

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-108

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

Johnson & Johnson
CONSUMER COMPANIES, INC.

NDA ORIG AMENDMENT

JUN 15 2000

XR

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

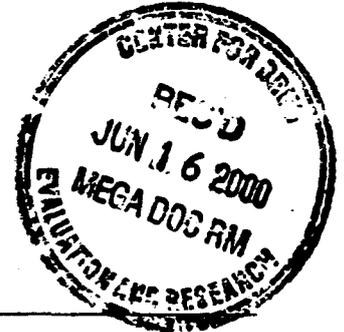
NDA 21-108

RENOVA®
(tretinoin emollient cream) 0.02%

Amendment to a pending
application

Attention: Olga Cintron, Project Manager

RENOVA® (tretinoin emollient cream) 0.02%



Dear Dr. Wilkin;

Purpose of this submission

Please find attached an amendment to Item 13, the Patent Information. The following page replaces page 013 0001 in NDA 21-108.

Briefly, patent no. 4,423,041 will be expiring and should be removed from the list of patents covering this product. Also, pages 013 0002-013 0006 should be removed from NDA 21-108.

Questions

Should you have any questions, please contact me.

Directly	908-874-1625
FDA only phone number	908-874-1700
Fax	908-874-1118

Sincerely,

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

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BEST POSSIBLE COPY



OFFICE OF
GENERAL COUNSEL

ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, N.J. 08933-7003

This is to certify that RENOVA brand (tretinoin emollient cream) 0.02% is covered under the following United States Patents:

U.S. Patent No. 4,423,041
U.S. Patent No. 4,603,146
U.S. Patent No. 4,877,805

This further certifies that the above-identified patents are in effect.

Andrea L. Colby
Associate Patent Counsel
Johnson & Johnson

Date: Feb. 2, 1999

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**NDA 21-108
RENOVA® 0.02%
(tretinoin emollient cream)**

**PATENT INFORMATION
ITEM 13**

RENOVA® (tretinoin emollient cream) 0.02%, the drug product subject of this application, is covered by three U.S. patents:

1. U.S. Patent No. 4,423,041 issued December 27, 1983
2. U.S. Patent No. 4,603,146 issued July 29, 1986
3. U.S. Patent No. 4,877,805 issued October 31, 1989

Copies of these patents are attached.

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AUG 31 1999

FINANCIAL DISCLOSURE

Johnson & Johnson Consumer Companies, Inc. certifies that no investigator involved in the clinical trials to support the safety and efficacy of Tretinoin Emollient Cream 0.02% was compensated in a manner that the amount of compensation would be affected by the outcome of the study (e.g. compensation would have been greater for a favorable result). No investigator involved in the clinical trials to support the safety and efficacy of Tretinoin Emollient Cream 0.02% holds a proprietary interest in the product (e.g. trademark, patent, copyright, or licensing agreement).

Robert B. Armstrong, M.D.
Vice President, Regulatory Affairs

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*Provided
in
original
submission*

EXCLUSIVITY SUMMARY FOR NDA # 21-108

SUPPL # N/A

Trade Name: RENOVA Cream, 0.02%

Generic Name: Tretinoin cream

Applicant Name: Johnson & Johnson

HFD # 540

Approval Date If Known: 8/31/00

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES / X / NO / ___ /

b) Is it an effectiveness supplement?

YES / ___ / NO / X /

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / X / NO / ___ /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, **EXPLAIN** why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety? No.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO - please indicate as such)

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other

non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA 16-921, Retin-A Liquid, 0.05%
NDA 17-340, Retin-A Cream, 0.1%
NDA 17-522, Retin-A Cream, 0.05%
NDA 17-579, Retin-A Gel
NDA 17-955, Retin-A Gel, 0.01%
NDA 19-049, Retin-A Cream, 0.025%

NDA 20-438, Vesanoid Capsules, 10 mg
NDA 20-475, Retin-A Micro, 0.1%
NDA 19-963, Renova Cream, 0.05%
NDA 20-400, Avita Gel, 0.025%
NDA 20-404, Avita Cream, 0.025%

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO / / N/A

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS.

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the

approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations?

(The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / /

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(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / / NO / /

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / /

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

The Sponsor submitted 5 studies: Study #1: J89-024
Study #2: J89-025
Study #3: J89-045
Study #4: L91-026
Study #5: K90-054

Sponsor designated studies J89-024, and J89-025 as pivotal. Additionally, study J89-045 was considered pivotal by the Agency.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation # 3 YES /___/ NO/_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Five studies: Study J89-024, J89-025, J89-045, L90-011, and L91-026.

The five studies were supportive for safety. Studies J89-024, J80-025, and J89-45 were supportive for efficacy.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

All five investigations:

IND ~~___~~ YES / X / NO / ___ / Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / ___ / Explain _____ NO / ___ / Explain _____

Investigation #2

YES / ___ / Explain _____ NO / ___ / Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / ___ / NO / X /

If yes, explain: _____

[/S/] 8/17/00 Project Manager.
Signature:Date:Title:

Signature of Office/Division Director

Signature:Date: [/S/] [8/27/00]

cc: Original NDA 21-108
HFD-540 Division File
HFD-93 Mary Ann Holovac

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CERTIFICATION OF NON-DEBARMENT

Johnson & Johnson Consumer Companies, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Robert B. Armstrong, M.D.
Vice President, Regulatory Affairs

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Clinical Team Leader Addendum: NDA 21-108

AUG 15 2000

SPONSOR: Johnson and Johnson Consumer Companies, Inc.
DRUG PRODUCT: RENOVA® (tretinoin emollient cream) 0.02%
CLINICAL INDICATION: mitigation of fine wrinkling

DATE of ADDENDUM: July 17, 2000

The following material is presented to complement the information about study K90-016 included in the Medical Review (pages 44-45).

