please do not hesitate to contact myself, Dr. Pelliccione, Sr. Director Worldwide Regulatory Affairs (907-740-5680) or Dr. Denise Flanagan, (908-740-2210).

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,

Elaine Potomski for

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

EP/pm

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

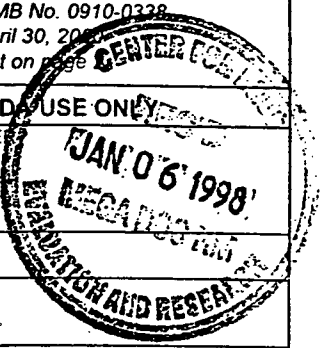
APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

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

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 200
See OMB Statement on page

FOR FDA USE ONLY

APPLICATION NUMBER



APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Schering Corporation	January 5, 1999
TELEPHONE NO *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(908)740-2628	(908) 740-2243

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code and U.S License number if previously issued).*

2000 Galloping Hill Road
Kenilworth, New Jersey 07033

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City State, ZIP Code, telephone & FAX number)* IF APPLICABLE

Joseph F. Lamendola, Ph.D.
Vice President
2000 Galloping Hill Road
Kenilworth, NJ 07033

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-010

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
LOTRISONE®	clotrimazole/betamethasone dipropionate

CHEMICAL, BIOCHEMICAL /BLOOD PRODUCT NAME *(if any)* 1) 1-(0-Chloro-a,a-diphenyl benzyl) imidazole
2) 9-Fluoro-11β, 17,21-trihydroxy-16β-methylpregna-1,4-diene-3, 20-dione 17, 21-dipropionate

CODE NAME *(if any)* SCH 370

DOSAGE FORM	STRENGTHS:	ROUTE OF ADMINISTRATION
Lotion		Topical

PROPOSED INDICATION(S) FOR USE

APPLICATION INFORMATION

APPLICATION TYPE (check one)

☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug

TYPE OF SUBMISSION (check one)

☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☒ CHEMISTRY, MANUFACTURING, AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
General Correspondence

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED_____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND 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)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6 Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11 Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13 Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14 A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15 Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
	17. Field copy certification (21 CFR 314.5 (k) (3))
x	18. User Fee Cover Sheet (Form FDA 3397)
x	19. OTHER (Specify) General Correspondence

CERTIFICATION

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

1 Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2 Biological establishment standards in 21 CFR Part 600.
3 Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4 In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5 Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72 , 314.97, 314.99, and 601.12.
6 Regulations on reports in 21 CFR 314.80, 314.81, 600 80 and 600.81.
7 Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

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

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

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Elaine Potanoski /for Dr. Lamendola	Joseph F. Lamendola, Ph.D. Vice President, U.S. Regulatory Affairs	January 5, 1999

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2000 Galloping Hill Road, Kenilworth, NJ 07033	(908) 298-2628

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

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

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

Please DO NOT RETURN this form to this address.

FORM FDA 356h (7/97)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: *OMB No. 0910-0297*
Expiration Date: *November 30, 1996.*

USER FEE COVER SHEET

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attn: Joseph F. Lamendola, Ph.D.

3. TELEPHONE NUMBER *(Include Area Code)*
(908)740-2628

4. PRODUCT NAME
LOTRISONE® Lotion

...OES THIS APPLICATION CONTAIN CLINICAL DATA? ☐ YES ☒ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

6. USER FEE I.D. NUMBER

7. LICENSE NUMBER/NDA NUMBER

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92

☐ THE APPLICATION IS SUBMITTED UNDER 505(b)(2) *(See reverse before checking box.)*

☐ AN INSULIN PRODUCT SUBMITTED UNDER 506

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

9. a. HAS THIS APPLICATION QUALIFIED FOR A **SMALL BUSINESS EXCEPTION**? ☐ YES ☐ NO *(See reverse if answered YES)*

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☐ NO *(See reverse if answered YES)*

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

...ATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Elaine Potomski /for Dr. Lamendola	Vice President U.S. Regulatory Affairs	January 5, 1999

NDA 20-010
Lotrisone Lotion

Background

Reference is made to our pending New Drug Application for Lotrisone Lotion (NDA 20-010) originally submitted on August 31, 1989 and FDA's approvable letter of July 31, 1991. Reference is also made to our June 6, 1994 amendment to NDA 20-010 in which we provided information on an [redacted] the Lotrisone Lotion bottles as well as a revision to the temperature storage range. In addition to the 1994 amendment, Schering has been in contact with the Division on several occasions regarding CMC information. A comprehensive update of all relevant CMC information was provided in the form of a Briefing Book in preparation for a meeting with the Division which took place on November 21, 1994. For your convenience, a chronological listing of all FDA correspondence relating to CMC information since the 7/31/91 approvable letter is provided in ***Attachment I.*** A copy of the 1991 approvable letter is also included for your convenience.

Proposal

We plan to accept the classification of Lotrisone Lotion as a high potency corticosteroid as recommended by the Division in the 1991 approval letter. Additionally, we plan to amend the Lotrisone Lotion application to reflect the current CMC information.

Request

We are requesting the opportunity to discuss with the Division our plans to update the CMC information. As indicated above, we accept the classification of Lotrisone Lotion as a high potency corticosteroid as recommended by the Division. Since the potency classification of Lotrisone Lotion was the only issue identified in the 1991 approval letter, we hope that upon review of the updated CMC information, final approval of our application will be granted.

Our amendment will serve to incorporate CMC changes, which have occurred since the initial filing and the June 6, 1994 amendment. It will also include revised labeling.

The summary of the changes detailed on the following pages is provided as background for the teleconference. We hope the teleconference can serve as a forum during which we can obtain the Division's concurrence that the information detailed below will be acceptable for obtaining approval of our application. We would also like to discuss the Division's timeframe for review and approval of this amendment.

SUMMARY OF CHANGES
(by NDA Section)

DRUG SUBSTANCE

The active ingredients used in Lotrisone Lotion are betamethasone dipropionate and clotrimazole. These active ingredients are used in many of Schering's dermatological products and as such, we requested approval from the Division to establish central repositories for all CMC information pertaining to these actives. We identified Diprolene Lotion (NDA 19-716) as the repository for betamethasone dipropionate (S-008; submitted 12/12/97; approved 6/15/98) and Lotrimin Lotion (NDA 18-813) as the repository for clotrimazole (S-019; submitted 3/12/98; approved 5/18/98).

