CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-452/S017

CORRESPONDENCE

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(151)

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Dermaceuticals, Inc.

Specialty Dermatologicals for Children & Adults

Derma-Smoothe/FS Topical Oil
NDA 19-452

NDA NO. 19-452 REF. NO. 017
NDA SUPPL FOR SE5

October 9, 2000

Jonathan K. Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
CDER
Food and Drug Administration
9201 Corporate Boulevard HFD 540
Rockville, MD 20850
Attn: Ms. Millie Wright
Project Manager

RE: Supplemental application to NDA 19-452: Derma-Smoothe/FS
Open-Label Safety Study on Derma-Smoothe/FS in atopic dermatitis patients ages 2 to 6, through plasma Cortisol analysis (Protocol 26).

Dear Dr. Wilkin:

Hill Dermaceuticals, Inc., is submitting this supplemental application to the approved NDA 19-452, Derma-Smoothe/FS (0.01% Fluocinolone acetonide), to seek approval for the treatment of *Atopic dermatitis* in pediatric patients 2 years and older. Derma-Smoothe/FS is approved for atopic dermatitis in pediatric patients ages 6 and older (approval date, August 18, 1999).

The purpose of this clinical study is to provide additional safety data in support of the previous safety study conducted for the pediatric indication. Prior study did not have sufficient data on children ages 2 to 5 for safety assessment. Protocol 26 study was therefore limited to ages 2 to 5 population. Data from this study is intended to show that the use of Derma-Smoothe/FS is safe and effective on atopic dermatitis patients 2 years and older.

The safety study conducted maintained the same strict criteria used in the previous clinical studies: (1) subjects should have moderate to severe atopic dermatitis; (2) disease should be present on 50% or greater, of the body surface area (generalized disease involvement); and, (3) evaluation of HPA axis suppression through morning plasma Cortisol levels, and post-ACTH Stimulation Cortisol levels before and after treatment.

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All 13 patients (with severe atopic dermatitis on ≥ 50% of skin surface area) evaluated in this study showed no abnormal decrease in Cortisol levels after 4 weeks exposure to Derma-Smoothe/FS. Statistical inference from the data (laboratory results) showed that there was no statistical significance between the initial pre and post-stimulation Cortisol values and the final 4th week Cortisol values. There was no suppression of HPA axis on any of the subjects that participated in the studies. Plasma Cortisol levels remained normal on all study subjects with severe, generalized atopic dermatitis, after treatment with Derma-Smoothe/FS on a twice daily application for 4 weeks.

The investigators that participated in this study are Amy Paller, M.D., pediatrician, head of the Pediatric Department, Children's Memorial Hospital, Chicago, Illinois; and Lawrence Eichenfield, M.D., head of Pediatric Dermatology, University of California - San Diego, San Diego, California. Copies of Case Report Forms will be submitted upon request.

The contents of this submission include all sections pertinent to this application. Other sections are referred to the original NDA and supplements. As a previously approved NDA, this supplement is understood to be exempt from the application fee.

Thank you for your consideration and continued cooperation.

Sincerely,

Rosario G. Ramirez
Medical/Regulatory Affairs

Jerry S. Roth
President

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Dermaceuticals, Inc.

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NEW CORRESP

Derma-Smoothe/FS Topical Oil
NDA 19-452

NC
SES-017

October 31, 2000

Jonathan K. Wilkin, M.D./Director
Division of Dermatologic and Dental Drug Product
CDER
Food and Drug Administration
HFD 540
9201 Corporate Boulevard
Rockville, MD 20850
ATTN: Ms. Millie Wright
Project Manager

RE: Amended Supplement (Supplement #17)
Open-Label Safety Study on Derma-Smoothe/FS in atopic dermatitis patients ages 2 to 6, through plasma Cortisol analysis (Protocol 26)

Dear Dr. Wilkin:

This submission is in reference to NDA 19-452, Supplement #17, filed October 9, 2000. The enclosed Form FDA 3397/USER FEE COVER SHEET was inadvertently left out of the above-mentioned submission. Please accept this completed form as an Amendment to Supplement #17. One original and 2 copies are included.

Please note that item #7 on Form FDA 3397 has been checked (A 505(b)(2) Application That Does Not Require a Fee) as an applicable exclusion. Should additional information be required please do not hesitate to contact us. Thanks again for your continued support and consideration.

Sincerely,

Criss Molasso

Criss Molasso
Assistant Regulatory Affairs

ORIGINAL

cc: R.G. Ramirez, MD
Medical/Regulatory Affairs
encls.

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Dermaceuticals, Inc.