Inclusion Criteria

1. Subjects are to be Caucasian, 18 to 60 years of age.
2. Subjects are to be in good general health.
3. Subjects (or their authorized representative) must read and sign the informed consent form after the nature of the study has been fully explained and a Confidential Follow-Up Form has been completed.
4. If female of childbearing potential (i.e., no prior hysterectomy or post-menopausal for less than one year) subject must have had a normal menstrual flow within 30 days prior to admission and a negative urine pregnancy test within one week prior to admission, and must be practicing an acceptable method of contraception, e.g., oral contraception for at least 30 days prior to admission, spermicide and condoms, tubal ligation.

Exclusion Criteria

1. Subjects are not to have any cutaneous or systemic disease that may interfere with the evaluation of the study results.
2. Subjects are not to have received any experimental drug and/or used any experimental device within 30 days prior to admission.
3. Subjects are not to have received any systemic drug within 90 days prior to admission or topical drug within 30 days prior to admission that has been shown to have a well-defined potential for cutaneous toxicity.
4. Subjects are not to have participated in any product testing or patch testing within 30 days prior to admission.
5. Subjects are not to have a history of unusual reactions to topical products or hypersensitivity or allergy to any of the study drug components.
6. Subjects are not to be pregnant or nursing.

Design: For induction, test products were applied semi-occlusively to skin sites on the upper back, by means of _____ occlusive tape with _____ (woven-cotton) material. Semi-occlusive patches were made by cutting off two sides of the occlusive patch. The test creams were applied at approximately 0.1 ml for each induction visit.

Neither the clinical study report nor the protocol specifies that the same evaluator rated the patch test sites throughout the study.

Comment: It is preferred that the same evaluator rate the patch test sites throughout the study.

The scores were rated as follows:

- 0 = No Reaction
- ± = Minimal Erythema
- 1+ =Erythema
- 2+ =Erythema and Induration
- 3+ =Erythema and Induration and Vesicles
- 4+ =Erythema and Induration and Bullae

If a Grade 3 or greater reaction was observed on any site, no further applications were to be made to that site, and the maximum score was to be assigned to that study drug for the duration of the study.

The following descriptive letter designations may have been added to the numerical score if noted at the test site:

- E =Edema
- I =Itching
- P =Peeling
- G =Slight glazing
- B/S =Burning/stinging

Statistical Analysis: For each study drug, the 15 individual scores were to be summed for a given subject to obtain an aggregate score for that subject. Grade of 0, 1+, 2+, 3+, and 4+ were to assigned scores of 0-4 respectively. Grades of ± (minimal erythema) were to be assigned a score of 0.5. No scores were to be assigned to the letter grades. A total cumulative irritation score for each study drug was to be obtained by summing the aggregate scores for all completed subjects.

Comment: In addition to the cumulative irritancy scores presented in the Medical Review, the number of patients with positive irritancy reactions, and the scoring associated with these reactions, are noted in the Results section.

Special Instructions to Subjects: Subjects were to keep the patch sites dry throughout the study.

Results

Subject Disposition and Demographics The study report does not indicate how many subjects were screened prior to study entry. Twenty-five subjects were enrolled, and all 25 completed the study. The mean age was 45.1 years. Age distribution was:

< 30	31-40	41-50	51-60	61-70
1	4	13	6	1

Patch Test Reactions The number of subjects with irritancy reactions, and each subject's highest observed score during the course of the study, following exposure to TEC II

0.02% with fragrance (the to-be-marketed formulation), TEC II vehicle with fragrance, and TEC II vehicle without fragrance, is depicted in the following table:

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Highest Observed Score	TEC II 0.02% tretinoin with fragrance	TEC II vehicle with fragrance	TEC II vehicle without fragrance
0	4	17	19
.5	4	2	2
1	13	4	4
2	3	0	0
3	0	0	0
4	1	0	0

Comment: Since \pm reactions are minimal irritant responses, subjects whose highest scores are 0 or 0.5 are assessed to have no significant irritation from the tested products. The distribution of the highest observed scores suggests: (1) the addition of fragrance to the vehicle is not associated with an increase in irritation; and (2) the addition of tretinoin is associated with clinically significant irritation.

It is disconcerting that 4% of subjects developed a severe (erythema + induration + bullae) reaction to semi-occlusive patch testing with the to-be-marketed formulation. A Poisson distribution is used to model the frequency of a signal of irritancy in a dermal irritancy clinical study. The 95% confidence interval for the population parameter λ (mean number of observed events) is [.0253, 5.571] when 1 event is observed in a sample. With 25 subjects involved in the irritancy study, this predicts a 95% confidence interval for the probability of irritancy per individual of [.001, .22], with a mean probability of .04. It is, however, somewhat problematic to extrapolate irritancy following application under semi-occlusive conditions to normal back skin to predict irritancy reactions following application under open conditions to actinically damaged facial skin.

The following material is presented to complement the information about study J89-024 presented on pages 16 to 22 of the Medical Review.

J89-024 Safety Addendum

Adverse Event Definition

The protocol specified that signs and symptoms of skin irritation were not recorded by the investigators as adverse events unless they prompted a change in the treatment regimen (e.g., missed application) or were otherwise significant (e.g., required topical steroid therapy).

Comment: This definition seems excessively restrictive for assessment of the safety profile of this product, and may lead to an underestimate of its irritancy profile. A patient who experiences severe burning/stinging, for example, who is able to "tough it out" without the physician having to tell him or her to discontinue the medication, is suffering a de facto adverse event, but this experience would not be counted as an "adverse event" according to the sponsor's definition.

Adverse Events Leading to Discontinuation

The sponsor provided brief narratives for the 4 subjects allocated to the active treatment arm who were discontinued from this study due to adverse events. No subjects allocated to the vehicle treatment arm were discontinued from this study due to adverse events. The narratives are summarized as follows:

Subject 216: A 55 year old female developed impetigo of the jawline/lip of 12 days' duration, which was treated with Bactroban and topical hydrocortisone. Following resolution of the impetigo, dry, scaly, erythematous patches developed on the face (near the temples), and subsequently extended to the neck. These erythematous patches caused the subject to discontinue from the study. The patches were treated with hydrocortisone and resolved three weeks after study drug discontinuation.