To maintain consistency and to facilitate review of drug substance information common to many of Schering's dermatological products, we ask for the Division's concurrence that the Drug Substance section of NDA 20-010 can be replaced with a cross-reference to NDA 19-716 for betamethasone dipropionate and to NDA 18-813 for clotrimazole.

DRUG PRODUCT

Site of Manufacture

The manufacturing site listed in our original application is Schering Corporation, Union NJ. We have since moved the manufacture of all liquids, ointments and creams to our Kenilworth facility, which is located four miles away. This move was part of a consolidation effort, which has affected a number of products over the past several years. As indicated in the Table provided in ***Attachment II***, the manufacturing processes and scale are the same as that described in our original application. The Kenilworth facility uses equipment that is either identical to or of the same operating principle as the equipment used in Union. For completeness and consistency with our current standards, we will provide a more detailed narrative description of the process to replace the one provided in the original application. An updated "Site of Manufacture" page will also be provided reflecting information relevant to the Kenilworth facility.

Packaging

[redacted]

[redacted] For completeness and ease of review, our CMC amendment will contain a new packaging section in its entirety. For your convenience, ***Attachment III*** contains a summary of [redacted] described above.

Stability Protocol
An updated stability report and marketed product stability protocol were presented during the 1994 meeting with the Division. For completeness, the CMC amendment will include both the report and the protocol along with the expiry page, which has been revised to reflect the storage statement, provided in the June 6,1994 amendment. For reference, the stability protocol and expiry page is provided in ***Attachment IV*** of this fax.

Environmental Assessment
An updated EA will be provided in accordance with the format recommended in the Guidance for Industry on Environmental Assessments issued July 1998.

Labeling
Revised labeling reflecting classification of Lotrisone Lotion as a high potency corticosteroid will be included in the CMC amendment.

Attachment 1

Chronological listing of all FDA correspondence relating to CMC information since the 1991 approvable letter:

• 2/6/92	Letter from FDA	Request for information establishing whether betamethasone dipropionate is in solution or suspension.
• 6/6/94	Letter to FDA	Amendment for [redacted] and revised storage temperature
• 9/16/94	Letter to FDA	Submission of briefing book for use in discussing the changes being made to the NDA after receipt of the 1991 approvable letter.
• 10/20/94	Letter to FDA	Packaging amendment correction
• 10/21/94	Letter to FDA	Updated microbiology information and submission of drug product specifications
• 10/21/94	Letter to FDA	Addendum to briefing book originally submitted 9/16/94.
• 11/21/94	FDA and Schering Meeting	Meeting to discuss manufacturing site change, [redacted], stability data, synthesis changes, microbiology information, labeling, package insert as found in the 9/16/94 briefing book, the 10/21/94 addendum, and the 10/20/94 packaging amendment.
• 12/1/94	Letter to FDA	Response to request for information on Clotrimazole and Betamethasone Dipropionate are in suspension.
• 12/14/94	Letter to FDA	Schering's minutes of 11/21/94 meeting.

1/23/95
hotd.

SCHERING CORPORATION

GALLOPING HILL ROAD KENILWORTH, N. J. 07033

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

ORIGINAL

December 14, 1994
NDA 20-010
Lotrisone (betamethasone dipropionate/clotrimazole) Lotion

Jonathan Wilkin, M.D., Director
Division of Topical Drug Products
Attn: Document Control Room 12B-30
HFD-540
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Subject: Lotrisone Lotion

Dear Dr. Wilkin:

We are submitting our understanding of the November 21, 1994 meeting with members of your Division to discuss the changes to Lotrisone Lotion NDA since the July 31, 1991 approvable letter.

FDA Representatives
Dr. DeCamp
Dr. W. Chambers
Ms. Cook
Dr. Harkins
Ms. Holmes
Dr. Raymond
Dr. Silver
Dr. Slifman
Dr. Wilkin

Schering Representatives
Dr. D. Chambers
Dr. Cuffie-Jackson
Dr. Dicken
Dr. Kaplan
Ms. Krhoun
Ms. Matlosz
Mr. Montefusco
Dr. Sequeira

BACKGROUND

Following receipt of an amendment (June 6, 1994) to provide for [redacted] to be used in the packaging components and revised storage temperature, Ms. Cook called on July 29, 1994 to determine whether there would be additional changes. Since we replied that additional revisions would be forthcoming, Ms. Cook suggested that a meeting be held to update the Division. The following changes were discussed at the November 21, 1994 meeting:

- Drug Product Manufacturing Site Change to Kenilworth
- [redacted]
- Additional Stability/Microbiology
- Revised Labeling/Potency Classification

DISCUSSION

- Drug Product Manufacture Site Change to Kenilworth

Relocation of the drug product manufacture from Union, N.J. to Kenilworth, N.J. (four miles apart) for Lotrisone Lotion was described by Mr. Montefusco. Lotrisone Lotion as well as several of our marketed products are involved in the transfer and consolidation activities from the Union facility to the upgraded Kenilworth facility.

Plans had been reviewed with the local District Office and they have not commented unfavorably. NDA supplements are to be submitted for several of the marketed products.

The Division found our approach for site change to be acceptable. Dr. DeCamp requested that the Division be kept apprised of the status of the NDA supplements for the marketed products in order to permit the local District Office to perform the site transfer inspection for all the involved products at the same time.

- [redacted]

Dr. Dicken summarized the package systems for the 10-mL sample and 30-mL commercial size and the [redacted] since the [redacted] described in the current NDA can [redacted] The same [redacted] will continue to be ultilized but the [redacted]. The change is required as part of the approval in order to have packaging available for product commercialization.

- Additional Stability/Microbiology

The additional stability data on NDA batches, stability data on the product packaged in the [redacted] and stability data for Union validation batches was reviewed. Except for the benzyl alcohol results for the

10-mL bottle, the data was within specifications. Based on the satisfactory Antimicrobial Preservative Effectiveness results at a benzyl alcohol level of [redacted] a proposal was now made to change the lower benzyl alcohol specification to [redacted]. Schering agreed to the following:

- Review the stability data to check if they were corrected for weight loss.

- Provide the rationale for the benzyl alcohol level in Lotrisone Lotion.

