SCHERING CORPORATION

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

July 27, 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 20-010
LOTRISONE LOTION

1 AMENDMENT
BL

SUBJECT: RESPONSE TO FDA REQUEST

Dear Dr. Wilkin:

Reference is made to the July 7, 2000 telephone call from Frank Cross in which he requested colored copies of our proposed bottle labels and cartons for Lotrisone Lotion.

In response to Mr. Cross's request, 4 colored copies of the proposed bottle labels and cartons are being submitted. A desk copy is also being provided.

The following pieces are attached:

30-mL Bottle Label	10-mL Bottle Label
30-mL Bottle Label (enlarged)	10-mL Bottle Label (enlarged)
30-mL Carton	10-mL Carton

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:js
Enclosures

Desk copy: Frank Cross, HFD-540

ORIGINAL

Number of Pages Redacted 2

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SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

TELEPHONE: (908) 298-4000

AMENDMENT
BC

July 21, 2000

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

NDA 20-010
LOTRISONE®
(betamethasone dipropionate, USP and clotrimazole, USP)
Lotion

SUBJECT: AMENDMENT, RESPONSES TO JUNE 21, 2000 INFORMATION REQUEST LETTER.

Dear Dr. Wilkin:

Reference is made to NDA 20-010 for Lotrisone Lotion and its amendment dated October 7, 1999 as well as the following subsequent Schering correspondences dated March 3, 2000, March 13, 2000, April 5, 2000, April 13, 2000, May 5,2000, and June 30, 2000. Reference is also made to the FDA "Information Request Letter" dated June 21, 2000 which contains questions regarding our 10/7/99 amendment.

Enclosed are Schering's responses to FDA's questions contained in the 6/21/00 Information Request Letter. Responses to comment 3 were previously supplied to FDA on 4/5/00 and responses to comments 4-6 were previously supplied to FDA on 5/5/00. For ease of review, we have enclosed copies of these previously submitted responses for comments 3 to 6 of the 6/21/00 request.

In both the 6-month and 9-month stability reports provided to the Agency on 3/13/00 and on 6/30/00 respectively, and based on the observations described in these reports, Schering has requested the opportunity to discuss the data with the Division. Schering has proposed [redacted] and one change in the product label to provide more explicit patient instructions for product delivery.

ORIGINAL

As previously mentioned in our June 30, 2000 letter, we request confirmation that the proposed changes mentioned above are acceptable.

In addition, we would also like to confirm that our proposed 24 month expiry period is acceptable as supported by 24 months of real time data submitted in the original NDA (submitted dated August 31, 1989) and as further supported by the 9-month stability data for recent batches stored under ICH conditions.

If you have any questions regarding the enclosed information, please contact Ms. Elaine Potomski at 908-740-4525. We are confident that our responses have adequately addressed your questions and look forward to quick approval of this NDA.

In accordance with 21 CFR 314.60 (c), Schering Corporation certifies that a copy of the technical section of this amendment is being sent to FDA's New Jersey District Office.

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

Desk Copy: Frank Cross

enclosures:
EP/sa

APPEARS THIS WAY
ON ORIGINAL

SCHERING CORPORATION

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

NEW CORRESP
NC

July 13, 2000

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

NDA 20-010
LOTRISONE®
(betamethasone dipropionate, USP and clotrimazole, USP)
Lotion

SUBJECT: CORRECTION TO LETTER SUBMITTED MAY 5, 2000.

Dear Dr. Wilkin:

Reference is made to NDA 20-010 for Lotrisone Lotion® and our May 5, 2000 responses to FDA comments dated March 14, 2000.

Please be advised that the first page of the response letter submitted 5/5/00 was incorrectly dated as April 5, 2000. The second page of the letter was correctly dated 5/5/00. A complete copy of the 5/5/00 letter is attached for your reference.

We are sorry for any confusion this error may have caused.

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 Potemski for

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

enclosures:
EP/sa

DUPLICATE

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Schering Corporation	July 13, 2000
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

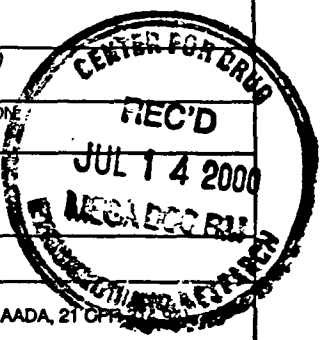
ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
clotrimazole/ betamethasone dipropionate	LOTRISONE Lotion

CHEMICAL/BIOCHEMICAL /BLOOD PRODUCT NAME *(if any)*
9-Fluoro-11β, 17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate/1-(o-Chloro-α,α-diphenylbenzyl)imidazole

CODE NAME *(if any)* SCH 370

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Lotion	0.05%	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

☐ 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 Holder of Approved Application

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
Correction to Letter Submitted May 5, 2000

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

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

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

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attn: Joseph F. Lamendola, Ph.D.

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

3. PRODUCT NAME
Lotrisone Lotion

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO____
(APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA NUMBER

7. 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 UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

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

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

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☐ NO
(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Please DO NOT RETURN this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Elaine Petronella /for Dr. Lamendola	Vice President U.S. Regulatory Affairs	07/13/00

ORM FDA 3397 (5/98)

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

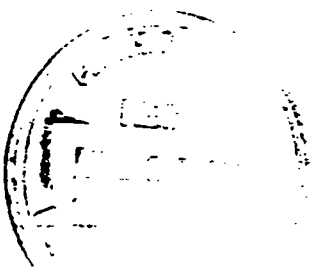
TELEPHONE: (908) 298-4000

BC

June 30, 2000

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

NDA 20-010
LOTRISONE®
(betamethasone dipropionate, USP and clotrimazole, USP)
Lotion



SUBJECT: 9-MONTH STABILITY REPORT

Dear Dr. Wilkin:

Reference is made to NDA 20-010 for Lotrisone Lotion and its amendment dated October 7, 2000 as well as the following subsequent correspondences dated March 3, 2000, March 13, 2000, April 5, 2000, April 13, 2000, and May 5,2000.

An updated stability report containing 9-months of data on three batches of Lotrisone Lotion manufactured at our Kenilworth facility is being sent to NDA 20-010 today (June 30, 2000) via overnight delivery. This update is provided in accordance with our prior discussion with the Division on February 24, 1999 regarding our amendment to NDA 20-010 for Lotrisone Lotion and in accordance with your recent requests for additional stability data.

In the 6-month stability report provided to you on 3/13/00 and based on the observations described in this report, Schering has requested the opportunity to discuss the data with the Division. Schering has proposed

, and one change in the product label to provide more explicit patient instructions for product delivery.

We would like to confirm that the proposed changes mentioned above are acceptable.

In accordance with 21 CFR 314.60 (c), Schering Corporation certifies that a copy of the technical section of this amendment is being sent to FDA's New Jersey District Office.

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/sb

APPEARS THIS WAY
ON ORIGINAL

2.1

NDA 20-010

JUN 29 1990

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

We also refer to your amendment dated December 15, 1989, and received December December 20, 1989.

We have completed our review of your NDA and have concluded that the information provided is inadequate and that the application is not approvable under section 505(b)(1) of the Act and 21 CFR 314.125(b) of the regulations.

Specifically, the information regarding bioavailability (vasoconstrictor study) is not complete. The following information must be supplied in support of this study:

1. A complete protocol for the study.

2. The raw data.

3. The name(s) and qualifications of the study investigators and the name and location of the facility where this study was done.

The review of the manufacturing and control portion of this application is, at present, incomplete. If, upon completion of this review, other concerns arise they will be conveyed to you.

