CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-781/S-015

17-781/S-022

CORRESPONDENCE

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033
TELEPHONE: (908) 298-4000

September 28, 2001

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
N216 Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

NDA 18-827 / S-020 & S-022
Lotrisone Cream
NDA 19-555 / S-016
Diprolene ® AF Cream
NDA 17-536 / S-024
Diprosone ® Cream
NDA 17-691 / S-024
Diprosone ® Ointment
NDA 17-781 / S-022
Diprosone ® Lotion

SUBJECT: RESPONSE TO FDA INFORMATION REQUEST

Dear Dr. Wilkin:

Reference is made to the teleconference between Mr. Frank Cross, Ms. Olga Cintron and Schering on September 28, 2001 regarding a date for implementation of proposed packaging and labeling changes for the above mentioned products.

Based on our discussion, Schering hereby confirms that packaging and labeling changes for the above mention products will be implemented within three (3) months of receipt of FDA's approval letter.

If you have any further questions, please contact Yvette Henderson at 908-740-2179 or Mary Jane Nehring at 908-740-5713.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 33 (j) as well as the FDA regulations.

Sincerely,

Mary Jane Nehring
Senior Director, Marketed Products
Support and Training
Worldwide Regulatory Affairs

Desk Copy: Frank Cross (via fax)
Olga Cintron (via fax)

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NDA SUPPL AMENDMENT
SES-022 / NC

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033
TELEPHONE: (908) 298-4000

September 25, 2001

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
N216 Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

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MEGA/CDER

NDA 18-827 / S-020 & S-022
Lotrisone Cream
NDA 19-555 / S-016
Diprolene ® AF Cream
NDA 17-536 / S-024
Diprosone ® Cream
NDA 17-691 / S-024
Diprosone ® Ointment
NDA 17-781 / S-022
Diprosone ® Lotion

SUBJECT: RESPONSE TO FDA INFORMATION REQUEST

Dear Dr. Wilkin:

Reference is made to the teleconference between Mr. Frank Cross, Ms. Olga Cintron and Schering on September 25, 2001 regarding a timeframe for implementation of proposed packaging and labeling changes for the above mentioned products.

Based on review of our current inventory and estimated timeframe required to revise artwork for all product labeling, Schering will implement packaging and labeling changes within six (6) months of receipt of FDA's action letter.

If you have any further questions, please contact Yvette Henderson at 908-740-2179 or Mary Jane Nehring at 908-740-5713.

ORIGINAL

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 33 (j) as well as the FDA regulations.

Sincerely,

Mary Jane Nehring
Senior Director, Marketed Products
Support and Training
Worldwide Regulatory Affairs

Desk Copy: Frank Cross (via fax)
Olga Cintron (via fax)

SE5-022 BC

NDA SUPPL AMENDMENT

SCHERING CORPORATION

RECEIVED

SEP 26 2001

MEGA/CDER

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033
TELEPHONE: (908) 298-4000

September 25, 2001

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
N216 Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

NDA 19-555 / S-016
Diprolene ® AF Cream
NDA 17-536 / S-024
Diprosone ® Cream
NDA 17-691 / S-024
Diprosone ® Ointment
NDA 17-781 / S-022
Diprosone ® Lotion

SUBJECT: DRAFT LABELING RESPONSE

Dear Dr. Wilkin:

Reference is made to our October 4, 2000 pediatric efficacy supplement, our May 31, 2001 Amendment to the pediatric efficacy supplement, the Agency's August 1, 2001 faxes of revised draft labeling for the betamethasone products and the September 20, 2001 teleconference between Schering and the Agency.

We have reviewed the Agency's proposed wording and accept all revisions with the exception of one section.

In the **INDICATIONS AND USAGE** section of all four package inserts:

Schering proposes the following statement:

"Diprosone Cream, Ointment or Lotion (Diprolene AF Cream) is a medium (high) potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 13 years and older."

ORIGINAL

In place of:

"Diprosone Cream, Ointment or Lotion (Diprolene AF Cream) is a medium (high) potency corticosteroid indicated in patients 13 years and older for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses."