- Review the benzyl alcohol data and regressional analysis with regard to the confidence limits and provide an explanation of the data variability at early vs later time points.

- Provide references to the data tables for the points in the regression plots.

- Review the benzyl alcohol stability data to determine the expiration dating and storage temperature. (Dr. W. Chambers (FDA) noted that it is preferable to change the expiration dating or storage temperature rather than the specification, e.g., [redacted] date for the 10-mL bottle or [redacted]). If the specification is changed, justification is need.

- <u>Revisions to Labeling/Potency Classification</u>

The proposed labeling included a mid-potency classification for betamethasone dipropionate in Lotrisone Lotion based on a potency (effect on the HPA axis) study with Lotrisone Cream. Initially the Division disagreed with the mid-potency classification since a potential for HPA-axis suppression was observed.

After the results of the potency study comparing Lotrisone Cream to Cutivate® Cream, Diprolene® Gel and Temovate® Cream were reviewed, it was agreed that there was a high degree of variability in cortisol measurements and the results of the study were inconclusive. The HPA axis study may not be the appropriate method to assign a potency ranking according to the Division. In response to Dr. Wilkin's question regarding the acceptability of corticosteroid potency classifications , (i.e., Stoughten Chart) Dr. Kaplan replied that we agreed with the current potency rankings, however, the choice of Cutivate® Cream, a low mid-potency corticosteroid may not have been appropriate.

The following actions were agreed to:

- The Division to provide guidance on a study design to determine the potency classification of betamethasone dipropionate in the product in December.

- Schering to contact the Division (Mr. Turtil) in a month to set up a conference call to discuss the study design to establish the potency of the corticosteroid.

- Schering to reevaluate the statement in the Clinical Pharmacology section of the package insert regarding no reports of clotrimazole-resistant strains since resistant strains of fungi are generally developed by all products.

- Schering to check if there is data to support that Lotrisone is fungicidal *in-vivo*.

- Schering to provide a safety update.

  Post Meeting Note: No additional studies have been conducted domestically and the product is not marketed abroad. Therefore, there is no safety update to submit.

Finally, we would appreciate a copy of the Division's minutes to this meeting.

Please be advised that the material and data contained in this submission are considered 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,

Ellen R. Kilcarr

Richard N. Spivey, Pharm.D., Ph.D.
Senior Director
U.S. Regulatory Affairs

EK:ms
L:\USRA\NDA\20010\LETTERS\12194.WPD

APPEARS THIS WAY
ON ORIGINAL

SCHERING CORPORATION

ORIGINAL

GALLOPING HILL ROAD KENILWORTH, N.J. 07033

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

4/27/95 hdcl. |S|

December 1, 1994

Wilson DeCamp, Ph.D.
Division of Topical Drug Products
HFD-540 Room 17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 18-827
Lotrisone Cream

NDA 20-010
Lotrisone Lotion

SUBJECT: Response to Request for Information

Dear Dr. DeCamp,

Reference is made to the May 20, 1992 ad hoc discussion, in which you requested data to support that the drug substances, betamethasone dipropionate and clotrimazole, are in suspension in Lotrisone Cream and Lotion formulations.

Reference is also made to the discussion on July 30, 1992 with you in which details for the request was clarified.

In response, we are submitting a report The Characterization of Betamethasone Dipropionate and Clotrimazole Drug Substances Suspended in Lotrisone Cream and Lotion Semi-Solid Products by [redacted]

The experimental evidence presented in this report demonstrates that (1) betamethasone dipropionate and clotrimazole drug substance as formulated in Lotrisone Cream and Lotion are solid suspension without [redacted] (2) the form of the isolated drug substances is consistent from batch to batch as demonstrated on three batches of each formulation, and (3) [redacted] offer viable methodology for the characterization of suspended drug substances in this semi-solid formulation.

Please be advised that the material and data contained in this submission are considered 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,

Richard N. Spivey, Pharm.D., Ph.D.
Senior Director
U.S. Regulatory Affairs

The Characterization of Betamethasone Dipropionate and Clotrimazole Drug Substance Suspended in Lotrisone Cream and Lotion Semi-Solid Products by [redacted] a [redacted]

Introduction: Topical semi-solid pharmaceutical products are often formulated using the drug active in suspension rather than solution in order to achieve the desired therapeutic effect. Verification of the suspension after manufacture or during stability studies can be made by direct examination of the drug particles using polarized light microscopy. However, microscopic methods do not provide an unambiguous identification particularly when micronized drug substances are used which do not exhibit any characteristic morphology. Also, more than one active may be present which would then preclude independent identification of the individual drug components. The Lotrisone products are examples of a complex formulation in which two [redacted] drug substances, clotrimazole and betamethasone dipropionate, are suspended in a white petrolatum and propylene glycol/water emulsion (see attached formulations).

Since microscopic methods could not identify both drug substances used in Lotrisone formulations, other methods were sought. [redacted] is a widely accepted method for the identification of [redacted] materials. However, [redacted] is primarily used for the analysis of solid substances and its application to semi-solid or liquid suspensions is only successful at high concentrations. Attempts to identify clotrimazole and betamethasone dipropionate directly were initially unsuccessful because of low drug concentration. Preconcentration of the drug phase using conventional centrifugation was also unsuccessful since sufficient betamethasone dipropionate could still not be isolated. However, only when [redacted] was used, could sufficient drug material be concentrated and recovered for the identification of both active substances.

Materials:

Lotrisone Cream, USP
Batches 2-NBN-115
3-NBN-104
3-NBN-105

Lotrisone Lotion, USP
Batches 31703-081
20073-038A
21959-013C

Diprosone Cream, USP
Batch 1-KGD-303

[redacted]

Results: [redacted] of Lotrisone Cream and Lotion formulations resulted in complete stratification of the samples into an [redacted]. After the solid was removed and analyzed by [redacted] the resulting patterns (Fig. 1-6) showed only peaks characteristic of the original drug substances, clotrimazole and betamethasone dipropionate. Since clotrimazole is formulated at nearly fifteen times the concentration of betamethasone dipropionate, the patterns are dominated by clotrimazole peaks that overlap many of the steroid peaks. However, characteristic betamethasone dipropionate peaks can still be observed at 11.2°, 14.9° and 21.5° two theta. Further confirmation for recovery of solid betamethasone dipropionate from formulated suspension was obtained by [redacted] one batch of Diprosone Cream, a similar formulation to Lotrisone but containing no clotrimazole. The [redacted] pattern (Figure 7) of the recovered drug shows only characteristic peaks of betamethasone dipropionate thus confirming suspension of the steroid.