Subject 314: A 59 year old female experienced minimal irritation during her first eight weeks of therapy, which progressed to moderate irritation during the third month of therapy, shortly after which the patient discontinued treatment. The facial skin irritation resolved within 6 weeks after discontinuation of the study drug.

Subject 325: A 68 year old female experienced moderate peeling of the skin on her earlobes, moderate irritation of the neck, and moderate facial burning beginning at approximately 11 weeks after therapy commenced. Patient temporarily discontinued study drug application and applied hydrocortisone to treat the peeling, which resolved after 12 days. Patient attempted to recommence application of the study drug, but continued neck irritation and facial burning obliged her to discontinue from the study after 15 weeks on therapy.

Subject 328: A 60 year old male developed facial cellulitis (probably erysipelas) after 5 weeks therapy. The papular, confluent, erythematous rash of the cheeks, nose, and eyelids with edema, crusting, and oozing was preceded by fever of 102° -103° F, rigors, and bronchitis. The subject was hospitalized for 4 days for IV antibiotic treatment, followed by 2 weeks of oral antibiotic therapy. The patient had mild residual post-inflammatory hyperpigmentation on the cheeks.

Comment: The background incidence rate of bacterial skin infections of the face in patients in this age group is likely to be considerably less than 2 per 90 subject-years. Also, no subjects in the vehicle arm developed bacterial skin infections of the face during the study period. Irritation from topically applied tretinoin may have predisposed these 2 subjects to develop facial bacterial skin infections, which may be serious adverse events.

Local Adverse Events

To obtain a more complete assessment of the safety profile of the study drug, an analysis was performed in which subjects who experience severe erythema, burning/stinging, itching, peeling, or dryness at any point during the clinical study (henceforth to be described as "subjects with severe local skin reactions") were pooled with those subjects who were classified by the sponsor's definition as "local adverse events". Many more subjects experienced mild or moderate local skin reactions than severe reactions, so counting subjects only with severe local skin reactions is probably a conservative estimate of the irritancy profile. As the table below indicates, there is considerable (but not complete) overlap of subjects with treatment-related local adverse events with subjects with severe local skin reactions:

	TEC II with 0.02% tretinoin	TEC II vehicle
No. of Subjects with treatment-related local adverse events ⁺	14	6
No. of Subjects with Severe Local Skin Reaction*	10	0
No. of Subjects with treatment-related local adverse events and/or with severe Local Skin Reaction	19	6
*Subjects who self-report severe erythema, burning/stinging, itching, peeling, or dryness at any point during the clinical trial.		
+This list includes those subjects listed above who discontinued from the study due to adverse events		

The following table depicts the types of severe local skin reactions reported by subjects in the active treatment arm, the timepoint at which these reactions commenced, and the duration of these reactions.

Severe local skin reactions	Frequency observed [#]	Time of Commencement	Duration
Burning/Stinging	10	mode: week 2; 1 subject each at weeks 4, 8, and 12	mode: 2 weeks; range 2-4 weeks
Erythema	3	week 2 for 2 subjects, week 12 for one subject	2 weeks for 2 subjects, 4 weeks for 1 subject
Dryness	2	week 4 for both subjects	2 weeks for both subjects
Itching	3	weeks 2, 4, and 12	2 weeks for 2 subjects, 4 weeks for one subject
[#] Some of the 10 subjects reported more than one type of severe local skin reaction			

The types of treatment-related local adverse events (as defined by sponsor) reported for subjects in the active treatment arm included irritation, burning/stinging, and cellulitis. As judged from the investigator's description of the events, the local adverse events were on the whole, not qualitatively different from the local skin reactions. The types of local adverse events reported for subjects in the vehicle treatment arm included irritation, papular eruption, and erythema multiforme.

For subjects in the active treatment arm who experienced local treatment-related adverse events, eleven events commenced within 30 days of treatment initiation, while seven adverse events commenced more than 30 days after treatment initiation. (Some subjects were reported to have experienced more than one adverse event during the study period.)

Comment: Use of the TEC II formulation containing 0.02% tretinoin was associated with clinically significant local toxicity, principally manifested as irritation, in approximately 20% of subjects during the study course. It appears that the likelihood of local toxicity is highest shortly after treatment commences, but the likelihood is non-zero even several months after the start of treatment. Among those subjects experiencing local treatment-related adverse events who were able to avoid permanently discontinuing treatment,

signs and symptoms of irritation did eventually resolve. The possibility exists that irritation from the study drug may predispose patients to bacterial infections of the facial skin.

The following material is presented to complement the information about study J89-025 presented on pages 22 to 28 of the Medical Review

J89-025 Safety Addendum

As the protocols for J89-024 and J89-025 were identical, J89-025 also has the same excessively restrictive definition of an adverse event.

Adverse Events Leading to Discontinuation

The sponsor provided brief narratives for the 2 subjects allocated to the active treatment arm who were discontinued from this study due to adverse events, and for the 1 subject allocated to the vehicle treatment arm who was discontinued from this study due to adverse events. The narratives are summarized as follows:

Subject 123: This 67 year old vehicle-treated subject with a history of palpitations controlled with digoxin developed congestive heart failure and gastrointestinal bleeding after approximately five weeks in the study, and the subject subsequently discontinued.

Subject 153: This 67 year-old actively-treated subject noted facial tingling prior to initiation of study therapy. Following the first and only application of study drug the subject developed an edematous facial rash accompanied by redness, swelling, and itch, which was treated with Locoid® cream. The rash was classified by investigator as not related to the study drug; the subject had a similar reaction to penicillin in the past and was taking propranolol.

Subject 337: This 52 year-old actively-treated subject reported moderate facial burning beginning four days after initiation of treatment. As a result of the adverse reaction, the subject stopped study drug applications for two days, then resumed applications for two days before stopping study drug entirely. The facial burning resolved after approximately 11 days.