Within 10 days after the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other alternatives under 21 CFR 314.120. In the absence of such action on your part, the Food and Drug Administration may take action to withdraw the application. Any amendment should respond to all the deficiencies listed. A partial reply will not be processed as a major amendment unless it addresses all remaining outstanding deficiencies, nor will the review clock be reactivated until all deficiencies have been addressed.

Sincerely yours,

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-82
HFD-420
HFD-500
HFD-710
HFD-520 /S/ 6/27/90
HFD-520/MO/CCEvans/sdj/6/27/90 S 6.28.90
HFD-520/MO/DCBostwick S 6/28/90
HFD-520/PHARM/KMainigi
HFD-520/PHARM/ROsterberg
HFD-520/CHEM/WDeCamp
HFD-520/PMS/VCSick sdj/6/27/90 S 6/28/90 S 6/28/90
HFD-520/PMS/JBona S 6/27/90
F/T: 6/27/90

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-010

INFORMATION REQUEST LETTER

Schering Corporation
Attention: Joseph F. Lamendola, Ph.D.
Vice President, U. S. Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

JUN 2 1 2000

Dear Dr. Lamendola:

Please refer to your new drug application (NDA) submitted August 31, 1989, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lotrisone (betamethasone dipropionate and clotrimazole) Lotion.

We also refer to your submissions dated October 13 and 28, 1999, and March 6 and 15, 2000.

We are reviewing the chemistry section of your submissions and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. Please specify how long each batch is held in a storage vessel before being transferred to the plastic containers. If the drug product is held for more than three months, supporting stability data (studies in a similar container) are required to show that the product continues to meet the regulatory specifications.
2. Please provide samples of your caps (closures) for the 10 mL and 30 mL size bottles. On April 13, 2000, you provided the agency with samples of the containers without the caps.

In addition, please respond to the following outstanding information requests which had been previously communicated by faxes dated March 3 and 14, 2000, and by teleconference on March 9, 2000:

3. Please provide the formulation disclosure statement for the [redacted] dispenser dropper tips and closures.
4. Please provide the name of each enrichment medium used in your test procedures for microbial limits, and its reference (location) in the AOAC Bacteriological Analytical Manual.
5. Please provide details of your sampling plan for the in-process packaging controls. (The description provided in Vol. 6.1 page 103 is deficient: The use of the term sufficient is not an adequate descriptor without specifying what constitutes a sufficient number).
6. Please specify the closure torque or alternately refer to USP 24 <671> if the USP procedure is being followed.

7. Please provide the available nine and twelve month stability data for all three batches.
8. Please provide the following phase 4 stability commitment to support your proposed twenty four months shelf life:
   a) to place the first three commercial batches into your ongoing stability program and to report the results as soon as they become available;
   b) to place at least one commercial batch per year on stability;
   c) to withdraw from the market any out of specification lots; and
   d) to use the same pull schedule for the intermediate ICH testing conditions (30°C/60%RH) as that for the long term testing (25°C/60%RH).

If you have any questions, call Frank H. Cross, Jr., Project Manager, at (301) 827-2020.

Sincerely,

/S/

Wilson H. DeCamp, Ph.D.
Chemistry Team Leader for the
Division of Dermatologic and Dental Drug Products,
(HFD-540)
DNDC III, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 20-010
HFD-540/Div. Files
HFD-540/Wilkin
HFD-540/Okun
HFD-540/Luke
HFD-540/Jacobs
HFD-540/Brown
HFD-520/Sheldon
HFD-805/Cooney
HFD-805/Hussong
HFD-540/Cross
HFD-540/DeCamp
HFD-540/Turujman SAT 6/22/00
HFD-830/Chen
DISTRICT OFFICE

APPEARS THIS WAY
ON ORIGINAL

Drafted by: whd/June 21, 2000
filename: N20010ir.wpd

INFORMATION REQUEST (IR)

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CLINICAL STUDY SYNOPSIS – LOTRISONE® CREAM

TITLE The Effect of Lotrisone® Cream on the HPA Axis of Normal Volunteers: Phase IV Study (Study No. C92-257)

STUDY DESIGN This study was designed to support a medium potency classification for Lotrisone (betamethasone dipropionate/clotrimazole) cream by comparing the effect of applications of the topical corticosteroid on the HPA axis of normal adult male volunteers to that of Cutivate® (fluticasone propionate) cream 0.05% (classified as medium potency). Temovate® (clobetasol propionate) cream 0.05% and Diprolene® (betamethasone dipropionate) gel 0.05% (each classified as super-high potency) were included in the study as positive controls. In each phase, subjects were to apply 3.5 g of their assigned treatment to the crural area for up to 2 weeks. Plasma cortisol levels were determined on 2 consecutive days prior to the initiation of treatment, during treatment after 2, 4, 6, 8, 10, 12, and 14 days of drug application, and on the two days immediately following the last treatment application. Pre- and posttreatment evaluations of adrenal function were also made using a standard Cortrosyn challenge test. A normal response to Cortrosyn stimulation was defined as a doubling of the Baseline plasma cortisol value and an absolute cortisol value >17 μg/dL following a 6-hour Cortrosyn IV infusion. Subjects were examined daily for evidence of side effects, and they were queried about any other adverse events.

PHASE I - OPEN-LABEL PHASE

Phase I was an open-label, pilot phase which was conducted in order to validate the study design. In Phase I, three subjects applied 3.5 g of Temovate cream 0.05% to the crural area BID. Since Temovate cream is a super-high potency topical corticosteroid that is known to suppress adrenal cortisol secretion, progression of the study to Phase II was contingent upon the ability of the study to detect corticosteroid induced effects as indicated by a decrease in the morning (8 AM) plasma cortisol level to below 5 μg/dL on two consecutive occasions in any one of the three subjects enrolled in Phase I.

In each of the 3 subjects enrolled in Phase I (all white, age 36 to 42), applications of Temovate cream 0.05% resulted in posttreatment plasma cortisol levels that were below the normal laboratory reference level of 5 μg/dL. One of the 3 subjects also exhibited low 24-hour urinary cortisol levels (<10 μg/24 hr) on two occasions. Each of the 3 subjects discontinued treatment applications because of subnormal plasma cortisol levels. One subject responded abnormally to the posttreatment Cortrosyn test. These results indicate that the study as designed was sensitive enough to detect the occurrence of adrenal effects, where they occurred, resultant from corticosteroid applications.

No adverse events were reported for subjects enrolled in Phase I.

PHASE II - RANDOMIZED PHASE

Phase II of the study was a randomized, investigator-blind, single-center, parallel-group evaluation of the HPA axis effects of Lotrisone cream compared to those of Cutivate cream 0.05% in which subjects applied 3.5 g of 1 of the test drugs to the crural area BID for up to 2 weeks. The positive controls, Temovate cream 0.05% and Diprolene gel 0.05% were applied according to the same treatment regimen.

PHASE II - POPULATION: Thirty-two subjects were enrolled in Phase II and were randomly assigned to 1 of the 4 treatment groups (8 per group - Lotrisone cream, Cutivate cream 0.05%, Temovate cream 0.05%, or Diprolene gel 0.05%). Eleven subjects were white and 21 were black; they ranged in age from 22 to 50 years.

PHASE II - RESULTS

HPA Axis Effects

Plasma Cortisol Levels: Despite the random assignment of subjects to the 4 treatment groups, there was an imbalance with regards to Baseline plasma cortisol levels at the time of study initiation, ie, subjects were not equally distributed. This was especially apparent when a comparison was made of mean Baseline plasma cortisol levels for Cutivate-treated subjects vs those for subjects in the remaining 3 treatment groups. The mean Baseline plasma cortisol level in the Cutivate treatment group increased by 5 μg/dL from Day 1 to Day 2; in the Lotrisone, Temovate, and Diprolene treatment groups mean increases were 1, 1, and 2 μg/dL, respectively.