Conclusions: The experimental evidence presented in this report demonstrates that (1) betamethasone dipropionate and clotrimazole drug substance as formulated in Lotrisone Cream and Lotion are in solid suspension without alteration of [redacted] form, (2) the form of the isolated drug substances is consistent from batch to batch as demonstrated on three batches of each formulation, and (3) [redacted] and [redacted] offer viable methodology for the characterization of suspended drug substances in this semi-solid formulation.

APPEARS THIS WAY
ON ORIGINAL

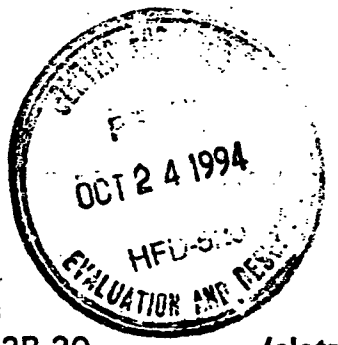
ORIGINAL

SCHERING CORPORATION

NEW CORRESPONDENCE

GALLOPING HILL ROAD
KENILWORTH, N.J. 07033

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



October 21, 1994

Jonathan Wilkin, M.D., Director
Division of Topical Drug Products
Attn: Document Control Room 12B-30
HFD-540
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-010
LOTRISONE
(clotrimazole and betamethasone dipropionate) LOTION

SUBJECT: MICROBIOLOGY INFORMATION

Dear Dr. Wilkin:

Reference is made to our forth-coming meeting November 21, 1994.

Reference is also made to conversations with Mr. Turtil and Ms. Childs during September and October 1994 requesting microbiological information regarding microbial limits, antimicrobial preservatives effectiveness and sterility. In an attempt to clarify what information, suitable for a microbiologist reviewer was needed, a draft of the proposed documents was faxed to Mr. Turtil October 5. 1994.

In response to his comments we are providing the microbiological information under separate cover. Copies of all information are included. As agreed, since the June 6, 1994 stability report is very long, only the introduction discussion and conclusion sections which include the microbial limits information are provided in this package.

The microbiolcgical information enclosed herein has been taken from our NDA, the NDA amendment submitted June 6, 1994 and our briefing book submitted September 16, 1994 for the meeting to be held November 21, 1994. The sources of the information are included in the index followed by the copies. This information pertains to microbial limits and antimicrobial preservative effectiveness. No information is provided for sterility since this is not a sterile product.

/S/
Rachel Sy
/S/
12/14/94

Please be advised that the material and data contained in this submission are considered 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,

Richard N. Spivey, Pharm.D., Ph.D.
Senior Director
U.S. Regulatory Affairs

EK:ms
Enclosures

Desk Copy: Mr. Turtil HFD-540, Room 17B-30

APPEARS THIS WAY
ON ORIGINAL

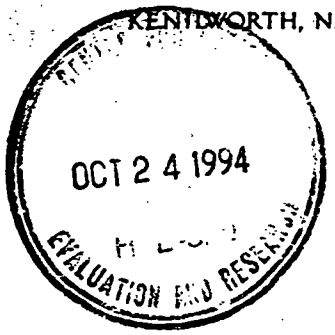
ORIGINAL

SCHERING CORPORATION

NR
/S/
11/29/94

GALLOPING HILL ROAD KENILWORTH, N.J. 07033

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



October 21, 1994

Jonathan Wilkin, M.D., Director
Division of Topical Drug Products
Attn: Document Control Room 12B-30
HFD-540
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-010
LOTRISONE
(clotrimazole and betamethasone dipropionate) LOTION

NEW CORRESPONDENCE

11/29/94
hand.
/S/

SUBJECT: ADDENDUM TO BRIEFING BOOK

Dear Dr. Wilkin:

Reference is made to conversations with Mr. Turtil and Ms. Childs during September and October 1994 requesting separate microbiological information, copies of correspondence since our July 31, 1991 approvable letter and two additional copies of the September 16th briefing book.

Reference is also made to the conversation with Ms. Childs October 17, 1994 when she called to tell us that the meeting date is **November 21, 1994.**

We are providing copies of the correspondence since July 31, 1991 in an addendum to the briefing book. Twelve desk copies of this package are provided together with two (2) additional copies of the September 16th briefing book.

As requested, the microbiological information is being provided under separate cover (October 21, 1994 - Subject: Microbiology Information). Also, an item pertaining to microbiology has been added to the agenda (page 1).

A corrected page 33 for the briefing book submitted September 16, 1994 is included herein (page 2). In the stability report for the [redacted] a summary of the microbial limits results was added.

Please be advised that the material and data contained in this submission are considered 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,

Richard N. Spivey, Pharm.D., Ph.D.
Senior Director
U.S. Regulatory Affairs

EK:ms
Enclosures
Desk Copies (12) : Steven Turtil, HFD-540,17B-30
Desk Copies (2) (9/16/94 submission) : Steven Turtil, HFD-540,17B-30

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

SCHERING CORPORATION

GALLOPING HILL ROAD KENILWORTH, N. J. 07033

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

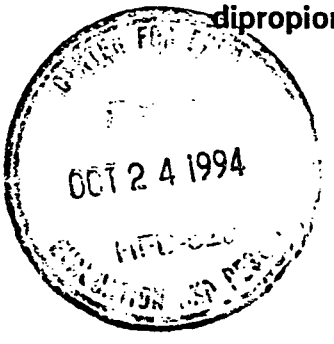
11/22/94 noted. /S/

October 20, 1994

NEW CORRESPONDENCE

Jonathan Wilkin, M.D., Director
Division of Topical Drug Products
Attn: Document Control Room 12B-30
HFD-540
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-010
Lotrisone
(clotrimazole/betamethasone dipropionate) Lotion



SUBJECT: Packaging Amendment - Correction

Dear Dr. Wilkin:

We are providing corrected pages for our NDA amendment submitted June 6, 1994 for Lotrisone Lotion NDA 20-010.