Local Adverse Events

To obtain a more complete assessment of the safety profile of the study drug, an analysis was performed in which subjects who experience severe erythema, burning/stinging, itching, peeling, or dryness at any point during the clinical study (henceforth to be described as "subjects with severe local skin reactions") were pooled with those subjects who were classified by the sponsor's definition as "local adverse events".

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	TEC II with 0.02% tretinoin	TEC II vehicle
No. of Subjects with treatment-related local adverse events [†]	32	8
No. of Subjects with Severe Local Skin Reaction*	4	1
No. of Subjects with treatment-related local adverse events and/or with severe Local Skin Reaction	33	9
*Subjects who self-report severe erythema, burning/stinging, itching, peeling, or dryness at any point during the clinical trial.		
†This list includes those subjects listed above who discontinued from the study due to adverse events		

The following table depicts the types of severe local skin reactions reported by subjects in the active or vehicle treatment arms, the timepoint at which these reactions commenced, and the duration of these reactions.

Severe local skin reactions	Treatment Arm	Frequency observed [#]	Time of Commencement	Duration
Burning/Stinging	Active	4	2 subjects at week 2, 1 subject at week 4, 1 subject at week 16	2 weeks
Itching	Active	1	week 8	2 weeks
Peeling	Vehicle	1	week 12	2 weeks
Dryness	Vehicle	1	week 12	2 weeks
[#] Some of the subjects reported more than one type of severe local skin reaction				

The types of treatment-related local adverse events (as defined by sponsor) reported for subjects in the active treatment arm included irritant and perioral dermatitis, edema, and folliculitis. As judged from the investigator's description of the events, the local adverse events were not qualitatively different from the local skin reactions. The types of local adverse events reported for subjects in the vehicle treatment arm included irritant dermatitis and acneiform eruption.

For subjects in the active treatment arm who experienced local treatment-related adverse events, thirty-four local adverse events commenced within 30 days of treatment initiation, while 14 adverse events commenced more than 30 days after treatment initiation. (Some subjects were reported to have experienced more than one adverse event during the study period.)

Comment: Use of the TEC II formulation containing 0.02% tretinoin was associated with clinically significant local toxicity, principally manifested as irritation, in approximately 36% of subjects during the study course, compared to 10% of subjects in the vehicle treatment arm. It appears that the most likely time at which local toxicity commences is shortly after treatment commences, but adverse events may start even several months after the start of treatment. Among those subjects experiencing local treatment-related adverse events who were able to avoid permanently discontinuing treatment, signs and symptoms of irritation did eventually resolve.

The following material is presented to complement the information about study J89-045 presented on pages 28 to 35 of the Medical Review.

The sponsor provided brief narratives for the 3 subjects allocated to the active treatment arm who were discontinued from this study due to adverse events. No subjects allocated to the vehicle treatment arm were discontinued from this study due to adverse events. The narratives are summarized as follows:

Subject 127: Mild facial irritation, considered definitely related to the study drug, was reported at the week 12 visit. Study drug was stopped for one day, and the symptoms resolved. Approximately five weeks later the subject experienced a recurrence of symptoms of moderate intensity and the subject discontinued the study. No topical or systemic concomitant medications were used at any time. The facial irritation resolved approximately three days after study drug discontinuation.

Subject 129: The subject was found to have a bronchial carcinoma while being treated for what was thought to be pneumonia. The subject was started on chemotherapy and discontinued the study.

Subject 208: The subject reported moderate edematous erythematous eruptions around both eyes after approximately 2 weeks of therapy. The investigator instructed her to apply hydrocortisone cream. The subject reduced the frequency of application of the study drug to every other day during the second month of therapy and continued to apply the topical steroid. Although the edematous periorbital eruptions continued during the third month of therapy, no study drug applications were missed during that month. The subject discontinued the study at the week 16 visit when it was determined that she had missed all but two applications of study drug during the previous 4 weeks due to the continuing edematous eruptions around the eyes. The subject reported resolution of the adverse event approximately one week after discontinuing the study.

Local Adverse Events

To obtain a more complete assessment of the safety profile of the study drug, an analysis was performed in which subjects who experience severe erythema, burning/stinging, itching, peeling, or dryness at any point during the clinical study (henceforth to be described as "subjects with severe local skin reactions") were pooled with those subjects who were classified by the sponsor's definition as "local adverse events".

	TEC II with 0.02% tretinoin	TEC II vehicle
No. of Subjects with treatment-related local adverse events ⁺	24	6
No. of Subjects with Severe Local Skin Reaction*	2	0
No. of Subjects with treatment-related local adverse events and/or with severe Local Skin Reaction	25	6
*Subjects who self-report severe erythema, burning/stinging, itching, peeling, or dryness at any point during the clinical trial.		
⁺ This list includes those subjects listed above who discontinued from the study due to adverse events		

No patients who were randomized to the vehicle treatment arm experienced a severe local skin reaction during treatment. The following table depicts the types of severe local skin

reactions reported by subjects in the active treatment arm during treatment, the timepoint at which these reactions commenced, and the duration of these reactions.

Severe local skin reactions	Frequency observed [#]	Time of Commencement	Duration
Burning/Stinging	1	week 2	2 weeks
Itching	1	week 2	2 weeks
Peeling	1	week 2	2 weeks
Erythema	1	week 2	2 weeks
Dryness	2	week 2, week 16	2 weeks, 4 weeks
[#] One subject reported all five types of severe local skin reaction			

The types of treatment-related local adverse events (as defined by sponsor) reported for subjects in the active treatment arm included irritant dermatitis, dryness, and edema. As judged from the investigator's description of the events, the local adverse events were not qualitatively different from the local skin reactions. The types of local adverse events reported for subjects in the vehicle treatment arm included irritant dermatitis, eye irritation, and angioedema.

Among the subjects in the active treatment arm who experienced local treatment-related adverse events, 16 first experienced their adverse event within 30 days of commencing treatment, while 8 first experienced their adverse event more than 30 days after treatment initiation.