Three subjects each in the Lotrisone and Cutivate treatment groups demonstrated posttreatment plasma cortisol levels that were decreased from their Baseline levels by 10 μg/dL or more. While posttreatment plasma cortisol levels for the 3 Lotrisone-treated subjects were subnormal (<5 μg/dL), posttreatment levels for the 3 subjects in the Cutivate treatment group remained above 5 μg/dL (normal) because of their higher Baseline levels (≥18 μg/dL). A subgroup evaluation considered only those subjects in each treatment group who had Baseline plasma cortisol levels that were comparable to those in the Cutivate treatment group (ie, ≥18 μg/dL). The results of the subgroup evaluation indicated that when Baseline plasma cortisol levels for Lotrisone-treated subjects were ≥18 μg/dL, posttreatment levels remained above 5 μg/dL and were comparable to those for Cutivate-treated subjects.

Posttreatment plasma cortisol levels for 6 of 8 subjects who applied Temovate cream and for 7 of 8 subjects who applied Diprolene gel were less than 5 μg/dL (subnormal) (Table 1).

Urinary Cortisol Levels: Of the subjects in the Lotrisone, Temovate, and Diprolene treatment groups with subnormal plasma cortisol levels, 1, 1, and 3, respectively, had urinary cortisol levels that were below the normal laboratory reference level of 10 μg/24 hr.

Cortrosyn Test: Seven of 8 subjects in both the Lotrisone and Cutivate treatment groups responded normally to Cortrosyn stimulation; one subject in each treatment group demonstrated a borderline abnormal response. The 1 Lotrisone-treated subject responded to Cortrosyn stimulation with a plasma cortisol level of 16 μg/dL (normal response >17 μg/dL), which was more than twice the Baseline level and thus, a normal response. The 1 Cutivate-treated subject failed to double the Baseline plasma cortisol level in response to Cortrosyn stimulation, but demonstrated a post-Cortrosyn plasma cortisol level (41 μg/dL) greater than 17 μg/dL. Three subjects each in the Temovate and Diprolene treatment groups responded to Cortrosyn stimulation with plasma cortisol levels that were double their Baseline levels, but less than 17 μg/dL.

Tolerance

A total of 4 subjects reported systemic adverse events (2 in the Lotrisone treatment group and 1 each in the Diprolene and Temovate treatment groups). Each of the 4 subjects reported mild headaches, which were considered to be possibly related to treatment. Headaches were first noted in each of the subjects after two days of treatment, were intermittent, and varied in duration from 1 to 5 hours.

Two subjects (1 each in the Lotrisone and Diprolene treatment groups) exhibited transient local reactions to treatment in the crural area. The 1 subject in the Lotrisone treatment group exhibited mild thinness and shininess of the skin at the application site. The Diprolene-treated subject exhibited mild skin thinness and shininess, loss of elasticity, and loss of normal skin markings. All local reactions disappeared shortly after treatment applications were discontinued.

Table 1. Subjects with Abnormal Posttreatment Plasma Cortisol Levels and/or Decreases in Plasma Cortisol Levels ≥10 µg/dL (Study No. C92-257).

Subject Number	Plasma Cortisol Levels (µg/dL)[a] Pretreatment (Day 2)	Posttreatment	Change in Plasma Cortisol Level
Lotrisone Cream			
9	17	≤3	≥14
18	13	≤3	≥10
25	17	≤3	≥14
Cutivate Cream 0.05%			
6	24[b]	9	-15
11	20[b]	10	-10
31	24[b]	11	-13
Temovate Cream 0.05%			
3	15	≤3	≥12
10	15	≤3	≥12
15	24[b]	≤3	≥21
21	14	≤3	≥11
26	18	≤3	≥15
30	12	≤3	≥ 9
Diprolene Gel 0.05%			
1	21[b]	≤3	≥18
7	19[b]	≤3	≥16
12	19[b]	≤3	≥16
17	12	≤3	≥ 9
23	19[b]	≤3	≥16
28	17	≤3	≥14
32	14	≤3	≥11

a: Normal laboratory reference range: 5 to 18 µg/dL; the lowest level of plasma cortisol detectable by the laboratory test used was 3 µg/dL.
b: High plasma cortisol; above normal laboratory reference range.

CONCLUSIONS: No clear-cut difference was seen between the effect of Lotrisone cream and that of Cutivate cream 0.05% on the HPA axis, however, both treatments were clearly differentiated from two super-high potency corticosteroids (Temovate cream 0.05% and Diprolene gel 0.05%). A comparison of posttreatment plasma cortisol levels for Lotrisone-treated subjects vs Cutivate-treated subjects when Baseline levels were comparable indicated similar responses in the two treatment groups. Differences observed between the effects of Lotrisone and Cutivate when all subjects were considered appear to have been the result of differences inherent among the subjects studied and can be ascribed specifically to the higher Baseline plasma cortisol levels of subjects in the Cutivate treatment group. On the basis of the results of this study, Lotrisone and Cutivate appear to belong to the same medium potency category of classification for topical corticosteroids. All adverse events were mild and transient; local effects were those that are typically associated with corticosteroid therapy.

AMERICAN ACADEMY OF PEDIATRICS

Committee on Fetus and Newborn
Committee on Drugs

Benzyl Alcohol: Toxic Agent in Neonatal Units

As advances have been made in the care of very low-birth-weight infants, some techniques or practices have caused unexpected complications. One such practice is umbilical vessel catheterization to monitor an infant's arterial blood pressure, infuse fluids and medications, and obtain blood specimens for laboratory examinations. The catheters frequently are flushed with sterile isotonic saline or a 5% solution of dextrose in water, with the flush solution frequently being obtained from a multiple-dose vial. *The United States Pharmacopeia* requires all medications or solutions marketed in a multiple-dose vial to contain an antimicrobial preservative. Benzyl alcohol, an aromatic alcohol, is used for this purpose in a wide variety of medications and fluids for parenteral therapy, usually in a concentration of 0.9%.

Two groups of investigators, Gershanik et al[1] (New Orleans) and Brown et al[2] (Portland), independently concluded that an intravascular infusion of flush solutions containing 0.9% benzyl alcohol caused severe metabolic acidosis, encephalopathy, respiratory depression with gasping, and perhaps other abnormalities leading to the death of a total of 16 infants. Blood and urine from several affected infants had high levels of both benzoic and hippuric acids, known metabolites of benzyl alcohol. Both groups stated that no additional cases occurred after solutions with benzyl alcohol preservative were banned in their nurseries.

Subsequently, in May 1982, the Food and Drug Administration[3] with the concurrence of the American Academy of Pediatrics and the Centers for Disease Control,[4] urged pediatricians and other personnel in hospitals not to use fluids preserved with benzyl alcohol (or other antimicrobial agents) as intravascular flush solutions for newborn infants and not to use diluents with this preservative to reconstitute or dilute medications for infants.

Metabolically, benzyl alcohol is oxidized to benzoic acid, conjugated with glycine in the liver, and excreted as hippuric acid. This metabolic pathway may not be functional in premature infants and may allow accumulation of benzoic acid (and perhaps unmetabolized benzyl alcohol) with resulting metabolic acidosis and toxicity. Known toxic effects on benzyl alcohol include respiratory failure, vasodilation, hypotension, convulsions, and paralysis; little is known specifically about toxicity of the compound in newborn infants. Most studies of benzyl alcohol toxicity in animals[5] have evaluated a single-rapid or slow infusion into adult animals of various species; none has evaluated multiple infusions over a prolonged period into a newborn or immature animal. Thus, benzyl alcohol appears to be a safe preservative for small-volume parenteral medications for adults; data are not available to justify the same conclusion for newborn infants.