If you have any further questions, please contact Todd Paporello, Pharm.D. at 908-740-4252 or Mary Jane Boyle at 908-740-5693.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 33 (j) as well as the FDA regulations.

Sincerely,

Todd Paporello for

Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

Copies:
Olga Cintron (Fax)

TP/es

NDA SUPPL AMENDMENT
SES-022/BL

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033
TELEPHONE: [redacted]

August 2, 2001

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
N216 Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

NDA 19-555/S-016
DIPROLENE AF Cream
NDA 17-536/S-024
DIPROSONE Cream
NDA 17-691/S-024
DIPROSONE Ointment
NDA 17-781/S-022
DIPROSONE Lotion

SUBJECT: RESPONSE TO FDA REQUEST

Dear Dr. Wilkin:

Reference is made to the telephone calls from Olga Citron on June 16 and August 1, 2001 in which she requested that product labeling be submitted for the supplemental applications submitted by Schering for Diprolene AF Cream, Diprosone Cream, Diprosone Lotion and Diprosone Ointment.

In response to Ms. Cintron's request, enclosed are cartons and labels for Diprolene AF Cream, Diprosone Cream, Diprosone Lotion and Diprosone Ointment.

If additional information is needed, please call Ms. Yvette Henderson at (908) 740-2179.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

Yvette Henderson

Mary Jane Nehring
Senior Director, Marketed Products
Support and Training
Worldwide Regulatory Affairs

Desk Copy: Frank Cross

YH/es: Attachment

J:\OPS\SUBMIT\USRA\NDA\19555\LETTERS\080101oc.doc

ORIGINAL

If you have any questions regarding this submission, please feel free to contact Elin Krhoun at (908) 740-5434 or Mary Jane Boyle at (908) 740-5693.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 33 (j) as well as the FDA regulations.

Sincerely,

Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

Copies:

Randy Levin: Letter
(via fax)

Electronic Submissions Coordinator: CD-ROM

EK/es: Attachment

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

TELEPHONE: (908) 298-4000

May 31, 2001

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
N216 Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

NDA 17-781 / S-022
DIPROSONE®
(betamethasone dipropionate) Lotion 0.05%

SUBJECT: FINAL SUBMISSION OF PEDIATRIC STUDY REPORTS; AMENDMENT TO SUPPLEMENT S-022

Dear Dr. Wilkin:

Enclosed is an amendment to the pending DIPROSONE® Lotion, 0.05% pediatric supplement NDA 17-781 / S-022. The supplement was submitted on October 4, 2000, in response to the July 16, 1999 official written and the April 19, 2000 amended request for betamethasone dipropionate products and LOTRISONE® (clotrimazole and betamethasone dipropionate) Cream, 0.05%. Reference is also made to the meeting on March 19, 2001 that was held in response to the December 21, 2000 letter regarding the DIPROLENE® AF and DIPROSONE® pediatric supplements.

Included in the amendment:

- Revised, annotated labeling (hard copy and electronic Microsoft WORD® format) that includes the updated study data from the final report. This version supercedes the labeling sent on October 4, 2000. The following sections of the DIPROSONE® Lotion, 0.05%, labeling have been modified (Please refer to the highlighted sections):

- CLINICAL PHARMACOLOGY
  - Pharmacokinetics
- INDICATIONS AND USAGE
- PRECAUTIONS
  - Pediatric Use
- ADVERSE REACTIONS
- DOSAGE AND ADMINISTRATION

The product labeling for the sections, CLINICAL PHARMACOLOGY: Pharmacokinetics and PRECAUTIONS: Pediatric Use, included in this submission used the study protocol criteria (i.e., adrenal suppression was indicated by either a ≤ [redacted] mcg/dL pre-stimulation cortisol, or a cosyntropin post-stimulation cortisol ≤ 18 mcg/dL and an increase of ≤ 7 mcg/dL from the baseline cortisol) to describe the number of patients experiencing adrenal suppression during the clinical studies.

