 2000. The items requested were:

- An electronic copy of the Integrated Summary of Safety Data (Volume 1.73)
- To integrate the safety data from the studies J89-022, J89-023, and J89-033 (submitted as an amendment October 25, 1999) with those in the original NDA.
- An electronic copy of the Clinical Data/Statistical Analysis section (Volume 1.2), and
- An electronic copy of the summaries of each of the studies submitted to this NDA.

Electronic Files:

Three diskettes are provided with zipped files. These contain an electronic copy of the Integrated Summary of Safety Data (Volume 1.73), an electronic copy of the Clinical Data/Statistical Analysis section (Volume 1.2), and available electronic copies of the study summaries submitted to this NDA. A description of the contents of the diskettes can be found in Table 1.

BEST POSSIBLE COPY

ORIGINAL

FEB 29 2000

We apologize that we can not provide electronic files for all study summaries; some of the older, Phase I study reports are not available electronically. These studies are listed in Table 2.

**TEC II 0.05%
Study Reports**

On October 25, 1999, Johnson & Johnson Consumer Companies, Inc. (J&J) submitted study synopses for the studies: J89-022, J89-023, J89-033, J89-035, and K90-10. The first four were double-blind studies to evaluate the safety and efficacy of TEC-II 0.05%. The fifth study was a regression study, and no study drug was administered.

To ensure that the Medical Reviewer has all available information, we are providing full reports for each of the study synopses submitted in the October 25, 1999 amendment, as well as electronic copies of the study summaries.

In addition to the Division's request for information, J&J is amending Item 12 of the RENOVA 0.02% NDA 21-108. This is to incorporate the additional case report forms for the patients who died/discontinued therapy due to an adverse event for the five studies of the October 25, 1999 amendment (J89-022, J89-023, J89-033, J89-035, and K90-010).

**Amended ISS
to follow under
separate cover**

As discussed with Ms. Cintron, J&J will submit an amendment to Item 8, Volume 1.73 of the NDA, integrating the safety information from the studies submitted with the October 25, 1999 amendment as soon as it is available. This amendment will be based on a new pool of patients (pool 5), summarizing the patients' safety data obtained from studies J89-022, J89-023, and J89-033.

In addition, the studies J89-035 and K90-010 will be discussed briefly for completeness and to ensure full disclosure. J89-035 was a discontinued study in non-Caucasians; biopsies, which were previously thought lost, have been recovered and read. The histology results, which will be discussed in more detail in the amendment to the ISS, were unremarkable and did not reveal any safety concerns. K90-010 was a regression study in which no active treatment was administered.

Because these provide safety data for a concentration of a formulation for which we have not requested market approval, the Benefit/Risk Summary (Item 3) will not change. J&J has also reviewed the draft labeling submitted with the original application, and we propose no changes to the draft labeling (Item 2) based upon the safety information obtained from these studies.

BEST POSSIBLE COPY

FEB 29 2000

In summary

The amended ISS will be submitted as soon as possible. All other requested information has been provided to the Division. J&J has also provided full final study reports for the five studies of the October 25, 1999 amendment to help facilitate the NDA review.

Questions

Should you have any questions, please contact me.

Directly	908-874-1625
FDA only phone number	908-874-1700
Fax	908-874-1118
e-mail	Kwille1@cpcus.jnj.com

Sincerely,



Kathleen K. Wille, Ph.D.
Manager, Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELEPHONE CONVERSATION

FEB 25 2000

DATE: October 6, 1999.

DRUG: Renova (tretinoin emollient cream), 0.02%

NDA: 21-108

SPONSOR: Johnson and Johnson Consumer Companies, Inc.
Paul Manley, Worldwide Director, Regulatory Affairs
Kathleen Wille, Regulatory Affairs

FDA: Dr. Jonathan Wilkin, Director, DDDDP, HFD-540
Olga Cintron, Project Manager, DDDDP, HFD-540

Subject: Potential Fileability Issue for NDA 21-108

[1512-25100
2/22/00

The Sponsor was contacted to inform them that a compact disk presumably containing the SAS data sets was being returned to the Sponsor via overnight mail. The information contained does not respond to the FDA previous request regarding the SAS data sets.

During this conversation, the potential fileability issue relayed to the Sponsor on 10/5/99 was further clarified. The Agency indicated that the rationale behind the Agency's request for additional comparative information between the approved formulation and the new formulation is that it was very difficult to identify, without comparative data, a new concentration of active in a particular dosage form as a different product from another concentration of the same active in the same dosage form. There are no quantitative rules that would assure that halving the concentration of the active would render a product with different performance. Since the range of concentrations varies gradually from the maximum amount that can be manufactured down to a limit approaching zero, the number of potential products could be very large without attention to dose-ranging principles and direct comparisons of clinical endpoints of efficacy and safety.

The Sponsor indicated that direct comparative studies have not been performed using Renova 0.02%. The Sponsor indicated that they will provide a rationale for the use of the Renova 0.02% and will identify parts of the NDA that may help address the FDA concerns.

Conversation ended amicably.