Pharmacologically, administration of preserved flush solutions to newborn infants and adults is considerably different. Infants receive a much larger flush relative to body weight than do adults, reducing considerably the therapeutic-toxic ratio for any substance infused. The increasingly aggressive treatment of tiny newborn infants over the last several years may have contributed both to the occurrence of the problem and to its recent recognition. In two studies,[1,2] the volumes of flush solution received by the infants were estimated; and from this, the amount of benzyl alcohol infused was calculated. A daily administration of benzyl alcohol approaching levels known to be toxic for a single infusion in adult rats, the most sensitive of the animals tested, was found.[5] Unfortunately, the actual amounts of benzyl alcohol received by the infants probably will remain unknown because precise information about the frequency and volume of flush solutions administered is not recorded in

PEDIATRICS (ISSN 0031 4005).

most neonatal intensive care units. Without this precise information, calculation of a dose-response effect in the infants is not possible.

The data reported by Gershanik et al[1] and Brown et al[2] are striking and warrant the action taken by the FDA, even though both studies were uncontrolled and the clinical information reported is not totally consistent. Preliminary data from other neonatal units suggest that the mortality for small premature infants (those weighing <1.1 kg) has declined after the preserved solutions were no longer used.[6] These data must be confirmed. Additional laboratory and animal studies are needed to assess the significance and pathophysiology of the problem,[7] especially since benzyl alcohol continues to be administered to newborn infants in small amounts in a variety of medications. To define pathologic changes in different organ systems that might be attributable to benzyl alcohol poisoning, histologic studies of tissues from infants who died after receiving solutions preserved with benzyl alcohol should be conducted and the sections carefully compared with specimens from matched infants who died but had not received preserved solutions.

The impact of eliminating benzyl alcohol as a preservative in flush solutions for infants also requires assessment. If the toxicity of the preserved solutions has been as great as the initial studies indicate, a significant decrease in mortality of small premature infants should be observed. Conversely, if the preservatives have been important in preventing solution contamination, an increase in neonatal septicemia with selected organisms such *Pseudomonas*, *Klebsiella*, *Enterobacter*, and *Serratia* may ensue.

As an emergency measure, manufacturers of commonly used solutions packaged in multiple-dose vials with benzyl alcohol preservative have agreed with the FDA request to include a warning, "Not for Use in Newborns," on the labels of these products. The FDA, *USP*, and others are reviewing the need for permanent changes in products, labels, and package inserts. At the hospital level, each neonatal unit should assess its patterns and needs in providing flush solutions for infants and should establish a system with its hospital pharmacy to assure a satisfactory and safe means of providing sterile, unpreserved solutions. Vials of normal saline and 5% dextrose solution are available without preservatives, although by *USP* standard these are labeled for single use only. Alternatively, unit-dose flushes in syringes or a single, large-volume container of a flush solution could be dispensed several times each day to the nursery area; unused syringes or fluid remaining in the container should be discarded when the new supply is received. Preparation of solutions, including addition of heparin if this is used, should be carried out in the pharmacy. Refrigeration will retard growth of most bacteria that inadvertently contaminate the solutions during preparation. Cold fluids should not be administered to infants; therefore, refrigerated solutions will need to be brought to room temperature before use. These flush solutions at room temperature should be used within a few hours or be discarded, a function that could coincide with the beginning of each nursing shift. These alternative methods of providing flush solutions have not been evaluated in clinical trials.

Other sources of benzyl alcohol should be identified in solutions and medications administered to infants. Many medications also contain benzyl alcohol as a preservative. In general, the volume of benzyl alcohol received by this route is negligible compared with the amount received in flush solutions. For newborn infants, it may be preferable to avoid use of medications with preservatives whenever possible. However, the presence of benzyl alcohol as a preservative should not proscribe use of medications indicated for treatment of an infant. Another potential source of exposure of infants to benzyl alcohol is through instillation of an isotonic solution into endotracheal tubes. Although pulmonary absorption of some pharmacologic agents is significant, information about absorption of benzyl alcohol by this route is unknown.

COMMITTEE ON FETUS AND NEWBORN, 1982–1983
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REFERENCES

1. Gershanik J, Boecler B, Ensley H, et al: The gasping syndrome and benzyl alcohol poisoning. *N Engl J Med* 1982;307:1384
2. Brown WJ, Buist NRM, Gipson HTC, et al: Fatal benzyl alcohol poisoning in a neonatal intensive care unit. *Lancet* 1982;1:1250
3. Food and Drug Administration Bulletin, Dept of Health and Human Services, May 28, 1982
4. Centers for Disease Control: Neonatal deaths associated with use of benzyl alcohol—United States. *MMWR* 1982;31:290
5. Kimura ET, Darby TD, Krause RA, et al: Parenteral toxicity studies with benzyl alcohol. *Toxicol Appl Pharmacol* 1971;18:60
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7. Lovejoy FH: Fatal benzyl alcohol poisoning in neonatal intensive care units: A new concern for pediatricians. *Am J Dis Child* 1982;136:974

DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration, HFI-22
Rockville, Maryland 20857

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August 1982 Volume 12 Number 2

FDA Drug Bulletin

Salicylate Labeling May Change Because of Reye Syndrome

FDA is evaluating possible changes in the labeling for products containing aspirin or other salicylates because of the association of salicylates with Reye syndrome (RS) in children.

First recognized about 19 years ago, RS is a rare, acute, life-threatening encephalopathy occurring mostly in children under 16 years of age who are recovering from viral infections, particularly influenza and varicella. It is characterized by vomiting and lethargy, which may progress to delirium, coma, and death.

The U.S. Centers for Disease Control (CDC) estimates that 600 to 1,200 cases of RS occur each year in the United States. The disease is fatal in 20 to 30 percent of all cases, and permanent brain damage results in other cases.

An association between RS and ingestion of various medications has been suspected for some time (see November 1976 *Drug Bulletin*). However, it was not until the results of recent case-control studies were available that an assessment of the possible association with specific drugs could be made.

Earlier this year, CDC reported on four studies (one each from Arizona and Ohio and two from Michigan). In these studies the use of salicylates and salicylate-containing drugs during the antecedent viral illness was more common in patients who developed Reye syndrome than in matched controls.

On the basis of these reports and upon recommendations of an advisory panel, in the Feb. 12, 1981, issue of its *Morbidity and Mortality Weekly Report*, CDC stated: "The exact pathogenesis of this disease and the possible role of salicylates in its pathogenesis remain to be determined. Additional well-controlled studies are also needed. Until definitive information is available, CDC advises physicians and parents of the possible increased risk of Reye syndrome associated with the use of salicylates for children with chickenpox or influenza-like illnesses."

The American Academy of Pediatrics' Committee on Infectious Diseases

FDA Drug Bulletin

Information of Importance To Physicians and Other Health Professionals

reviewed the data in these studies and issued a statement in the June 1982 issue of *Pediatrics*, advising that the use of salicylates should be avoided in children suffering from influenza or varicella.

The committee recommended "that consideration should be given to the advisability of using any antipyretic medications for these illnesses."