Comment: Use of the TEC II formulation containing 0.02% tretinoin was associated with clinically significant local toxicity, principally manifested as irritation, in approximately 42% of subjects during the study course, compared to 10% of subjects in the vehicle treatment arm. It appears that the most likely time at which local toxicity commences is shortly after treatment commences, but adverse events may start even several months after the start of treatment. Among those subjects experiencing local treatment-related adverse events who were able to avoid permanently discontinuing treatment, signs and symptoms of irritation did eventually resolve.

Summary of Safety: K90-016, J89-024, J89-025, J89-045

Taking together the reports of treatment-related local adverse events from the three pivotal trials discussed herein, approximately 32% of patients receiving active treatment experienced clinically significant treatment-related local adverse events, either necessitating permanent or temporary discontinuation of therapy, or treatment with topical corticosteroids, or that were characterized by patients as severe in intensity. These local adverse events arose predominantly, but not exclusively, within the first month of use, and gradually diminished in intensity during conduct of the trial in most patients. These clinical findings are consistent with the conclusions from the cumulative irritancy test which demonstrated that TEC-II was an irritant in a small percentage of subjects.

Two active-treatment subjects in the 3 pivotal studies developed bacterial skin infections of the face, a relatively unusual occurrence for individuals in this age group. One subject's illness resulted in hospitalization and treatment with intravenous antibiotics. The irritation induced by daily application of TEC II .02% may have predisposed these subjects to secondary bacterial infection of the treated skin.

No clinical use studies have been conducted to compare the relative frequency or severity of facial irritation induced by RENOVA® 0.02% versus RENOVA® 0.05%. The active ingredient tretinoin is present at lower concentration in the RENOVA® 0.02%, but this does not necessarily translate into an improved irritancy profile, because the relationship between irritancy and dose has not been characterized with dose-ranging studies, and the vehicles of RENOVA® 0.02% and RENOVA® 0.05% differ.

[/S/] 7/17/00

Martin M. Okun, M.D., Ph.D.
Clinical Team Leader

cc:

Archival NDA
HFD-540
HFD-540/Dermatology Medical Reviewer/Luke
HFD-725/Biostatistics Team Leader/Al-Osh
HFD-725/Biostatistician/Thomson
HFD-880/Biopharm/Bashaw
HFD-540/Pharm/Nostrandt
HFD-540/Chemistry/Timmer
HFD-540/Project Manager/Cintron

[/S/] 8/15/00

**APPEARS THIS WAY
ON ORIGINAL**

APPEARS THIS WAY
ON ORIGINAL

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%

Phase IV Commitments /
Packaging Commitments

Attention: Olga Cintron, Project Manager

RENOVA® (tretinoin emollient cream) 0.02%

Dear Dr. Wilkin;

Purpose of this letter	The purpose of this letter is to restate our commitments based on the telephone conversation on August 31, 2000 for NDA 21-108.
Revised Draft Labeling	We agree with the changes to the revised draft labeling.
Carton and Container Labeling	<ul style="list-style-type: none"> • We will ensure that the drug name and strength are represented in a typeface identical to the brand name in design and boldness, and that the drug name and strength are no smaller than ½ the size of the brand name on both the container and the carton. • Also, as discussed, we will differentiate RENOVA 0.02% and RENOVA 0.05% by using contrasting colors on both the container and the carton. • We will use "For topical use only" on the container and carton, coupled with full instructions in the package insert. • We will relocate "Rx Only" to the principal display panel. • We are aware that the statements: "new Strength" and "New Formula" can only be utilized for a period not to exceed six months. • The storage statement on the carton will be consistent with the FDA approved storage statement in the label.

BEST POSSIBLE COPY

**Phase IV
Commitments**

We agree to the following:

Chemistry:

1. _____

A desk copy of the _____ investigations cross-referenced to the RENOVA (TEC-IA) NDA 19-963 will be provided within 7 days of approval.

Clinical

1. The applicant will conduct one comparative efficacy (in fine wrinkling only) and safety study between RENOVA 0.02% and the currently marketed RENOVA 0.05% (TEC-IA). The protocol will be submitted to the agency within six months of approval and results of this study will be submitted within 3 1/2 years approval. No comparisons between RENOVA 0.02% and the previously marketed RENOVA 0.05% will be made with regard to efficacy or safety without an appropriate supporting study.
2. To submit the results of the currently ongoing RENOVA (TEC-IA) 0.05% phase IV study in non-Caucasians to demonstrate local tolerance in Asian and Hispanic skin. The demographics will be adequately representative of the Asian and Hispanic demographics as reported in the year 2000 United States Census. The results will be submitted to the agency within 3 1/2 years of approval.
3. To conduct a UV analysis of the new/different components of the RENOVA (TEC-II) 0.02% formulation versus the RENOVA (TEC-IA) 0.05% formulation. If the new ingredients in the RENOVA (TEC-II) 0.02% contribute to the UV absorption, then the applicant will conduct a phase IV study to evaluate the phototoxicity and photosensitizing nature of the fragranced RENOVA (TEC-II) 0.02% within 9 months of approval.

APPEARS THIS WAY
ON ORIGINAL

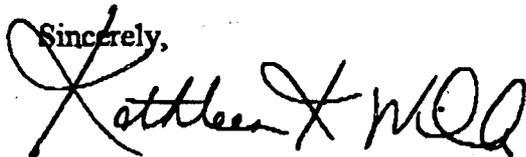
BEST POSSIBLE COPY

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

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

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%

Phase IV Commitments /
Packaging Commitments

Attention: Olga Cintron, Project Manager

RENOVA® (tretinoin emollient cream) 0.02%

Dear Dr. Wilkin;

Purpose of this letter The purpose of this letter is to provide you with the revised draft labeling for NDA 21-108, our commitments on the carton and container, and the phase IV commitments.

Revised Draft Labeling The revised draft labeling is attached.