Specialty Dermatologicals for Children & Adults

Derma-Smoothe/FS Topical Oil NDA ORIG AMENDMENT
NDA 19-452

November 3, 2000

Jonathan Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
CDER
Food and Drug Administration, HFD 540
9201 Corporate Boulevard
Rockville, MD 20850
Attention: Ms. Millie Wright
Project Manager

XR

RE: Supplement # 17 (file date: October 9, 2000) Amendment to a pending application.
Request for Exclusivity: For the indication Atopic Dermatitis in Pediatric Patients Ages 2 to 5 years.

Dear Dr. Wilkin:

In reference to Supplement # 17 (to NDA 19-4520), a claim for exclusivity for the additional indication atopic dermatitis in pediatric patients 2 to 5 years, is respectfully requested.

Supplement # 17 submission contains report on HPA axis suppression study on atopic dermatitis patients ages 2 to 5 years. The study was conducted to provide additional safety data to the pediatric approval for Derma-Smoothe/FS, approval date August 1999.

Supplement # 17 is understood to be exempt from the application fee. This supplemental application (Supplement # 17) was amended to include a User Fee Cover sheet (Form 3397), submitted October 31, 2000.

Sincerely,

Rosario G. Ramirez

Rosario G. Ramirez
Medical/Regulatory Affairs

DUPLICATE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-452/S-017

Hill Dermaceuticals, Inc
2650 South Mellonville Avenue
Sanford, FL 32773

Attention: Rosario G. Ramirez, Regulatory Affairs

Dear Mr. Ramirez:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Derma-Smoothe/FS Topical Oil (fluocinalone acetonide)

NDA Number: 19-452

Supplement Number: S-017

Date of Supplement: October 09, 2000

Date of Receipt: October 10, 2000

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on December 09, 2000 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Dermatologic and Dental Drug Products, HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Mary J. Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic and Dental
Drug Products, HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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SE5-017/X B09

Dermaceuticals, Inc.

Specialty Dermatologicals for Children & Adults

Derma-Smoothe/FS Topical Oil
NDA 19-452
S-017.

March 6, 2001

Jonathan Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
CDER
Food and Drug Administration, HFD 540
9201 Corporate Boulevard
Rockville, MD 20850
Attention: Ms. Millie Wright
Project Manager

RE: Response to FDA Request for Additional Information for
NDA 19-452 S-017

Dear Dr. Wilkin:

The information requested by the medical reviewer on Derma-Smoothe/FS Study # 26, Open-label safety study on pediatric patients with atopic dermatitis ages 2-5 years, regarding safety data that were collected in the case report forms and specific information on the subjects that were dropped from the study (no evaluation) are provided.

The efficacy data collected at week 2 and week 4 evaluations are presented in the enclosed table. Explanation regarding the 2 subjects that were not included in the analysis is also provided.

Thank you for your continued assistance and cooperation,

Sincerely,

Rosario G. Ramirez
Medical/Regulatory Affairs

ORIGINAL

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NDA SUPPLEMENT
SES-017 BZ

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Specialty Dermatologicals for Children & Adults

Derma-Smoothe/FS Topical Oil
NDA 19-452
S-017

July 27, 2001

Jonathan Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
CDER
Food and Drug Administration, HFD 540
9201 Corporate Boulevard
Rockville, MD 20850
Attention: Ms. Millie Wright
Project Manager

RE: Proposed Package Insert Label with Electronic copy
Under Supplement no. 017

Dear Dr Wilkin,

This submission contains the proposed Package Insert Label for Derma-Smoothe/FS topical Oil, for the indication of atopic dermatitis in the pediatric population 2 years and older. We concur with the changes conveyed by the Medical Reviewer, in the Clinical Studies section of the labeling. Additional changes made to the proposed insert label are as follows:

[redacted]

2. The term "*refined*" precedes "peanut oil".
3. The term "*hypopigmentation*" was included twice in the list of adverse reactions, in the Adverse Reactions section. One was deleted.
4. The temperature range for storage condition was changed to 68° to 77°F (20°-25°C) to comply with the official compendium, USP 23 / NF 19.

All changes have been highlighted for easy reference.

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Clarification is in order regarding the surface area involvement listed as >75% in the original supplement submission dated October 9, 2000, and listed as 75% in Additional Information Request submission dated March 6, 2001. The correct entry is >75%, as stated in the original supplement. This was inadvertently missed in the subsequent submission. We apologize for this error.