Because of a number of criticisms of the conduct of these studies and the interpretation of the data, FDA undertook an independent analysis of the matter. This analysis included: (1) a review of materials available from the investigators in Arizona, Michigan, and Ohio; (2) a review of summaries provided by CDC on studies concerning RS and salicylates; (3) a review of analyses by employees and consultants of manufacturers of salicylate drug products and consumer representatives; (4) site visits to the Michigan and Ohio state health departments to obtain further details on how these studies were conducted and to audit data on case records; and (5) a review of a subset of the data from the Ohio study containing day-by-day information on disease symptoms and drug use.

In the course of the review, questions were raised about study design; however, these were not considered sufficient to change substantially the interpretation of the data. The FDA analysis generally supported the association between salicylates and RS shown in the earlier evaluations of the data.

The studies performed are not able to demonstrate conclusively whether the association is causal, but the accumulated evidence is sufficiently strong to justify the FDA's advisory caution on the use of salicylates in children with those viral illnesses particularly associated with the development of RS.

FDA presented its analyses at an open public meeting on May 24, 1982, which it sponsored jointly with CDC and the National Institutes of Health (NIH). At the completion of the meeting, the majority of the scientific experts believed that the new analyses supported the earlier evidence suggesting an association between use of salicylates and the development of RS.

Aspirin and other salicylates are found in single ingredient products or in combination with other medicines; labels of over-the-counter drug products contain a list of ingredients. Aspirin remains a medically useful drug with anti-inflammatory actions not found in other over-the-counter antipyretics.

Benzyl Alcohol May Be Toxic to Newborns

Solutions containing benzyl alcohol or other preservatives should not be used in newborns to flush intravascular catheters. Solutions for diluting or reconstituting medications for newborns also should contain no benzyl alcohol or other preservatives.

FDA has received reports of 16 fatalities in newborns weighing less than 2,500 grams in whom bacteriostatic sodium chloride for injection containing 0.9 percent benzyl alcohol had been used for flushing intravenous catheters.[1,2] Some of the infants received additional benzyl alcohol when bacteriostatic water was used to dilute or reconstitute medications.

The deaths were preceded by a syndrome consisting of metabolic acidosis, central nervous system depression, respiratory distress progressing to gasping respirations, hypotension, renal failure and sometimes seizures and intracranial hemorrhages. Blood and urine samples of affected infants revealed high levels of benzyl alcohol, benzoic acid or its metabolite, hippuric acid.

Toxicity from benzyl alcohol appears to have been caused by large daily doses of benzyl alcohol per kilogram of body weight; daily intake in these cases ranged from 99-404 mg/kg/day. Each milliliter of 0.9 percent solution contains 9.0 mg of benzyl alcohol.

In the two medical centers reporting
: 16 cases, no additional cases of the
ic syndrome were seen after solu-
ns containing benzyl alcohol were
minated.[1,2] There have been no re-
rts of toxicity in older infants, chil-
n, and adults.

On May 28, FDA sent letters to ped-
icians, hospital pharmacists, and
pital administrators, recommending
t solutions used to flush intravascu-
catheters or for diluting or reconsti-
ing medications in newborns not
ntain benzyl alcohol or any other
servative. Sterile sodium chloride for
ection (not bacteriostatic sodium
oride for injection) should be used
flushing intravenous catheters.

The agency is working on labeling
nges with the manufacturers and
U.S. Pharmacopoeia for the practi-
ner insert and the containers of so-
m chloride and water containing
alcohol.

ution must be used in attributing
ess or death to benzyl alcohol in in-
idual babies; many of the clinical
ures ascribed to benzyl alcohol tox-
y are found in newborns seriously ill
n other causes. The babies described
n benzyl alcohol toxicity had serious
lerlying disease, but they also had
chemical evidence of benzyl alcohol
city.

DA is involved in gathering more
n on the problem, in cooperation
n the Armed Forces Institute of
nology, neonatologists, and the U.S.
ters for Disease Control (CDC).
Collaborative efforts with drug man-
turers, the American Society of
pital Pharmacists, the American
demy of Pediatrics, the American
sing Association, the U.S. Pharma-
oeial Convention, CDC[3], and others
under way to insure that the health
community is fully informed of
recent information.

hysicians can assist in this effort by
ng the form on the back of this
g *Bulletin* to report any possible or
te cases of toxicity associated with
alcohol.

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rences:

1. Brown WJ, Buist NRM, et al: Fatal ben-
kohol poisoning in a neonatal intensive care unit (letter). *Lancet*, May 29, 1982; 1: 1250.

2. Gershanik JJ, et al: The gasping syndrome: benzyl alcohol (BA) poisoning? *Clin Res* 1981; 29: 895A.

3. *Morbidity and Mortality Weekly Report* 1982; 31: 290.

Hepatotoxic Potential of Ketoconazole Under Investigation

Three cases of fatal, massive hepatic necrosis, one case of nonfatal hepatitis and necrosis, and 20 cases of liver injury (usually with jaundice) have been reported in patients taking ketoconazole (Nizoral).

The drug is the only oral therapy approved for systemic fungal infections and is valuable for serious, systemic infections. (See November 1981 *Drug Bulletin.)*

Several cases of hepatitis were reported in the literature[1-3] just prior to and shortly after the drug's approval in June 1981. In these cases jaundice cleared and liver enzyme levels returned to normal after treatment was stopped or, in one case,[3] with continued ketoconazole treatment.

The three reported deaths occurred despite discontinuation of ketoconazole. The first occurred in a 67-year-old woman on ketoconazole therapy for 8 weeks. The second occurred in a 64-year-old man taking the drug for 28 days who had major surgery despite abnormal liver function and subsequently died of sepsis. The third case was a 22-year-old woman on ketoconazole therapy for 6 days. This patient was being treated for leukemia with drugs of known hepatotoxic potential.[4]

Although these cases were confounded by medical history and concomitant or preceding treatment with other drugs, the similar sequence and pattern of liver function abnormalities suggest that ketoconazole also played a role.

In the nonfatal case of hepatic necrosis, the 75-year-old female patient had been on ketoconazole therapy for 3 months with no concomitant medication.[4]

Manufacturer Sends Letter

Upon learning of the first case of fatal hepatitis that developed during ketoconazole therapy, the manufacturer, Janssen Pharmaceutica, sent a letter in March 1982 to prescribers informing them of the possibility of hepatotoxicity and alerting them to the consequent additions to the labeling.

The following was added to the Warnings section of the package insert for ketoconazole:

> Several cases of possible idiosyncratic hepatocellular dysfunction have been reported during NIZORAL treatment. It is important to recognize that liver disorders may occur with NIZORAL therapy. The rare occurrences of liver disorders could be potentially fatal unless properly recognized and managed. It is desirable to perform liver function tests, such as SGGT, alkaline-phosphatase, SGPT, SGOT and bilirubin, before treatment and at periodic intervals during treatment (monthly or more frequent), particularly in patients who will be on prolonged therapy or who have a history of liver disease. Instances of minor elevations of liver enzyme levels in patients on NIZORAL have been shown to normalize during therapy and may not necessitate discontinuation of treatment. However, if liver function tests are significantly elevated or other signs and symptoms are suggestive of hepatocellular dysfunction, ketoconazole should be discontinued.

The following has been added to the Precautions section:

> Information for Patient: Patient should be instructed to report any signs and symptoms which may suggest liver dysfunction so that appropriate bio-chemical testing can be done. Such signs and symptoms may include unusual fatigue, nausea or vomiting, jaundice, dark urine or pale stools.