Carton and Container Labeling

- We will ensure that the drug name and strength are represented in a typeface identical to the brand name in design and boldness, and that the drug name and strength are no smaller than ½ the size of the brand name on both the container and the carton.
- Also, as discussed, we will differentiate RENOVA 0.02% and RENOVA 0.05% by using contrasting colors on both the container and the carton.
- We will use "For topical use only" on the container and carton, coupled with full instructions in the package insert.
- We will relocate "Rx Only" to the principal display panel.
- We are aware that the statements: "new Strength" and "New Formula" can only be utilized for a period not to exceed six months.
- The storage statement on the carton will be consistent with the FDA approved storage statement in the label.

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

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

WITHHOLD 1 PAGE (S)

199 Grandview Road
Skillman, NJ 08558-9418
Phone 908-874-1625
Fax 908-874-1118

Johnson & Johnson

Fax

To: Olga Cintron

From: Kathleen K. Wille

Fax: 301-827-2075

Pages: 5

Phone: 301-827-2020

Date: 08/30/00

Re: NDA 21-108

CC:

Title: Discussion Items on Draft Labeling and Phase 4 Studies for NDA 21-108

● **Comments:**

Please refer to the following pages; these list the points we would like to discuss at the telephone conference call. The call is scheduled for 4:30 on Wednesday, August 30, 2000, and the phone number for the conference room is 908-874-1300. Thank you for the opportunity to discuss these matters.

Sincerely,



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

APPEARS THIS WAY
ON ORIGINAL

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August 30, 2000

Johnson & Johnson Consumer Companies, Inc. has reviewed the draft labeling for NDA 21-108 RENOVA (tretinoin cream) 0.02% which was faxed on August 28. We agree with much of the labeling, and we appreciate your careful consideration of this NDA. We would like to focus on the points listed below.

CLINICAL PHARMACOLOGY:

Page 2, line 22 and line 23. The reference to "TEC II" may be confusing. We suggest eliminating those references.

INDICATIONS AND USAGE:

We believe that the results of the clinical trials submitted in the NDA supported additional indications. Please clarify your rationale and analyses that led to the one indication of fine wrinkling.

Please refer to page 2, line 36. We would like to eliminate the word ~~fine~~ from the phrase "fine facial wrinkles".

Page 3, line 6. We believe the modification shown to following statement more accurately reflects the conduct of our clinical trials.

[]

Clinical Trials

Page 3, line 48 and page 4, line 1. For consistency and clarity, we would like to refer to this condition as "skin yellowing".

Page 5, line 2. We agree that efficacy has not been demonstrated in darkly pigmented subjects, and propose the following text to be used instead of the table.

[]

Page 5, line 10. We cannot read the graph on the bottom of the page, could you provide us with a legible copy?

Page 8, line 1. We submitted a cumulative irritation study in the NDA. Therefore, we would like to recommend the following changes.

[]

[]

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August 30, 2000

PRECAUTIONS:

Page 10, line 19. Please provide clarification on the inclusion of the statement: "Patients aged 65 and over may demonstrate slightly more irritation, although the differences were not statistically significant in the clinical studies for RENOVA 0.02%."

ADVERSE REACTIONS:

Page 10, line 32. We believe that the line _____ is confusing when the statement regarding local reactions is also included beginning at line 40. We suggest eliminating the statement beginning on line 32. We would also like to modify the statement beginning at line 40, as follows:

One or more of the following local reactions such as peeling, dry skin, burning, stinging, erythema, and pruritus were reported by almost all subjects during therapy with RENOVA 0.02%.

DOSAGE AND ADMINISTRATION:

Page 11, line 30. We agree with the inclusion of "5 millimeter diameter" regarding the amount of medication to apply, because it adds clarification. We would like to suggest that every reference to the amount be changed to say "a small pearl-size (5 millimeter diameter) amount". Similar changes should be made at page 7, line 25 and in the patient instruction leaflet at page 14, line 37.

HOW SUPPLIED:

Page 12, line 8. We plan to launch a 40 gram tube; references to the _____ and the _____ tube should be deleted.

Page 12, line 14. There is no need for the _____ instruction.

Patient Instruction Leaflet

Page 13, line 42. We recommend the following change.

[_____]
Page 14, line 4. The added statement that _____ is strong language which we believe may lead to the patient into premature decisions about aborting the pregnancy which may not be medically warranted. We would like to propose the following alternative language:

If you become pregnant while taking RENOVA, please contact your physician immediately.

Actual Product Labels:

Coupled with full instructions in the package insert, "For Topical Use Only" provides adequate instruction on the carton.

BEST POSSIBLE COPY

August 30, 2000

Phase 4 Studies**Chemistry:**

[Empty box for Chemistry response]

Clinical:

1. Please provide some discussion clarifying your rationale for this request.
2. We propose to submit the results of the RENOVA 0.05% phase 4 study in non-Caucasians to demonstrate local tolerance. Do you agree?
3. Please provide more information on the results expected and the actions steps that would result from this study request.

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OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST



NDA # 21-108 Drug: Renova (TRETINOIN CREAM), 0.02%
 Applicant: JOHNSON AND JOHNSON Chem/Ther/other Types: 3S
 PM: O. CINTRON Phone: 7-2020 HFD- 540
 USER FEE GOAL DATE: SEPT 1/00 DATE CHECKLIST COMPLETED: _____

Arrange package in the following order (include a completed copy of this CHECKLIST): Check or Comment

1. ACTION LETTER with supervisory signatures
Are there any Phase 4 commitments? AP AE
Yes ✓ No _____

2. Have all disciplines completed their reviews?
If no, what review(s) is/are still in draft? Yes ✓ No _____

3. LABELING (package insert and carton and container labels).
(If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.)
Draft _____
Revised Draft ✓
Final _____