Page 4
In the letter from [redacted] the designation for the [redacted] was corrected to [redacted]

Page 85
In the discussion section of the stability report supporting use of the [redacted] a statement summarizing the microbial limits results was added.

Please be advised that the material and data contained in this submission are considered 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,

Ellen R Kilen for

Richard N. Spivey, Pharm.D., Ph.D.
Senior Director
U.S. Regulatory Affairs

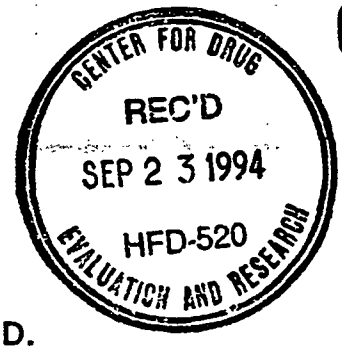
EK:ms
Attachment

SCHERING CORPORATION [redacted]

GALLOPING HILL ROAD KENILWORTH, N.J. 07033

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

ORIGINAL



September 16, 1994

/S/ /S/ 9.29.94

Jonathan Wilkin, M.D.
Director, Division of Topical Drug Products
Attn: Document Control Room 12B-30
HFD-540
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-010
Lotrisone (clotrimazole and betamethasone dipropionate)
Topical Lotion

SUBJECT: Briefing Book for Meeting

Dear Dr. Wilkin:

Reference is made to our August 25, 1994 request for a meeting (pages 1 to 4) to discuss the changes being made to our Lotrisone Lotion NDA.

Reference is also made to your July 31, 1991 approvable letter for NDA 20-210.

As promised in our August 25, 1994 letter, we are submitting a briefing book which summarizes the changes to be made to the NDA. The items to be discussed are identified in the agenda.

We also plan to update the Environmental Assessment to reflect the manufacturing site change and be in line with the current guidelines.

Finally, please note that Dr. Chambers is Associate Director, Physical and Analytical Chemical Research and Development not of Formulation Research as noted in the August 25, 1994 letter. In addition, Mr. Bruce Shutts, Senior Director, Chemical Development will attend.

Please be advised that the material and data contained in this submission are considered 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,

Richard N. Spivey, Pharm.D., Ph.D.
Senior Director
U.S. Regulatory Affairs

EK:kk/Attachments

Desk Copy
Ms. Cook (10 copies)

APPEARS THIS WAY
ON ORIGINAL

Lotrisone Lotion
Briefing Book for FDA Meeting
Index

Lotrisone Lotion
Briefing Book for FDA Meeting
Index

Page(s)

Revisions to Labeling (continued)

SCHERING CORPORATION

GALLOPING HILL ROAD KENILWORTH, N.J. 07033

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

August 25, 1994

Jonathan Wilkin, M.D.
Director, Division of Topical Drug Products
Attn: Document Control Room 12B-30
HFD-540
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Lotrisone Lotion - NDA 20-010

SUBJECT: REQUEST FOR MEETING

Dear Dr. Wilkin:

Reference is made to our July 31, 1991 approvable letter for Lotrisone (clotrimazole, 1% and betamethasone dipropionate, 0.05%) Topical Lotion.

Reference is also made to Ms. R. Cook's July 29, 1994 telephone call to ascertain all potential changes to the pending NDA. This request was prompted by our recent NDA amendment of June 6, 1994 which contained changes to the packaging components and storage temperature. Per her suggestion, we are requesting a meeting to discuss the following changes:

- Manufacturing Site for Lotrisone Lotion: The manufacturing site for Lotrisone Lotion is being transferred to Schering's facilities in Kenilworth, New Jersey from Union, New Jersey. This is part of a [redacted] had been discussed with Dr. DeCamp (July 26, 1993), and Dr. Kumkumian and the Newark District Office.

  Since Lotrisone Lotion is a new product we will plan [redacted] to validate the manufacturing process at the Kenilworth, New Jersey site. Initial results from these batches will be included in the NDA amendment. The batches will be placed on stability for the shelf-life of the product according to a stability protocol. In addition, the first three production batches will be placed on stability and tested according to the marketed stability program. An inspection of the facilities is being planned by the District Office for the marketed

products affected by the consolidation project. Stability data from the batches run to validate the process at Union, New Jersey will be reviewed. The manufacturing procedure is the same. The few minor differences in equipment will be discussed.

- [redacted] for the Bottle, Dispensing Tip and Screw Closure: An NDA amendment was submitted June 6, 1994 to provide for the following resins.

  - Bottle: [redacted]

  - Dispensing Tip: [redacted]

  - Screw Closure: [redacted]

- Stability:

  - Stability data supporting the [redacted] will be presented.

  - Revised Storage Temperature: Based on stability data obtained on Lotrisone Lotion packaged in the components made from the [redacted] as well as data obtained on the product in the current packages, the product is not projected to remain within specifications when stored at 30°C due to loss of benzyl alcohol below the [redacted] lower limit. However, stability data obtained at 25°C does support a 24-month expiration date.

  - Stability data for the validation batches made at the current NDA site (Union, New Jersey) will be summarized. The proposed stability protocols to be used to generate data for the Kenilworth, New Jersey site will also be presented.

- Updated Package Insert: The package insert for Lotrisone Lotion will be updated as requested in the FAX of 2/6/94 regarding Lotrisone Cream and Lotion and as discussed at the May 20, 1992 meeting with members of your division (then Division of Anti-Infective Drug Products).

- Proposed Bottle Labels and Cartons: The company designation is being changed to "Schering/Key" as was discussed with Dr. DeCamp, 2/16/93.

No safety update will be submitted since no additional studies have been conducted.

We would like to propose the following dates for the meeting:

September 26	October 26
October 5	October 28
October 7	

Our proposed participants are:

Dr. Donald Chambers
Associate Director
Formulation Research

Dr. Cynthia A. Cuffie-Jackson
Distinguished Clinical Research Physician
Dermatology/Endocrinology Clinical Research

Dr. C. Michael Dicken
Director
Package Development & Formulation Research

Dr. Allan Kaplan
Vice President
Pharmaceutical Sciences

Ms. Elin R. Krhoun
Manager
U.S. Regulatory Affairs

Ms. Barbara Matlosz
Director
U.S. Regulatory Affairs

Mr. Nicholas Montefusco
Manager
Process Validation

Dr. Joel Sequeira
Senior Associate Director
Formulation Research

Dr. Richard N. Spivey
Senior Director
U.S. Regulatory Affairs

An agenda is attached and a briefing book with the background information will be submitted shortly.