Additional Cases

In addition to the four cases discussed previously, FDA has received reports of 20 additional cases of other liver injury, signs and symptoms of which included jaundice, elevated transaminases, bilirubin and alkaline phosphatase, anorexia, nausea, and/or

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

TELEPHONE: (908) 298-4000

June 8, 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 20-010
LOTRISONE (clotrimazole and betamethasone dipropionate) Lotion

SUBJECT: RESPONSE TO FDA COMMENTS (MICROBIOLOGY)

Dear Dr. Wilkin:

Reference is made to the February 23, 2000 and March 1, 2000 telephone conversations with Frank Cross.

Attached are the responses to the microbiology questions. Each comment is followed by the response. Related comments from the telephone conversations are listed together with one response.

These responses complete all responses to comments received to date except for submission of 9 and 12- month stability data that are to be available in June and September 2000, respectively.

As discussed with Mr. Cross on May 16, 2000, submission of revised draft labeling should wait until after the June 29, 2000 Dermatologic and Ophthalmic Drug Advisory Meeting.

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
Desk Copy: Frank Cross

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A-2

Number of Pages Redacted 194

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Commercial Information

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

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NDA ORIG AMENDMENT

May

~~April~~ 5, 2000 BC

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

NDA 20-010
LOTRISONE®
(betamethasone dipropionate, USP and clotrimazole, USP)
Lotion

SUBJECT: AMENDMENT, RESPONSE TO FDA FAX OF MARCH 14, 2000.

Dear Dr. Wilkin:

Reference is made to our pending new drug application for Lotrisone Lotion, NDA 20-010, as amended on October 7, 1999 and April 5, 2000. Reference is also made to FDA's fax dated March 14, 2000 requesting additional clarification regarding our October 7, 1999 amendment.

Enclosed are Schering's responses to FDA's questions contained in the 3/14/2000 FAX. Please note that questions 4 and 5 have been answered in Schering's previous response to FDA dated April 5, 2000. If you have any questions regarding the information provided herein, please contact Ms. Elaine Potomski at 908-740-4525.

In accordance with 21 CFR 314.71 (b) Schering Corporation certifies that a copy of these responses is being sent to FDA's New Jersey Distrsict Office.

DUPLICATE

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

TELEPHONE: (908) 298-4000

NDA ORIG AMENDMENT

April 13, 2000

BC

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

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

SUBJECT: FDA REQUEST FOR FORMULATIONS COMPARISON

Dear Dr. Wilkin:

Reference is made to Lotrisone Lotion NDA 20-010 and its amendment dated October 7, 1999. Reference is also made to a Schering letter dated 3/3/00 containing a table comparing formulations of Lotrisone Cream, Lotrimin Cream, and Diprosone Cream used for the pivotal study submitted to the original Lotrisone Lotion NDA as requested by Mr. Frank Cross, CSO.

The original table supplied in the 3/3/00 submission contained an error in the amount of water used in the formulation of Lotrimin Cream. A revised table is attached which contains the correct amount of water used, [redacted] in the manufacture of Lotrimin Cream.

If you have any questions please contact Ms. Elaine Potomski at 908-740-4525.

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

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

NDA [illegible]

April 13, 2000

BC

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Division of Dermatologic and Dental Drug Products
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Attn: Document Control Room
FDA, CDER, ODE 5

NDA 20-010
LOTRISONE®
(betamethasone dipropionate, USP and clotrimazole, USP)
Lotion

11 4/25/2000

SUBJECT: RESPONSE TO FDA REQUEST FOR BOTTLE AND TIP PACKAGING COMPONENTS

Dear Dr. Wilkin:

Reference is made to our October 7, 1999 amendment to Lotrisone Lotion NDA 20-010.

As requested by Mr. Frank Cross, CSO on 3/31/00, we are submitting samples of the bottle and tip packaging components used in the manufacture of Lotrisone Lotion for the 10ml and 30ml package presentations. If you have any questions regarding these samples, please contact Ms. Elaine Potomski at 908-740-4525.

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

Desk Copy: Mr. Frank Cross

enclosures: EP/jb

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ORIGINAL

SCHERING CORPORATION

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TELEPHONE: (908) 298-4000

April 5, 2000

NDA [illegible]
Su

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

NDA 20-010
Lotrisone Lotion

SUBJECT: FDA REQUEST FOR INFORMATION

Dear Dr. Wilkin:

We refer you to the teleconference with Mr. Cross and Dr. Okun and Ms. Krhoun on March 31, 2000 regarding the request for safety information for Lotrisone Cream.

As discussed, since an updated Integrated Summary of Safety for the past 10 years is in preparation and not yet available, we are providing a copy of the 5-year Periodic Safety Update Report which had been prepared recently for our international subsidiaries. This report contains a summary of important safety information for the period of June 1, 1994 to May 31, 1999.

Please note that since this report was prepared for our international subsidiaries, it contains information for Lotrisone Ointment which is not marketed in the U.S. The company core data sheet, i.e., international labeling, (Appendix A.1.), which is included, contains essentially the same information as the U.S. product information sheet. However, it contains an additional indication, treatment of candidiasis due to *Candida albicans*, which is not in the U.S labeling. The data in this report do not reveal any significant new safety issues or trends. No changes to the labeling were recommended.

ORIGINAL

APPENDIX A.1

APPENDIX A.2

APPENDIX B.1

se be advised that the material and data contained in this submission are onsidered to be confidential. The legal protection of such confidential ommercial material is claimed under the applicable provisions of 18 U.S.C., ection 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

Desk Copy: Frank Cross

APPEARS THIS WAY
ON ORIGINAL

APPENDIX A.1

APPENDIX A.2

APPENDIX B.1

APPENDIX B.2

APPENDIX B.3

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

TELEPHONE: (908) 298-4000

April 5, 2000

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Division of Dermatologic and Dental Drug Products
HFD-540
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Rockville, MD 20857
Attn: Document Control Room
FDA, CDER, ODE 5

NDA 20-010
LOTRISONE®
(betamethasone dipropionate, USP and clotrimazole, USP)
Lotion

SUBJECT: **AMENDMENT, RESPONSE TO FDA FAX OF MARCH 14, 2000.**

Dear Dr. Wilkin:

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Enclosed are Schering's responses to FDA's questions contained in the 3/14/2000 FAX. Please note that questions 4 and 5 have been answered in Schering's previous response to FDA dated April 5, 2000. If you have any questions regarding the information provided herein, please contact Ms. Elaine Potomski at 908-740-4525.

In accordance with 21 CFR 314.71 (b) Schering Corporation certifies that a copy of these responses is being sent to FDA's New Jersey Distrsict Office.

APPEARS THIS WAY
ON 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 331(j) as well as the FDA regulations.

Sincerely,

Elaine Potomski for

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

enclosures:
EP/jb

APPEARS THIS WAY
ON ORIGINAL

COMMENT 1.

Please provide the name of each enrichment medium used in your test procedures for microbial limits, and its reference (location) in the AOAC Bacteriological Analytical Manual.

RESPONSE 1.

The enrichment media used in the Microbial Limit test is [redacted] referenced in the AOAC Bacteriological Analytical Manual,6th edition, 1984. This media formula is the same as Media I, [redacted] referenced in USP 24 <61> Microbial Limit Tests.

APPEARS THIS WAY
ON ORIGINAL

COMMENT 2.

Please provide details of your sampling plan for in-process packaging controls (The description provided in Vol 6.1, page 103, is deficient: the use of the term "sufficient" number is not adequate without specifying what constitute a "sufficient" number).

RESPONSE 2.

Physical attribute checks are performed by Quality Control packaging operation and at approximately individually packaged units are evaluated for physical appearance as well as verification of the batch number, expiration date and product name.