4. PATENT INFORMATION INCLUDED

5. EXCLUSIVITY CHECKLIST INCLUDED

6. PEDIATRIC PAGE (all NDAs) INCLUDED

7. DEBARMENT CERTIFICATION
(Copy of applicant's certification for all NDAs submitted on or after June 1, 1992). INCLUDED

8. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES
If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status.
If no audits were requested, include a memo explaining why. INCLUDED

9. REVIEWS & MEMORANDA:
 DIVISION DIRECTOR'S MEMO | If more than 1 review for any | _____
 GROUP LEADER'S MEMO | 1 discipline, separate reviews | _____
 MEDICAL REVIEW | with a sheet of colored paper. | _____
 SAFETY UPDATE REVIEW | Any conflicts between reviews | _____
 STATISTICAL REVIEW | must have resolution documented | _____
 BIOPHARMACEUTICS REVIEW | _____
 PHARMACOLOGY REVIEW (Include pertinent IND reviews) | _____
 Statistical Review of Carcinogenicity Study(ies) | _____
 CAC Report/Minutes | _____
 CHEMISTRY REVIEW | _____
 (OPDEA) Labeling and Nomenclature Committee Review Memorandum | _____
 Date EER completed _____ (attach signed form or CIRT's printout) | _____
 FUR needed No FUR requested N/A | _____
 Have the methods been validated? Yes (attach) _____ No ✓ | _____
 Environmental Assessment Review /FONSI | FONSI Yes X CATEGORICAL EXCLUSION GRANTED | _____
 MICROBIOLOGY REVIEW | _____
 What is the status of the monograph? _____

6/16/00 ; 8/15/00 (2) ; 8/27/00 (2)
6/6/00
8/1/00
5/1/00
7/5/00

6/5/00 ; 7/18/00
INCLUDED

10. CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes INCLUDED

11. MINUTES OF MEETINGS
 Date of End-of-Phase 2 Meeting: _____
 Date of pre-NDA Meeting: _____
FORWARD FORWARDING MTS included

12. ADVISORY COMMITTEE MEETING MINUTES
 or, if not available, 48-Hour Info Alert or pertinent section of transcript.
 Minutes _____ Info Alert _____
 Transcript _____ No mtg ✓

13. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS _____

**OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST**

Page 2

14. If approval letter, has ADVERTISING MATERIAL been reviewed?
If no and this is an AP with draft labeling letter, has
advertising material already been requested?

Yes _____ No ✓
Yes, documentation attached _____
No, included in AP ltr _____

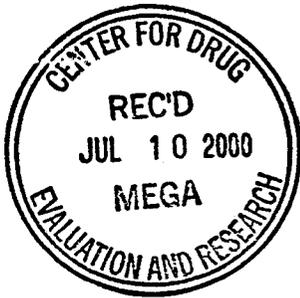
15. INTEGRATED SUMMARY OF EFFECTIVENESS (from NDA)

INCLUDED

16. INTEGRATED SUMMARY OF SAFETY (from NDA)

INCLUDED

**APPEARS THIS WAY
ON ORIGINAL**



Johnson & Johnson
CONSUMER COMPANIES, INC.

NDA ORIG AMENDMENT JUL - 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%

Amendment to a pending
application

Attention: Olga Cintron, Project Manager

RENOVA® (tretinoin emollient cream) 0.02%

[/S/]

Dear Dr. Wilkin;

Purpose of this submission This is in response to the July 6, 2000 request for tube and carton artwork for the subject of NDA 21-108, RENOVA® (tretinoin emollient cream) 0.02%.

Contents of this submission In this submission, you will find three pieces of artwork:

- 2 gram physician's sample
- 40 gram tube
- carton for the 40 gram tube

These are the sizes that we are planning to use for the launch.

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

ORIGINAL

Bm

JUN 23 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%



Dear Dr. Wilkin;

Purpose of this submission This is in response to the June 19, 2000 request for information from the clinical reviewer. Responses to the two questions can be found below.

In addition, we have attached a letter from the investigator regarding patient #328 from study protocol J89-024. This is a follow-up to the request for information dated June 9, 2000. The patient had secondary hyperpigmentation at the conclusion of the study, and in response to the agency's query, we can confirm that the hyperpigmentation has resolved.

Topical steroid use Table 1 displays topical steroid use on or near the treatment site due to an adverse event. This information was compiled from protocols J89-024, J89-025, J89-045, L91-026, K90-011, and K90-054. Individual tables can also be found in the study reports in the NDA.

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ON ORIGINAL

JUN 23 2000

The _____ metered dosing system was not used in the pivotal studies for
metered dosing NDA 19-963.

In the pivotal studies for NDA 19-963 (G86-074, G86-082, and H87-064), patients were instructed to squeeze a pea-sized amount of the test cream onto their fingertip and apply to the entire face. Product was weighed at study visits, and based on a once daily usage rate of 0.5 grams per treatment area, compliance was assessed.

Questions

Should you have any questions, please contact me.

Directly	908-874-1625
FDA only phone number	908-874-1700
Fax	908-874-1118

Sincerely,



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

APPEARS THIS WAY
ON ORIGINAL

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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 19, 2000. Number of Pages (including cover sheet) - 2
TO: Kathleen Wille, Ph.D., 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 the clinical reviewer.

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/Luke

NDA 21-108
Renova Cream, 0.02%

Request for Information-Clinical:

1) Regarding topical steroid use for irritation to facial skin resulting from treatment, what topical steroid was used, what was the duration of use, how many patients from each of the studies used topical steroids? Please provide the individual subject numbers for those subjects that used steroids.

2) Was the _____ used in the pivotal studies for NDA 19-963?

APPEARS THIS WAY
ON ORIGINAL

NDA ORIG AMENDMENT JUN 15 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:
June 9 fax and product samples

Attention: Olga Cintron, Project Manager

RENOVA® (tretinoin emollient cream) 0.02%



Dear Dr. Wilkin;

Background

On June 9, 2000, Johnson & Johnson Consumer Companies, Inc., received a fax with an information request from the medical reviewer, and in addition, Ms. Olga Cintron requested samples of fragranced and unfragranced product using the TEC II formulation.