- Response to Reviewer's comments dated March 20, 2001 including Environmental Assessment for Categorical Exclusion

The following components were submitted this same day under NDA 19-555 / S-016 (DIPROLENE® AF [augmented betamethasone dipropionate] Cream, 0.05%):

- The final study report with re-analysis according to Cortrosyn® labeling and the ICH guidelines for age group distribution for the four betamethasone dipropionate safety studies in pediatric subjects with atopic dermatitis. These safety studies include: DIPROLENE® AF (augmented betamethasone dipropionate) Cream, 0.05%, (Protocol P01260); DIPROSONE® (betamethasone dipropionate) Ointment, 0.05%, (Protocol P01261); DIPROSONE® (betamethasone dipropionate) Cream, 0.05%, (Protocol P01262); and DIPROSONE® (betamethasone dipropionate) Lotion, 0.05%, (Protocol P01263).
- Abbreviated SAS data sets annotated for abnormal cortisol values with annotated case report forms and dictionary of terms
- A Microsoft WORD® format of the final study report text
- Environmental Assessment for Categorical Exclusion
- Spontaneous Adverse Event Reports
- Literature Search
- Serious Adverse Event Case Report

Schering Corporation certifies that a copy of the cover letter and technical section of this amendment is being sent to FDA's New Jersey District Office.

If you have any questions regarding this submission, please feel free to contact Todd Paporello, Pharm.D. at (908) 740-4252 or Mary Jane Boyle at (908) 740-5693.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 33 (j) as well as the FDA regulations.

Sincerely,

Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

Copies:

Kevin White (for Olga Cintron): DESK COPY and WORD Disk

TP:es

Enclosure

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

TELEPHONE: (908) 298-4000

NDA # 17-781 / 022
NDA SUPPL. # SE8

October 4, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room (HFD-540)
5600 Fishers Lane
Rockville, MD 20857
Attention: Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products

NDA 17-781
DIPROSONE® (betamethasone dipropionate) Lotion

SUBJECT: SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED LABELING SUPPLEMENT

Dear Dr. Wilkin:

Enclosed is a labeling supplement to approved NDA 17-781, DIPROSONE® (betamethasone dipropionate cream) Lotion, 0.05%, in response to an official Written Request for pediatric studies dated July 16, 1999 amended April 19, 2000 for betamethasone dipropionate products and LOTRISONE® (clotrimazole and betamethasone dipropionate cream) Cream. Reference is made to the teleconference on September 15, 2000 that was held to discuss difficulties in enrollment of tinea cruris patients ages 12 to 16 years and broadening of the evaluable atopic dermatitis subgroup patients ages 6 to 8 years. A request for further amendments to the Pediatric Request was submitted on September 28, 2000. **(ENCLOSURE 1)**

As discussed with Ms. Fornaro, included in a supplement submitted this same day to NDA 19-555 is a combined study report for the four betamethasone dipropionate safety studies in pediatric subjects ages 3 months to 12 years with atopic dermatitis with DIPROLENE® AF (augmented betamethasone dipropionate cream) Cream, 0.05%, (Protocol P01260); DIPROSONE® (betamethasone dipropionate cream) Cream, 0.05%, (Protocol P01262); DIPROSONE® (betamethasone dipropionate ointment) Ointment, 0.05%, (Protocol P01261); and DIPROSONE® (betamethasone dipropionate lotion) Lotion, 0.05% (Protocol P01263). Safety studies were also conducted with LOTRISONE® (clotrimazole and betamethasone dipropionate cream) Cream in patients 12 to 16 years of age with tinea cruris or tinea pedis. Results of these studies also are being submitted to NDA 18-827 this same day, October 4, 2000.