Please be advised that the material and data contained in this submission are considered 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,

Richard N. Spivey, Pharm.D., Ph.D.
Senior Director
U.S. Regulatory Affairs

EK:kk
Attachments

Desk Copy: R. Cook

APPEARS THIS WAY
ON ORIGINAL

L:\USRA\KK\DERM\LTRS\REQUFORM.2

Lotrisone Lotion
FDA Meeting
Agenda

1 - Introduction

2 - Manufacturing Site Change to Kenilworth

- History of Discussion with FDA Regarding Marketed Products
- Comparison of Kenilworth and Union Procedures and Equipment
- Validation Studies
- Proposed Information to be Included in NDA Amendment

3 - [redacted] for Packaging Components

- Description of [redacted]
- Comparison to Current Packaging

4 - Additional Stability Data

- Data Supporting [redacted]
- Data Supporting Revised Storage Condition
- Stability Data from Union Validation Batches
- Proposed Stability Protocols for Kenilworth Validation and Marketed Batches

5 - Revisions to Labeling

6 - Summary

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

SCHERING CORPORATION

GALLOPING HILL ROAD KENILWORTH, N.J. 07033

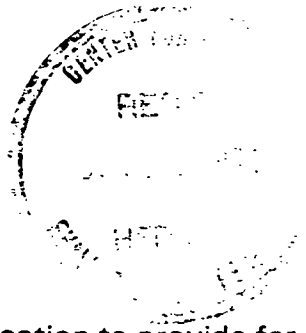
CABLES: SCHERING KENILWORTH
TELEX: 138316
138280
TELEPHONE: (908) 298-4000

NC

June 6, 1994

Jonathan Wilkin, M.D.
Director, Division of Topical Drug Products
Attn: Document Control Room 12B-30
HFD-540
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-010
LOTRISONE LOTION



SUBJECT: PACKAGING AMENDMENT

Dear Dr. Wilkin:

We are submitting an amendment to the subject New Drug Application to provide for the following [redacted] the Lotrisone Lotion packaging components and to change the temperature storage range [redacted] to 25°C [redacted]

The following a [redacted] are included:

Bottle:

[redacted]

Dispensing Tip:

[redacted]

Screw Closure:

Stability data is provided to support the use of these [redacted] for packaging Lotrisone Lotion.

Based on these stability data and statistical analyses provided in the attached reports, Lotrisone Lotion packaged in a 10-mL bottle is not projected to remain within specifications for 24 months when stored at 30°C due to loss of benzyl alcohol below the [redacted] lower limit. However, stability data obtained at the 25°C station does support a 24-month expiration date. Therefore, Lotrisone Lotion, packaged in 10-mL and 30-mL [redacted] bottles made from [redacted] is projected to remain within specifications for at least 24 months when stored between 2°C and 25°C. The stability data of Lotrisone Lotion packaged with the [redacted] are in agreement with data obtained for Lotrisone Lotion packaged in [redacted]

In accordance with the stability commitment and protocol submitted in our NDA, samples of the [redacted] production batches packaged with bottles, dropper tips and caps made from the [redacted] will be placed into our ongoing stability program. We will [redacted] s fall outside the approved specifications for the product.

Please be advised that the material and data contained in this submission are considered 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,

Ellen R. Kligman for

Alexander R. Giaquinto, Ph.D.
Senior Vice President
Worldwide Regulatory Affairs

EK:ss/kk
Attachments

INDEX

Schering-Plough
Research

3000 Galloping Hill Road
Kenilworth, New Jersey 07033
Telephone (201) 298-4000
Telex 6853298 SP KEN

May 6, 1992

ORIGINAL NEW CORRESPONDENCE

Murray Lumpkin, M.D., Director
Division of Anti-Infective Drug Products
CDER-II, HFD-520
Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

CENTER FOR DRUG
REC'D
MAY 7, 1992
HFD-520
EVALUATION AND RESEARCH

[S] 5-19-92 [S]

SUBJECT: NDA 18-827, LOTRISONE Cream
NDA 20-010, LOTRISONE Lotion
NDA 19-555, DIPROLENE AF Cream
Briefing Package

Dear Dr. Lumpkin:

We are submitting a briefing package in preparation for our meeting on May 20th to discuss labeling for Lotrisone Lotion, Lotrisone Cream and Diprolene AF Cream. We will focus on the potency classification of betamethasone dipropionate (BDP) in these preparations. In addition to the five Schering representatives to the meeting noted in our March 26, 1992 correspondence, Dr. Douglass Given (Vice President, U.S. Regulatory Affairs) is expected to attend this meeting. The agenda for the meeting is attached (Attachment 1).

Copies of the cover letters from recent correspondence between Schering and the Agency which form the basis for this meeting are enclosed (Attachment 2) as follows:

NDA	Product	Date	Subject	Page (s)
18-827	Lotrisone Cream	6-25-91	FDA approvable letter for labeling supplement (S-007/S-009)	4
		9-30-91	Schering response	5-7
		2-6-92	FDA fax response	8
20-010	Lotrisone Lotion	7-31-91	FDA approvable letter for Lotion	9-10
		9-16-91	Schering response	11-13
		2-6-92	FDA fax response	14
19-408	Diprolene Gel	11-22-91	FDA approval letter for Gel supplement (S-006)	15-16

The history of our correspondence on the labeling for Lotrisone Cream and Lotion is outlined in Attachment 3 (p.18). We will be presenting the technical and clinical support for our proposal to classify the BDP component of these formulations; [redacted]. The proposed changes in the labeling from your requested labeling for these products are summarized in Attachment 4 (pp. 20-22).

In your approval letter for our Diprolene Gel supplement (NDA 19-408/S-006, 11-22-91), you requested that we conform the labeling for all of our Diprolene products to that approved for the Gel. Such labeling changes are in progress for our Diprolene Ointment and Lotion products. However, we have data which indicates that BDP as formulated in Diprolene AF Cream results in a high potency rather than a super-high potency product as is the case with the other Diprolene dosage forms. The relevant portions of our proposed labeling for Diprolene AF Cream, where potency is directly or indirectly referenced, are found in Attachment 5 (p.24). We will also be presenting data to support this labeling at the meeting.