Historical perspective

- The conclusion date of the last clinical trial, that was included in NDA 21-108, was December of 1993.
- The consumer evaluations of the fragranced and unfragranced product were conducted in 1993.
- J&J requested approval for a fragranced product based upon consumer acceptability. The stability batches are fragranced product in order to support the expiration date of the product proposed for marketing.

Therefore, the sponsor has no unfragranced product available.

Contents of this submission

Enclosed you will find a tube of a laboratory sample _____ of fragranced product that was manufactured August 12, 1998 and has been stored at ambient temperatures.

Responses to the questions faxed to J&J follow.

ORIGINAL

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JUN 15 2000

**Patient #328,
Study J89-024**

Patient #328 was hospitalized on _____ for treatment of facial cellulitis with an eventual diagnosis of erysipelas. The subject improved clinically following four days of intravenous nafcillin and was discharged on _____ with oral dicloxacillin for 10 days. The facial cellulitis resolved after 3 weeks.

The investigator next saw the subject on 2/9/90 at which time he noted "mild post inflammatory hyperpigmentation" of the cheeks. The subject last used the test product on 1/20/90 when the facial symptoms first appeared.

On 3/9/90 the subject was seen for the discontinuation visit. The progress notes state "postinflammatory hyperpigmentation, secondary to erysipelas, remains".

J&J is continuing to seek more information on the status of the secondary hyperpigmentation of this patient. If we obtain any further information, we will forward it to the agency.

Pregnancies

No pregnancies occurred to any women enrolled in any of the studies included in NDA 21-108.

**Number of
women of child-
bearing age**

Please refer to the following table for information on the number of women of childbearing age enrolled in studies supporting safety for RENOVA 0.02% and the number exposed to RENOVA 0.02%.

Protocol	Total (N)	All Females <= 50 yrs	TEC II Females <= 50 yrs
J89-011	25	14 (56.0%)	14 (56.0%)
J89-024	179	31 (17.3%)	15 (8.4%)
J89-025	179	27 (15.1%)	15 (8.4%)
J89-045	119	21 (17.6%)	9 (7.6%)
K90-011	80	8 (10.0%)	5 (6.3%)
K90-016	25	13 (52.0%)	13 (52.0%)
K90-017	219	112 (51.1%)	112 (51.1%)
K90-054	120	21 (17.5%)	21 (17.5%)
L91-026	117	29 (24.8%)	16 (13.7%)
Only K90-054	19	5 (26.3%)	5 (26.3%)
Total	962	260 (27.0%)	204 (21.2%)

K90-054 was a follow-up study to J89-045; however, some patients did not participate in J89-045 and were enrolled in only K90-054. The total accounts for the patients that were in J89-045 and K90-054.

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JUN 15 2000

**Questions /
Follow-up**

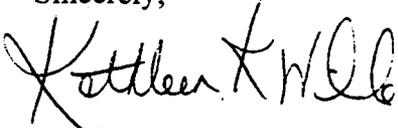
The currently marketed RENOVA (tretinoin emollient cream) 0.05% contains the same fragrance as that included in the RENOVA 0.02% (TEC II) formulation. RENOVA 0.05% contains _____ at 0.005%, and RENOVA 0.02% contains _____ at 0.10%. The formulations for RENOVA 0.05% and RENOVA 0.02% are different; the concentration of the fragrance for TEC II was chosen during the formulation development for optimal consumer acceptability.

J&J has no plans to market an unperfumed product. If the Division considers the fragrance an issue that could impact the approvability of NDA 21-108, J&J requests a written response to this effect prior to the action letter. Thank you for your prompt attention to this matter and for your cooperation in coming to closure on this issue.

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

**APPEARS THIS WAY
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

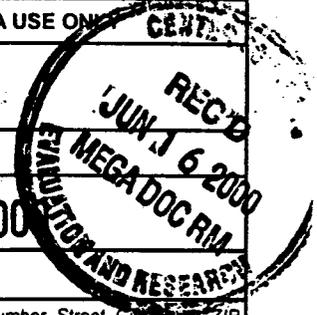
APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved : OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER



APPLICANT INFORMATION

NAME OF APPLICANT Johnson & Johnson Consumer Companies, Inc.		DATE OF SUBMISSION JUN 15 2000
TELEPHONE NO. (Include Area Code) 908-874-1700		FACSIMILE (FAX) Number (Include Area Code) 908-874-1118
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 199 Grandview Road Skillman, NJ 08558		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Kathleen Wille, Manager Regulatory Affairs 199 Grandview Road Phone: 908-874-1625 Skillman, NJ 08558 FAX: 908-874-1118

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)		NDA 21-108
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) tretinoin	PROPRIETARY NAME (trade name) IF ANY RENOVA(R)	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) all-trans-retinoic acid	CODE NAME (if any) RWJ 8203	
DOSAGE FORM: cream	STRENGTHS: 0.02%	ROUTE OF ADMINISTRATION: topical

(PROPOSED) INDICATION(S) FOR USE:
adjunctive agent for use in the mitigation (palliation) of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin in patients who do not achieve such palliation using comprehensive skin care and sun avoidance programs alone

APPLICATION INFORMATION

APPLICATION TYPE (check one)			
<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)	<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)	
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b) (1) <input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 507			
IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug: _____ Holder of Approved Application: _____			
TYPE OF SUBMISSION (check one)			
<input type="checkbox"/> ORIGINAL APPLICATION	<input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION	<input type="checkbox"/> RESUBMISSION	
<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT	<input type="checkbox"/> SUPAC SUPPLEMENT
<input type="checkbox"/> EFFICACY SUPPLEMENT	<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT	<input type="checkbox"/> OTHER

REASON FOR SUBMISSION

Change to Item 13.

PROPOSED MARKETING STATUS (check one)	<input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx)	<input type="checkbox"/> OVER-THE-COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>1</u>	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC	

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)

NDA 19-963