The four atopic dermatitis safety studies in pediatric subjects were each terminated due to HPA effects as described in the "Rate-Limiting" safety, "Deviation (reduction of 10% or greater) from the lower normal limit for plasma (serum) cortisol and/or the Cosyntropin® (ACTH) challenge response in 10% of subjects" (Amendment to the Pediatric Request dated April 19, 2000). Therefore, enrollment of 50 evaluable subjects ages 3 months to 12 years with 30 evaluable subjects ages 6-8 years was not achieved. The Agency was notified of the termination of these studies:

- DIPROSONE® Lotion Study P01263: [redacted] on April 21, 2000 due to "Rate-Limiting" safety in the 8 to 12 year and 6 to 8 year age groups.
- DIPROSONE® Cream Study P01262: [redacted] on July 14, 2000 due to "Rate-Limiting" safety in the 6 to 8 and 2 to 5 year age groups.
- DIPROSONE® Ointment Study P01261: [redacted] on September 26, 2000 due to "Rate-Limiting" safety in the 6 to 8 age group.
- DIPROLENE® AF Cream Study P01260: [redacted] on September 26, 2000 due to "Rate-Limiting" safety in the 2 to 6 year age group.

Based on the available safety data from the **Study P01263** included in the study report submitted in the supplement to NDA 19-555, the following sections of the DIPROSONE® Lotion, 0.05%, labeling have been modified:

CLINICAL PHARMACOLOGY:
Pharmacokinetics:
INDICATION AND USAGE:
PRECAUTIONS:
Pediatric Use:
ADVERSE REACTIONS:

Betamethasone dipropionate products and LOTRISONE® (clotrimazole and betamethasone dipropionate cream) Cream were included in the Food and Drug Administration's list of approved drugs for which additional pediatric information may produce health benefits in the pediatric population and appeared in the Federal Register Docket No. 98N-0056. Therefore, labeling supplements dated October 4, 2000 are also being submitted for the following products in fulfillment of this Written Request:

NDA 17-536 DIPROSONE® Cream
NDA 17-691 DIPROSONE® Ointment
NDA 19-555 DIPROLENE® AF Cream
NDA 18-827 LOTRISONE® Cream

The reports for betamethasone dipropionate products and Lotrisone Cream submitted on October 4, 2000 contain 2-week, post-treatment follow-up data. Final reports with 4-week, post-treatment follow-up data will be submitted in full labeling supplements pursuant to the Amended Pediatric Request dated April 19, 2000.

We believe that we have met all the requirements in the Written Request and amended Written Request with the exception of the required 45 tinea cruris subjects. However, we have requested a revision to the Written Request on September 28, 2000 due to the limited availability of patients 12 to 16 years of age with tinea cruris. **(ENCLOSURE 1)** All studies referenced herein are responsive to the Written Request, Amendments and Requested Amendments and were conducted in accordance with commonly accepted scientific principles.

In accordance with the Agency's guidance,[a] we are requesting a pediatric exclusivity determination based on the studies included in this submission, and the studies and labeling supplements submitted to the other NDA's as cited above.

The revisions requested to Diprolene Gel, Diprolene Ointment and Diprolene Lotion have been implemented. Copies of this labeling is provided in Section 20, Other Information in the supplement to NDA 19-555.

These supplements have been prepared in accordance with 21 CFR 314.50, 314.70 and 201.57. The following guidances were also used in preparation of this supplement: "The Content and Format for Pediatric Use Supplements" and "Qualifying for Pediatric Exclusivity Under Section of the Federal Food, Drug and Cosmetic Act". A Table is attached with identifies the kind of pediatric data submitted **(ENCLOSURE 2)**. The study reports were prepared in a format consistent with FDA's "Guidelines for Format and Content of Clinical and Statistical Sections of New Drug Applications (July 1988)" and "ICH:E3: Structure and Content of Clinical Study Reports (July 1996)"

References to the requested data and information in the official Pediatric Written Request have been included in Volume 1, Section 20 of this submission. In addition, a faxed copy of this letter and those for the other supplements was sent, at time of this mailing, to the OFFICE OF GENERIC DRUGS (OGD), Attn: Director, OGD (HFD-600), 301-594-0183.

Pursuant to 21 USC 379(h)(a)(1)(F), no fee is due upon submission of this supplement since it only includes new pediatric safety information to an approved product.