APPEARS THIS WAY
ON ORIGINAL

cc:
NDA 21-108
HFD-540/Div Files
HFD-540/Cintron



Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: February 7, 2000. Number of Pages (including cover sheet) - 1

TO: Kathleen Wille, Ph.D., Manager, Regulatory Affairs
COMPANY: Johnson and Johnson Consumer Products, Inc.
FAX #: 908-874-1118

MESSAGE: RE: NDA 21-108 Renova, 0.02%

Medical Officer's Request for Information:

Please forward an electronic copy of the Integrated Summary of Safety Data (Volume 1.73)

Please integrate safety data from the studies J89-022, J89-023, and J89-033 (submitted as an amendment) with those in the original NDA. This was not provided in the safety update.

Please forward an electronic copy of the Clinical Data/Statistical Analysis section (Volume 1.2). An electronic copy of the summaries of each of the studies submitted to this NDA would facilitate review.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

**APPEARS THIS WAY
ON ORIGINAL**

cc: NDA 21-108

HFD-540/DIV FILES

HFD 540/Lake

HFD 540/OKun



HFD-540

Clinton

Food and Drug Administration
Rockville MD 20857

FEB 4 2000

[]

Dear _____

Between December 6 and 7, 1999, Ms. Stephanie E. Hubbard, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol # J89-024) of the investigational drug Renova (tretinoin emollient cream 0.02%), performed for R. W. Johnson Pharmaceutical Research Institute. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Hubbard during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301)594-1032.

Sincerely yours,

[/S/]

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

**APPEARS THIS WAY
ON ORIGINAL**

Page 2 - _____

CFN: _____

Field Classification: NAI

Headquarters Classification:

1) NAI

2) VAI-no response required

3) VAI-response requested

cc:

HFA-224

HFD-540 Review Div. Dir.

HFD-540/ MO/Luke

HFD-540/ PM/Cintron

HFD-540/Doc. Rm. NDA # 21-108

HFD-45 r/f

HFD-47 c/r/s GCP file# 1454

HFD-47/Carreras

HFD-47/Currier

HFR-SE150/Kline

HFR-SE150/Todd

HFR-SE150/Hubbard

**APPEARS THIS WAY
ON ORIGINAL**

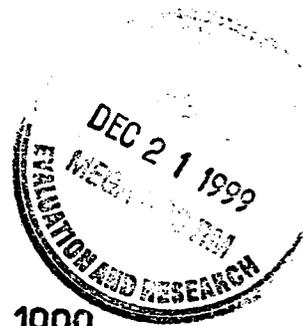
Note to Rev. Div. M.O.

This investigator enrolled 60 subjects in the study. Fifty five subjects completed the study. D.O. investigator examined 10 subject records. Data audit did not reveal any significant discrepancies and/or deficiencies in the conduct of the study. The data collected from this site appears acceptable.

Johnson & Johnson
CONSUMER COMPANIES, INC.

34

NDA ORIG AMENDMENT



DEC 20 1999

Jonathan Wilkin, M.D.
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-540
Attn: DOCUMENT CONTROL ROOM N115
9201 Corporate Boulevard
Rockville, MD 20850

NDA 21-108

RENOVA®
(tretinoin emollient cream) 0.02%

Amendment to a pending
Application: 120 Day Safety
Update Report

Attention: Olga Cintron, Project Manager

Dear Dr. Wilkin;

Reference: Pursuant to 21 CFR 314.50(d)(5)(vi)(b), Johnson & Johnson Consumer Companies, Inc. is updating the safety information submitted in NDA 21-108 on August 31, 1999. The initial submission can be found in volume 1.73 on page 008 22888. This submission fulfills the requirement to submit an update to the safety information four months after the initial submission.

Adverse events in clinical trials There are no clinical trials in progress using the TEC II; therefore, there is no update to this information.

Adverse events from foreign sources TEC II is not marketed in any other country; therefore, there are no adverse events from foreign sources to report.

Annual Report to the IND The annual report to IND ~~was~~ submitted November 3, 1999 for the reporting period May 1, 1998 - April 30, 1999. There were no IND safety reports.

Continued on next page

BEST POSSIBLE COPY ORIGINAL

DEC 20 1999

**Post-marketing
adverse events**

Johnson & Johnson Consumer Companies, Inc. have submitted periodic reports to the agency for the tretinoin products listed in the table below.

NDA	Product	Reporting Period	Submission Date
19-963	RENOVA® (tretinoin emollient cream) 0.05%	Sept 29, 1998 - Dec 28, 1999	Jan 26, 1999
17-340	RETIN-A (tretinoin) Cream 0.1% (tretinoin)	January 1, 1998 – December 31, 1998	January 26, 1999
17-522	RETIN-A (tretinoin) Cream 0.05% (tretinoin)	July 1, 1998 – June 30, 1998	August 13, 1999
17-579	RETIN-A Gel (tretinoin) Gel 0.025%	April 1, 1998 – March 31, 1998	May 13, 1999
17-955	RETIN-A (tretinoin) Gel 0.01%	October 1, 1998 – September 30, 1999	November 1, 1999
19-049	RETIN-A (tretinoin) Cream 0.025%	September 1, 1998 – August 31, 1999	September 21, 1999
20-475	RETIN-A MICRO™ (tretinoin gel) microsphere, 0.1%	Aug 7, 1999 – Nov 6, 1999	November 18, 1999

**15-day Alert
Reports**

NDA 19-963

The periodic report for RENOVA® (tretinoin emollient cream) 0.05% was submitted on January 26, 1999. Since then, there have been four 15 day alert reports made to the FDA; these reports included 1) a cataract, 2) a miscarriage, 3) an arrhythmia, and 4) lost voice and tingling on tongue and chest.