Enclosed is an electronic copy of the proposed Package Insert Label for Derma-Smoothe/FS Topical Oil, for atopic dermatitis in children 2 years and older. As requested, the chemical structural formula for fluocinolone acetonide has been incorporated in the text of the labeling.

The following requested information is also included in this submission.

1. Environmental assessment statement claiming categorical exclusion, under 21 CFR 25.31(a).
2. Patent information.
3. Debarment statement.
4. Financial disclosure information.
5. Statement that the proposed changes in the supplement do not affect the CMC section, as submitted in the NDA.

Please advise if further information is required. As always, thank you for your continued support and cooperation.

Sincerely,

Rosario G. Ramirez
Director
Medical / Regulatory Affairs

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Dermaceuticals, Inc.

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SES.017/6 DM

NDA SUPPL AMENDMENT

Derma-Smoothe/FS Topical Oil
NDA 19-452
S-017

August 8, 2001

Jonathan Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
CDER
Food and Drug Administration, HFD 540
9201 Corporate Boulevard
Rockville, MD 20850
Attention: Ms. Millie Wright
Project Manager

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 09 2001
MEGA

RE: Response to Information Request

Dear Dr. Wilkin,

In reference to the facsimile correspondence from the Agency Reviewer regarding the proposed changes in the package insert label for Derma-Smoothe/FS, the response from Hill is as follows:

FDA comment # 1

Hill response:

FDA comment # 2. Please provide the data (frequencies of the reactions listed) to support removal of one of the appearances of "hypopigmentation" in the ADVERSE REACTIONS, since the reactions are listed in order.

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Hill response: There is no reference data or guideline in support of this proposal, as this was thought to be an editorial error. If the Reviewer recommends that there should be no change from the original verbage, Hill Dermaceuticals, Inc. will comply.

FDA comment # 3. Please provide your clinical plan for the age group under 2 or request a waiver.

Hill response: Hill Dermaceuticals intends to conduct clinical studies in children less than 2 years, for the same indication, atopic dermatitis. The investigational plan for such study has not been structured at the present time.

Included in this submission is a corrected copy of the proposed package insert label with the changes already in place.

Sincerely,

Rosario G. Ramirez
Director
Medical / Regulatory Affairs

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Derma-Smoothe/FS Topical Oil
NDA 19-452
S-017

August 28, 2001

Jonathan Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
CDER
Food and Drug Administration, HFD 540
9201 Corporate Boulevard
Rockville, MD 20850
Attention: Ms. Millie Wright
Project Manager

SE5-017/PL

NDA SUPPL AMENDMENT

RE: Response to Information Request
Request for deferred submission, 21 CFR 314.55(b)

Dear Dr. Wilkin,

Hill Dermaceuticals, Inc respectfully requests deferred submission of the required pediatric assessment in children less than 2 years, in accordance with 21 CFR 314.55 (b). Included in this submission is the certification from HILL indicating the grounds for deferral, a description of the planned studies, and evidence that the studies will be conducted with due diligence and at the earliest possible time.

Sincerely,

Rosario G Ramirez

Rosario G. Ramirez
Director
Medical / Regulatory Affairs

DUPLICATE

NDA SUPPL AMENDMENT SES-017 BC

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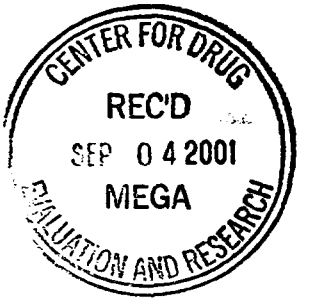
Derma-Smoothe/FS Topical Oil
NDA 19-452
S-017

August 31, 2001



Jonathan Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
CDER
Food and Drug Administration, HFD 540
9201 Corporate Boulevard
Rockville, MD 20850
Attention: Ms. Millie Wright
Project Manager

RE: Response to Information Request CMC
Environmental Assessment : Request for Categorical Exclusion

Dear Dr. Wilkin,

Hill Dermaceuticals, Inc respectfully requests categorical exclusion for this supplemental NDA pursuant to the provisions in 21 CFR 25.31(b), which states that preparation of an EA is not required if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb), to which this request complies.

Rationale for the categorical exclusion request, and calculation of the EIC is enclosed.

Please advise if further information is needed. Thank you for your continued support and assistance.