---

[a]Guidance for Industry, Qualifying for Pediatric Exclusivity Under Section 505A of the Food, Drug, and Cosmetic Act, September 1999

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

EK/it

Enclosure

Copy (letter): OFFICE OF GENERIC DRUGS (OGD)
Attn: Director
OGD (HFD-600)
Fax: 301-594-0183

Mary Jean Kozma-Fornaro
Fax: 301-827-2075

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Response to a pediatric written request dated 7/16/97 DC 1/26/99

SCHERING CORPORATION

ORIGINAL

GALLOPING HILL ROAD KENILWORTH, N.J. 07033

CABLES: SCHERING KENILWORTH
TELEX: 138316
138280
TELEPHONE: (908) 298-4000

May 23, 1997

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Products
HFD-540
5600 Fishers Lane
Rockville, MD 20857
Attn: Document Control Room
FDA, CDER, ODE 5

DIPROSONE® Cream
NDA 17-536
DIPROSONE® Lotion
NDA 17-781
DIPROSONE® Ointment
NDA 17-691.

17781 SERIAL
NDA SUPPL REQ: LABELING

SUBJECT: LABELING SUPPLEMENT

Dear Dr. Wilkin:

We are submitting supplements in accordance with the notice published in the Federal Register December 13, 1994, Volume 59, No. 238 regarding Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of the "Pediatric Use" Subsection in the Labeling. These supplements are being submitted for DIPROSONE® Cream (NDA 17-536), DIPROSONE® Lotion (NDA 17-781) and DIPROSONE® Ointment (NDA 17-691) which have the same product family labeling. A similar supplement also is being submitted to the DIPROSONE® Topical Aerosol NDA (17-829).

The supplements consist of proposed draft labeling (Attachment 1) and a report supporting the proposed labeling, Assessment of the use of DIPROSONE® (Betamethasone Dipropionate) Cream, Ointment, Lotion and Aerosol in Pediatric Patients (Attachment 2).

The following revisions to the labeling have been made:

PRECAUTIONS - General and Pediatric Use:

"Children" has been revised to "pediatric patients."

PRECAUTIONS - Pediatric Use:

Guidance for use on pediatric patients under 12 years of age has been included.

A recommendation is included for not using DIPROSONE® Cream on infants less than 1 year of age because this product contains ceteareth-30, a drug-absorption enhancer. The supporting reference is included (Attachment 3).

Additional details regarding the greater risks of glucocorticosteroid insufficiency and HPA axis suppression in pediatric patients and greater susceptibility of pediatric patients to skin atrophy have been added.

DOSAGE AND ADMINISTRATION:

Guidance for use on pediatric patients under 12 years has been included.

The recommendation for not using DIPROSONE® Cream on infants less than 1 year of age because this product contains ceteareth-30 is included here also.

A statement has been added advising not to use DIPROSONE® in the diaper area if the child still requires diapers or plastic pants as these garments may constitute occlusive dressing.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

EK/nf

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

TELEPHONE: (908) 298-4000

June 18, 2001

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
N216 Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

NDA 17-781 / S-022
DIPROSONE®
(betamethasone dipropionate) Lotion
0.05%

SUBJECT: AMENDMENT TO SUPPLEMENT S-016
RESUBMISSION OF ELECTRONIC FILES

Dear Dr. Wilkin:

Reference is made to the amendment to Diprosone Lotion Supplement NDA 17-781 / S-022 submitted on May 31, 2001.

Reference also is made to a teleconference on June 12, 2001 with Randy Levin (Electronic Submission Coordinator) regarding the supplement amendment submitted to Diprolene AF Cream NDA 19-555/S-016 in which he requested another disk with copies of the letter, FDA Form 356H and SAS datasets with the dictionary of terms and annotated case report forms. PDF and WORD files of the draft labeling and the case report form for the subject with a serious adverse event were also requested to be included on the disk.

In response to his request, a revised CD-ROM disk for the amendment for the supplement to Diprosone Lotion NDA (NDA 17-781/S-022) is being submitted to the Electronic Submission Coordinator. The following items are being includedon the disk:

- A copy of this letter. A copy of the May 31, 2001 letter submitted with amendment to NDA 17-781/S-022 is provided in Attachment 1. (PDF Format)
- FDA Form 356H (PDF Format)
- Draft labeling and annotated draft labeling (PDF and WORD Format)

DUPLICATE