Vacuum leak integrity testing of the container closure and dispensing tip seals are performed by Quality Control personnel on per chuck (capping station). For a line with 10 chucks (capping stations) this equates to

Gravimetric fill weight tests of filled units are performed at and at approximately by Quality Control personnel on Additionally, the packaging department monitors the net fill of primary containers at the and throughout the filling run on each fill head.

Immediate removal torque tests of capped units are thereafter by Quality Control personnel on per chuck (capping station). Additionally the packaging department records the immediate removal torque at throughout the filling run.

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COMMENT 3.

Please specify the closure torque, or alternately refer to the USP procedure being followed, e.g. USP 24 <671> if the USP procedure is being followed.

RESPONSE 3.

Immediate removal torque is used to determine the closure torque. As presented in the table below, an immediate removal torque guideline of 5 – 8 in-lbs is used with the 18 mm cap on the 30 mL bottle size. An immediate removal torque guideline of 4 – 6 in-lbs is used with the 15 mm cap on the 10 mL bottle size The application torque identified in the "Torque Applicable to Screw-Type Container" table in USP 24 <671> was utilized to determine the immediate removal torque guideline for these container closure systems, in conjunction with the data generated on both the process validation batches and historical data generated on similar container closure systems.

In summary:

Cap (mm)	Bottle (mL)	Immediate Removal Torque Guideline (in-lbs)
18	30	5 – 8
15	10	4 - 6

APPEARS THIS WAY
ON ORIGINAL

SCHERING CORPORATION

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

NEW CORRESP

April 5, 2000

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

NDA 20-010
LOTRISONE®
(betamethasone dipropionate, USP and clotrimazole, USP)
Lotion

DFC
BC

SUBJECT: RESPONSE TO FDA FAX OF MARCH 3, 2000.

Dear Dr. Wilkin:

Reference is made to our October 7, 1999 amendment to Lotrisone Lotion NDA 20-010. Reference is also made to a FDA FAX dated March 3, 2000 containing questions regarding information found in our amendment.

Enclosed are Schering's responses to FDA's questions contained in the 3/3/00 FAX. If you have any questions regarding the information submitted, please contact Ms. Elaine Potomski at 908-740-4525.

In accordance with 21 CFR 314.71 (b) Schering Corporation certifies that a copy of these responses is being sent to FDA's New Jersey Distrsict Office.

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.

DUPLICATE

Sincerely,

Elaine Potomski for

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

enclosures:
EP/jb

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SCHERING CORPORATION

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

NDA SUPPLEMENT

March 13, 2000

Mr. Frank Cross
Division of Dermatologic and Dental Drug Products
HFD-540
5600 Fishers Lane
Rockville. MD 20857
Attn: Document Control Room
FDA, CDER, ODE 5

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

SUBJECT: LOTRISONE LOTION 6 MONTH STABILITY REPORT

Dear Mr. Cross:

An updated stability report containing 6-months of data on three batches of Lotrisone Lotion manufactured at our Kenilworth facility is being sent to NDA 20-010 today (March 13, 2000) via overnight delivery. This update is provided in accordance with our prior discussion with the Division on February 24, 1999 regarding our amendment to NDA 20-010 for Lotrisone Lotion, and in accordance with your recent requests for additional stability data. Based on the observations described in this report, which are a consequence of the current sampling technique, Schering is requesting the opportunity to discuss the data with the Division. Specifically, we would like to propose _____ for Assay/Degradation products, which affect sample size and analytical sampling procedure. We are also requesting a change in the product label to provide more explicit patient instructions for product delivery.

We are requesting the opportunity to discuss this via teleconference at the Division's earliest convenience to allow the Division to complete it's review of our application. As additional stability samples are scheduled to be tested next week, it will be helpful if we can speak with the Division prior to the analysis of these samples.

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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

APPEARS THIS WAY
ON ORIGINAL

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

TELEPHONE: (908)

March 7, 2000 NEW CORRESP
NC

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

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

SUBJECT: LOTRISONE LOTION METHOD VALIDATION PACKAGE

Dear Dr. Wilkin:

Reference is made to Lotrisone Lotion NDA 20-010 and its amendment dated October 7, 1999. Reference is also made to Schering's letter dated March 3, 2000, which supplied the proposed labeling and the method validation package previously requested by Mr. Frank Cross, CSO.

The labeling information contained in the 3/3/2000 letter was incomplete, as it did not contain the proposed labeling for Lotrisone Lotion. Enclosed in this letter is the proposed labeling which completes your request for this information.

We apologize for this omission. If you have any questions please contact Ms. Elaine Potomski at 908-740-4525.

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

ORIGIN

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SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

TELEPHONE: (908) 298-4000

March 3, 2000

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

NDA 20-010
LOTRISONE LOTION

SUBJECT: FDA REQUEST FOR INFORMATION

Dear Dr Wilken:

We refer you to the February 11, 2000 request from Frank Cross regarding Lotrisone Lotion NDA. Mr. Cross requested a safety update and notification that there will be no patient instructions nor medical guide for the product.

No additional studies have been conducted since the original NDA. Therefore, there is no safety update to submit.

There will be no patient instructions nor medical guide in the labeling for Lotrisone Lotion.

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/lt

Enclosure

Desk Copy: Frank Cross (via fax)

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

March 3, 2000

DC BC

a.. .Vilkin, M.D., Director
1 of Dermatologic and Dental Drug Products
10
shers Lane
le, MD 20857
Document Control Room
FDA, CDER, ODE 5

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

BEST POSSIBLE COPY

CT: LOTRISONE LOTION METHOD VALIDATION PACKAGE

:. Wilkin:

ice is made to Lotrisone Lotion NDA 20-010 and its amendment dated 7, 1999.

iested, enclosed are two copies of the labeling section and the method in section originally submitted on 10/7/99 for purposes of method validation s by the FDA analytical testing laboratories.

ave any questions regarding these documents please contact Ms. Elaine ki at 908-740-4525.

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

NAE, Cleared
/S/ 3/30/2000

RECEIVED FOR FILING
MAR 6 2000

Sincerely,

Elaine Potomski for

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

/ EP:jb

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Attachment 1 Labeling Attachment 2 Labeling Attachment 3

4.C.3.2 SPECIFICATIONS
4.D.3.3 ANALYTICAL METHODS
4.D.3.4 ANALYTICAL METHODS VALIDATION

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

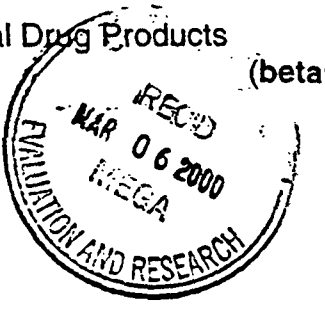
TELEPHONE: (908) 298-4000

NDA [illegible]

BC

March 3, 2000

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



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

SUBJECT: FDA REQUEST FOR FORMULATIONS COMPARISON

Dear Dr. Wilkin:

Reference is made to Lotrisone Lotion NDA 20-010 and its amendment dated October 7, 1999.

As requested by Mr. Frank Cross, CSO, enclosed is a table comparing formulations of Lotrisone Cream, Lotrimin Cream, and Diprosone Cream used for the pivotal study submitted to the original Lotrisone Lotion NDA.

Mr. Cross also requested an updated stability report containing six-month data on the three batches submitted in the 10/7/99 amendment. This information will be provided under separate cover on week of March 13, 2000.

If you have any questions please contact Ms. Elaine Potomski at 908-740-4525.