Our presentations will require the use of an overhead projector and possibly a slide projector. If you need any more information prior to the meeting, please contact Margaret Dillon at (908) 298-5714. We look forward to meeting with you.

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

Sincerely,

Margaret Dillon for

Douglass B. Given, M.D., Ph.D.
Vice President
U.S. Regulatory Affairs

MD:hah
Enclosures

Desk Copies:
Ms. Sandy Childs[11], HFD-520, Room 12B-05
Ms. Rosemary Cook[1], HFD-520, Room 12B-45

ATTACHMENT 1

APPEARS THIS WAY
ON ORIGINAL

AGENDA

May 20, 1992 - 10 A.M.

POTENCY CLASSIFICATION OF BETAMETHASONE DIPROPIONATE IN LOTRISONE CREAM/LOTION AND DIPROLENE AF CREAM

INTRODUCTION/BACKGROUND: INCLUDING LABELING REQUESTED FOR LOTRISONES AND DIPROLENE AF	Mr. Richard Tkach
FORMULATION/MANUFACTURING ISSUES/VASOCONSTRICTOR FINDINGS	Dr. Joel Sequeira
CLINICAL EFFICACY/SAFETY FINDINGS	Dr. Edwin Peets
DISCUSSION	

Schering-Plough
Research

NDA 19-555, Diprolene AF Cream
NDA 18-827, Lotrisone Cream

ORIG

Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530
Telephone (908) 298-4000
Telex 6853298 SR KEN

March 26, 1992

Murray Lumpkin, M.D., Director
Division of Anti-Infective Drug Products
CDER-II, HFD-520
Document Control Room 12B-30
5600 Fishers Lane
Rockville, MD 20857

/S/ /S/ 4-6-92

SUBJECT: **NDA 20-010, Lotrisone Lotion**
Request for Meeting

Dear Dr. Lumpkin:

We are requesting a meeting with members of your Division to discuss labeling for Lotrisone Lotion, Lotrisone Cream, and Diprolene AF Cream. The labeling issue is common to these three products and concerns the classification of the potency of the betamethasone dipropionate (BDP) in the preparations. We feel it will be most expedient to combine the discussion of this issue for the three products in a single meeting. We plan to present the technical and clinical evidence which supports the classification of the BDP in Lotrisone Lotion and Cream as [redacted] and that in Diprolene AF Cream [redacted]. Our proposed agenda is attached.

The following individuals are expected to represent Schering at this meeting:

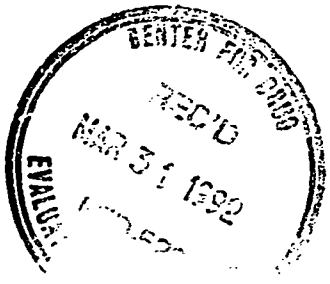
Dr. Allan Kaplan
Vice President, Pharmaceutical Sciences

Dr. Edwin Peets
Senior Director, Clinical Research/Dermatology

Dr. Joel Sequeira
Associate Director, Pharmaceutical Sciences

Dr. Margaret Dillon
Manager, Regulatory Affairs

Mr. Richard Tkach, JD
Associate Director, Regulatory Affairs



A meeting duration of 1-1/2 hours will be sufficient for our purposes. The following dates are proposed:

April 27 or April 28

We will contact Ms. Rosemary Cook early next week to confirm a meeting date and time. A briefing package will be submitted at least two weeks in advance of the meeting date.

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

Sincerely,

Margaret Dillon /for

Douglass B. Given, M.D., Ph.D
Vice President
U.S. Regulatory Affairs

MD/cy

Enclosure

Desk Copy: Ms. Rosemary Cook (8)

APPEARS THIS WAY
ON ORIGINAL

R

Number of Pages Redacted 13

❖❖❖

Draft Labeling
(not releasable,

Schering-Plough
Research

Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530
Telephone (908) 298-4000
Telex 6853298 SP KEN

August 30, 1991

Murray Lumpkin, M.D., Director
Division of Anti-Infective Drug Products
CDER-II, HFD-520
Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

Subject: NDA 20-010, Lotrisone Lotion

Dear Dr. Lumpkin:

Enclosed are three copies of our proposed labeling for the bottles and carton for Lotrisone Lotion. Included are labels for the 10 ml professional samples, the 30 ml bottle and the carton for the 30 ml bottle. The colors for the 10 ml bottle label will be identical to those proposed for the 30 ml bottle. There is no individual carton for the 10 ml sample.

We would like your input on the proposed labeling for these components as soon as possible so that we proceed with ordering necessary packaging supplies.

We are in the process of finalizing our package insert, taking into account the comments contained in your letter of July 31, 1991. Once agreement is reached on this labeling, we will submit final printed labeling for the package insert. In addition, advertising copy for use in our initial promotional campaign for Lotrisone Lotion is being prepared for submission.

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

Sincerely,

Margaret Dillon | for

Douglass B. Given, M.D., Ph.D.
Vice President
U.S. Regulatory Affairs

Desk Copies: Ms. Rosemary Cook (3 copies)

MD:lnm/Enclosures

ORIG

Schering-Plough
Research

Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530
Telephone (908) 298-4000
Telex 6853298 SP KEN

ORIG

August 6, 1991

Murray Lumpkin, M.D., Director
Division of Anti-Infective Drug Products
CDER-II, HFD-520
Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

/S/ /S/

Subject: NDA 20-010, Lotrisone Lotion

Dear Dr. Lumpkin:

This is in response to your letter of July 31, 1991 concerning the above referenced submission. We are in the process of compiling a response which will contain the information requested. This information will be submitted to you as soon as it is available.

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

Sincerely,

Margaret B. Given for

Douglass B. Given, M.D., Ph.D.
Vice President
U.S. Regulatory Affairs

MD:lnm

D. B. GIVEN

AUG 5 1991

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-010

JUL 31 1991

Douglass B. Given, M.D., Ph.D.
Vice President
U.S. Regulatory Affairs
Schering Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

Dear Dr. Given:

Reference is made to your New Drug Application (NDA) dated August 31, 1989, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lotrisone (clotrimazole, 1% and betamethasone dipropionate, 0.05%) Topical Lotion.

Reference is also made to the not approvable letters dated June 29 and December 31, 1990 and to your additional correspondence of January 9 and 14, March 19, and May 31, 1991.