Sincerely,

Rosario G. Ramirez
Director
Medical / Regulatory Affairs

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SE5.017 /BL

NDA SUPPL AMENDMENT

Derma-Smoothe/FS Topical Oil
NDA 19-452 **S-017**

September 5, 2001

Jonathan Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products / CDER
Food and Drug Administration, HFD 540
9201 Corporate Boulevard
Rockville, MD 20850
Attention: Ms. Millie Wright
Project Manager

SEP 0 6 2001
MED RM
EVALUATION AND RESEARCH

RE: Response to Information Request: Labeling corrections and additional data

Dear Dr. Wilkin,

The proposed draft label submitted in Supplement 017 contained ADVERSE REACTIONS listing based on the labeling approval for Derma-Smoothe/FS, in April 1992, which conformed to the labeling revisions made by the Agency. To comply with the newer corticosteroid class label of 1995, Hill Dermaceuticals proposes to change the listing of adverse reactions to follow the order set forth in the 1995 corticosteroid class labeling.

A revised physician insert label showing the change in the order of adverse event listing, is included. Adverse events, probably or possibly related to the drug product, collected from recent pediatric studies show occurrence of burning, itching, irritation, erythema, papules and pustules in 6 patients, and slight change in pigmentation in 1 patient. This frequency supports the order of adverse event set forth in the 1995 corticosteroid class label.

In the 2000 USP 24 / NF 19, the chemical name for the anhydrous form of Fluocinolone acetonide is "*Pregna-1,4-diene-3,20-dione,6,9-difluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-, (6α, 11β, 16α)-.*" To comply with the official compendium, the chemical name currently in place is revised to reflect the above name.

Please advise if further information is needed. Thank you.

Sincerely,

Rosario G. Ramirez

Rosario G. Ramirez
Director
Medical / Regulatory Affairs

DUPLICATE

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SE5.017/C

NEW CORRESPONDENCE

Derma-Smoothe/FS Topical Oil
NDA 19-452 **S-017**

October 2, 2001

Jonathan Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products / CDER
Food and Drug Administration, HFD 540
9201 Corporate Boulevard
Rockville, MD 20850
Attention: Ms. Millie Wright
Project Manager

RECEIVED
OCT 0 3 2001
NEG/ORDER

RE: Response to FDA facsimile correspondence: NDA 19-452/S-017 dated 10/01/01.

Dear Dr. Wilkin,

Hill Dermaceuticals, Inc. agrees with the Agency regarding the nomenclature of Fluocinolone acetonide, to remain as (6α,11β,16α)-6,9-difluoro-11,21-dihydroxy-16,17[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione, cyclic 16,17 acetal with acetone. Therefore, the wording in the Description section of the physician insert label will reflect the above name for fluocinolone acetonide.

Respectfully,

Rosario G. Ramirez
Director
Medical / Regulatory Affairs

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SE5-017/C

SUPPL NEW CORRESP

Derma-Smoothe/FS Topical Oil
NDA 19-452 **S-017**

October 2, 2001

Jonathan Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products / CDER
Food and Drug Administration, HFD 540
9201 Corporate Boulevard
Rockville, MD 20850
Attention: Ms. Millie Wright
Project Manager

RECEIVED
OCT 0 3 2001
NEG/VODER

RE: Response to Information Request: NDA 19-452/S-017 dated 09/05/01.

Dear Dr. Wilkin,

The purpose of this letter is to clarify that the adverse events "*burning, itching, irritation, erythema, papules and pustules*", judged to be possibly or probably drug related, all occurred in the 6 pediatric patients as reported. Of the 6 patients, 4 had moderate to severe papules, pustules, burning, itching and irritation, and 2 patients had mild to moderate erythema, papules, pustules, burning, itching and irritation (referenced to the NDA supplemental application S-015, dated November 24, 1998).

The occurrence of events is consistent with the order stated in the class labeling.

Sincerely,

Rosario G. Ramirez
Director
Medical / Regulatory Affairs

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Derma-Smoothe/FS Topical Oil
NDA 19-452 / **S-017**

October 3, 2001

SE5-017/BL

Jonathan Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products / CDER
Food and Drug Administration, HFD 540
9201 Corporate Boulevard
Rockville, MD 20850
Attention: Ms. Millie Wright
Project Manager

NDA SUPPL AMENDMENT

RE: NDA 19-452 / S-017
Physician Insert Label

Dear Dr. Wilkin,

Hill Dermaceuticals, Inc. agrees with the Agency's final version of the physician insert label for Derma-Smoothe/FS. There are no changes in the text of the label. The date of revision, found in the last page of the label has been adjusted to show **10/03/01**.

Enclosed is a hard copy of the insert label as well as an electronic copy of the label on diskette, as Microsoft word file. Final printed label will be submitted to the NDA.

Respectfully,

Rosario G. Ramirez

Rosario G. Ramirez
Director
Medical / Regulatory Affairs

ORIGINAL

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