NDA 17-522

There has been one 15-day alert report since the submission of the periodic report NDA 17-522; this was for a miscarriage.

Continued on next page

**APPEARS THIS WAY
ON ORIGINAL**

DEC 20 1999

Conclusions

Based on a comprehensive review of adverse events reported from all sources since the March 31, 1998 adverse event cut-off date for NDA 21-108, we conclude the following:

There are no trends indicating a change in adverse events.

There is no new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling.

Questions

Should you have any questions, please contact me.

Directly	908-874-1625
FDA only phone number	908-874-1700
Fax	908-874-1118
e-mail	Kwille1@cpcus.jnj.com

Sincerely,

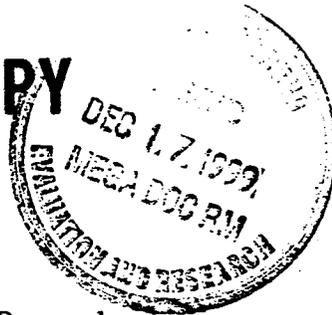


Kathleen K. Wille, Ph.D.
Manager, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

N(BZ)

BEST POSSIBLE COPY



DEC 16 1999

Jonathan Wilkin, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products
HFD-540
5600 Fishers Lane
Rockville, MD 20857

NDA 21-108

RENOVA®
(tretinoin emollient cream) 0.02%

Information request: Amendment
to a pending application

Attention: Olga Cintron, Project Manager

Dear Dr. Wilkin;

Reference

Please refer to correspondence from the agency to Johnson & Johnson Consumer Companies, Inc. dated November 10, 1999 and December 10, 1999.

For your convenience, copies of this correspondence are included in this submission.

Description of this submission

Following this cover letter, FDA Form 356h, and a field copy certification, responses to the information request are presented in the sequential order of the correspondence from the agency. You will find a section addressing questions for each of the following topics:

- A. Clinical
- B. Chemistry
- C. Pharmacology/Toxicology
- D. Biopharmaceutics
- E. Statistics
- F. Microbiology

**APPEARS THIS WAY
ON ORIGINAL**

ORIGINAL

DEC 16 1999

Attachments

The following attachments are included in this submission.

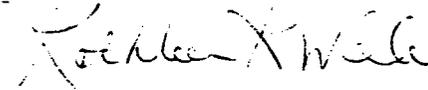
- Investigators meeting participants
- Investigators meeting agenda
- Reference photographs
- Description of the photographic system
- Original protocol J89-024
- Amended protocol J89-024
- Original protocol J89-025
- Amended protocol J89-025
- Audited final draft of the Segment I study
- Annotated case report forms for J89-024
- Annotated case report forms for J89-025

Questions

Should you have any questions, please contact me.

Directly	908-874-1625
FDA only phone number	908-874-1700
Fax	908-874-1118
e-mail	Kwille1@cpcus.jnj.com

Sincerely,



Kathleen K. Wille, Ph.D.
Manager, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY



Division of Dermatologic and Dental Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: December 10, 1999.

Number of Pages (including cover sheet) 2

TO: Kathleen Wille, PhD, Manager, Regulatory Affairs

COMPANY: Johnson & Johnson Consumer Companies, Inc.

NUMBER: 908-874-1118

MESSAGE: RE: NDA 21-108 Renova (tretinoin emollient cream, 0.02%)

Please find list of deficiencies from the microbiologist regarding the above mentioned NDA.

NOTE: We are providing the attached information via telefacsimile for your convenience. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.

TITLE: Project Manager

TELEPHONE: 301- 827-2020

FAX NUMBER: 301-827-2075

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

**APPEARS THIS WAY
ON ORIGINAL**

CC: NDA 21-108
HFD-540/Div Files
HFD-540/Timmer
HFD-805/Sweeney

List of Microbiology Deficiencies and Comments

1. Microbial limits regulatory specifications were listed as follows:

*"Shall contain no detectable _____
_____ The total count
shall not exceed _____ colony forming units per gram."*

The applicant should revise the microbial limits acceptance criteria to include both Total Aerobic Microbial Count and Total Combined Yeasts and Molds. A suggested limit for Total Combined Yeasts and Molds is ≤ 50 cfu/g.

2. The marketed product stability program includes USP Microbial Limits at finished product release, and USP Antimicrobial Preservative Effectiveness testing at expiry _____ for the _____ commercial batches (and yearly thereafter).

As part of the marketed product stability program, the drug product should be tested for both Antimicrobial Preservative Effectiveness and Microbial Limits at 0, _____ months, and yearly if the expiration date is extended.

**APPEARS THIS WAY
ON ORIGINAL**