We have completed the review of this application as amended, and it is approvable. Before the application may be approved, however, we request that you submit twelve copies of the final printed labeling (FPL) for the drug product that are identical to the enclosed revised version of the draft labeling submitted on August 31, 1989. Seven of the copies should be individually mounted on heavy-weight paper or similar material. Should additional information relating to the safety and effectiveness of this drug product become available, further revision of the labeling may be required.

Safety update reports should also be submitted in accordance with the requirements of 21 CFR 314.50(d)(5)(vi).

In addition, please be advised that we cannot approve this application until satisfactory Establishment Inspection Reports have been received for all facilities involved in the manufacture and packaging of the bulk drug and the drug product.

Please submit, in duplicate, the advertising copy which you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one copy to the Division of Anti-Infective Drug Products and the second copy to the Division of Drug Advertising and Labeling, HFD-240, 5600 Fishers Lane, Rockville, Maryland 20857. Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FDA 2253 for this submission; that form is for routine use, not proposed materials.

For your information, please be informed that in the future, vasoconstrictor assays will not be accepted as a method to establish equivalence of steroid activity for products that contain a steroid in combination with another active ingredient.

Validation of the analytical methodology in our laboratories is in progress. Upon receipt of the laboratory reports, we will advise you of our conclusions. We expect your continued cooperation to resolve any technical issues with regard to the analytical methods which may be identified.

Within 10 days of the date of this letter, you are required to amend the application, or notify us of an intent to file an amendment, or follow one of the other alternatives described in 21 CFR 314.110. In the absence of such action, on your part, the Food and Drug Administration (FDA) may proceed to withdraw the New Drug Application.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions concerning this application, please contact Ms. Maria Rossana R. Cook, Project Manager, at 301-443-0335.

Sincerely yours,

/S/

Murray M. Lumpkin, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

Attachment 2

	Union	Kenilworth
Batch Size	[redacted]	
Compounder	[redacted]	[redacted]
Disperser	[redacted]	

The operators and supervisors from the Union operation are being moved to Kenilworth.

APPEARS THIS WAY
ON ORIGINAL

(5)

Number of Pages Redacted 1

❖❖❖

Confidential,
Commercial Information

A-3

Number of Pages Redacted 1

❖❖❖

Confidential,
Commercial Information

A-3

G.4 Lotrisone Lotion

DRUG PRODUCT EXPIRY DATE

The finished dosage form in the marketed package will bear a 24 month expiry date. This date will appear on the immediate container and on the outer package.

In addition, a storage statement (store between 2° and 25°C) as determined by stability studies, will appear on the labeling.

The expiration dating period may be extended without prior approval if additional stability studies (as indentified in the protocol on the previous page)* and statistical analysis of these data warrant such a revision. In this event, the change and supporting data will be included in the Periodic Report following the extension.

* Page 03 0293 submitted 8/31/89.

Replaces page 03 0294 submitted 8/31/89

Schering-Plough
Research

2000 Galloping Hill Road
Kenilworth, New Jersey 07033
Telephone (201) 298-4000
Telex 6853298 SP KEN

May 31, 1991

Murray Lumpkin, M.D., Director
Division of Anti-Infective Drug Products
CDER-II, HFD-520
Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

Subject: NDA 20-010 Lotrisone Lotion

Dear Dr. Lumpkin:

As requested by Rosemary Cook of your division the date and outcome from the latest FDA inspection at every site included in the Lotrisone Lotion NDA are as follows:

Union, NJ: Pre-approval inspection for Lotrisone Lotion NDA 20-010, 1/91, approval recommended.

Manati, P.R.: Pre-approval inspection for [redacted]. A 483 was issued with one observation concerning a [redacted] A response to this observation was provided.

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

Sincerely,

Douglass B. Given, M.D., Ph.D.
Vice President
U.S. Regulatory Affairs

Desk Copy: Rosemary Cook (2)
ESW:lnm

NDA 20-010

APR 30 1991

Douglass B. Given, M.D., Ph.D.
Vice President
U.S. Regulatory Affairs
Schering-Plough Research
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

Dear Dr. Given:

Reference is made to your New Drug Application (NDA) and to your amendment dated March 19, 1991, received by the Food and Drug Administration (FDA) on March 25, 1991, for Lotrisone (clotrimazole, 1% and betamethasome dipropionate, 0.05%) Topical Lotion.

We consider your submission a major amendment under 21 CFR 314.60 and have determined that 120 additional days will be required for its review.

The new due date is July 23, 1991.

If questions arise concerning this NDA, please contact Maria Rossana R. Cook of the Project Management Staff at 301-443-0211.

Sincerely yours,

/S/ 4/30/91

Murray M. Lumpkin, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Orig NDA 20-010
HFD-520
HFD-520/MO/DBostwick /S/ 4.29.91
HFD-520/SUPV MO/CCEvans
HFD-520/SUPV PHARM/ROsterberg
HFD-520/CHEM/DKatague
HFD-520/SUPV CHEM/WDe Camp
HFD-521/PROJ MGR/RCook /S/ 4/30/91

Schering-Plough
Research

2000 Galloping Hill Road
Kenilworth, New Jersey 07033
Telephone (201) 298-4000
Telex 6853298 SP KEN

ORT

March 19, 1991

Murray Lumpkin, M.D., Director
Division of Anti-Infective Drug Products
CDER-II, HFD-520
Document Control Room 12B-30
5600 Fishers Lane
Rockville, Maryland 20857

NDA ORIG AMENDMENT

See review April 22, 1991 AM
[S] 8/13-91

Subject: NDA 20-010 Lotrisone Lotion

Dear Dr. Lumpkin:

Attached is our response to your non-approvable letter of December 31, 1990. Specifically, we are providing data which is responsive to your concerns regarding the vasoconstriction study conducted to support the Lotrisone Lotion utilized in our clinical trial. Statistical analysis of the raw data, previously submitted to you on July 20, 1990, and additional vasoconstriction data from studies which included this formulation, support our conclusion that the vasoconstriction effect of the proposed commercial Lotrisone Lotion formulation is similar to that of Lotrisone Cream.

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

Sincerely,

Douglass B. Given, M.D., Ph.D
Vice President
U.S. Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 2 5 1991
HFD-520

ESW:lnm
Attachment