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CONCENTRATION OF INGREDIENT/PRODUCT

Ingredient	Lotrisone Cream	Lotrimin Cream	Diprosone Cream
Betamethasone Dipropionate Micronzied	0.643 mg/g*		0.643 mg/g*
Clotrimazole, [redacted]	10.0 mg/g	10.0 mg/g	
Mineral Oil			
White Petrolatum			
Cetostearyl Alcohol			
Polyethylene Glycol 1000 Monocetyl Ether			
Benzyl Alcohol			
Sodium Phosphate			
Phosphoric Acid			
Propylene Glycol			
Water Purified			
Sorbitan Monostearate			
Polysorbate 60			
Cetyl Esters Wax			
Cetearyl Alcohol, 70/30			
Octyldodecanol			
Chlorocresol			
Ceteareth 30			

* Equivalent to 0.5 mg/g Betamethasone

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SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

TELEPHONE: (908) 298-4000

October 26, 1999

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

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

SUBJECT: LOTRISONE LOTION METHOD VALIDATIONS PACKAGE

Dear Dr. Wilkin:

Reference is made to Lotrisone Lotion NDA 20-010 and its amendment dated October 7, 1999. This is to inform you that a complete copy of volume 3 containing sections 4.D.1 List of Samples, 4.D.3.2 Drug Product Specifications, 4.D.3.3 Analytical Methods, and 4.D.3.4 Analytical Methods Validation Reports was submitted to the FDA laboratories located in Philadelphia, PA and in San Juan, Puerto Rico.

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 Petomalos for

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

Desk Copy: Ms. Kozma-Formaro
EP/jb

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

TELEPHONE: (908) 298-4000

ORIG AMENDMENT

AZ

October 7, 1999

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

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

SUBJECT: AMENDMENT TO NDA 20-010, LOTRISONE LOTION

Dear Dr. Wilkin:

We are submitting an amendment to the Lotrisone Lotion NDA 20-010 that provides updated labeling and CMC information.

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 (included in ***Attachment 1*** for reference). Reference is also made to our June 6, 1994 amendment to NDA 20-010 in which we provided information on an [redacted] Lotrisone Lotion bottles as well as a revision to the label storage statement. In addition to the 1994 amendment, Schering has been in contact with the Division on several occasions regarding Chemistry, Manufacturing, and Control (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. At this meeting the potency classification of betamethasone dipropionate in Lotrisone Lotion was also discussed. For your convenience, chronological listings of FDA correspondence relating to labeling and CMC information since the 7/31/91 approvable letter are provided in ***Attachments 2 and 3***, respectively.

On February 24, 1999, a teleconference took place between Schering's Denise Flanagan and Elaine Potomski and FDA's Frank Cross, Mary-Jean Kozma-Fornaro, Paul Brown, Wilson DeCamp, and Jonathan Wilkin to discuss our 1/5/99 proposal to submit an amendment to the Lotrisone Lotion NDA. During this teleconference several agreements were reached regarding revisions to the application. The

DUPLICATE

agreements, as well as the Agency's requests for information are summarized below. We have complied with each of the Agency's requests and we have indicated the NDA section where the referenced information can be found.

- Labeling requires updating to current standards. *(Section 2)*
- A complete Chemistry Manufacturing and Controls section should be submitted in accordance with current standards. *(Sections 4A and 4B)*
- FDA will accept information on the drug substances by cross reference to Diprolene Lotion (NDA 19-716) as the central repository for betamethasone dipropionate (S-008; submitted 12/12/97; approved 6/15/98) and Lotrimin Lotion (NDA 18-813) as the central repository for clotrimazole (S-019; submitted 3/12/98; approved 5/18/98). *(Section 4A)*
- The first three batches of Lotrisone Lotion manufactured in the new manufacturing site, Kenilworth, NJ, should be placed on marketed stability under ICH conditions. *(Section 4B.9)*
- As previous stability data was not generated under ICH conditions, FDA will not make a direct comparison to new stability data generated under ICH conditions. A copy of previously submitted stability data (1994) will be provided for reference. *(Section 4B.9)*
- Stability data from the Kenilworth site should be included if available at the time of submission. *(Section 4B.9)*
- Complete addresses for all manufacturing, packaging and control sites for drug substance and drug product should be provided. *(Section 3D.1, 4A and 4B.4)*.
- A statement should be included that the manufacturing and testing sites for both drug substances and drug product are ready for FDA inspection. Dates of last inspection and inspection results for each site should be included. *(provided below)*
- Certain sections of the CMC portion of the NDA will remain unchanged from what was previously submitted. These sections will be submitted for completeness. *(Sections 4B.7 and part of 4B.9)*
- FDA has committed to respond within 180 days from date of receipt of the amendment.

In addition to the changes discussed during our 2/24/99 teleconference, the amendment also includes the following:

- An improved method for the Assay of betamethasone dipropionate, clotrimazole, benzyl alcohol, betamethasone monopropionates, and (o-Chlorophenyl) diphenylmethanol on the finished product.
- A minor change to the bottle —

A more detailed summary of changes to the CMC sections (organized as they appear in the NDA) is provided (***Attachment 4***). The changes described for each section are also included as a "Detailed List of Changes" within the NDA itself.

In accordance with FDA's request for site inspection information the following is provided:

The last site inspection at the Schering Corp. Manati, PR facility, the sole supplier of betamethasone dipropionate, occurred on May 12 to May 20, 1999 resulting without any 483 issuance. Schering Corp. Kenilworth, NJ site and Union, NJ site were last inspected on September 13 through September 27, 1999 resulting in an issuance of an FDA 483. Of the three observations noted, two were corrected and one response is forthcoming.

The following site inspection information was obtained for our suppliers of clotrimazole: The last site inspection at the [redacted], occurred on June 9 through 13, 1997. FDA's recommendation was to continue the approval status of the facility. The last site inspection at [redacted] occurred on April 11, 14 through 17, 1997. FDA has stated the firm is an acceptable supplier to the United States. (This information was obtained through Freedom of Information).

Schering Corporation's Manati PR, Kenilworth NJ, and Union NJ facilities are ready for FDA inspection.

As referenced earlier, our 11/21/94 meeting with the division addressed the potency classification of betamethasone dipropionate in Lotrisone lotion. This amendment provides revised labeling which includes a "high potency" classification. Since the labeling has been revised several times, we have provided a clean copy of our proposed package information sheet together with another copy delineating the revisions since the July 31, 1991 approvable letter with the reasons for revisions. The labeling would also include updates in accordance with current labeling regulations. The major revisions include:

- Updated information for betamethasone dipropionate to conform to the Division's labeling recommendations for topical corticosteroids dated July 3, 1995.
- [redacted]
- [redacted]
- Updated Carcinogenesis, Mutagenesis, Impairment of Fertility and Pregnancy information for both clotrimazole and betamethasone dipropionate.
- A more prominent statement in the 'Pediatric Use' section regarding 'not to be used under the age of 12' and not to be used in diaper dermatitis.
- An updated label storage statement to conform to ICH guidelines and currently available stability data.
- Updated drafts of the packaging components, which had been agreed upon by the Division on February 24, 1993.

ATTACHMENT 1

ATTACHMENT 2

ATTACHMENT 3

ATTACHMENT 4

A disc with the updated labeling is provided.

Updated patent information and debarment statement has been included. These are located in sections 13 and 16 found at the beginning of this submission.

If you have any questions regarding this submission, please contact Dr. Nicholas J. Pelliccione at (908) 740-5680.

In accordance with 21 CFR 314.71 (b) Schering Corporation certifies that a copy of this supplement is being sent to FDA's New Jersey District Office.

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/pc

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

SCHERING CORPORATION

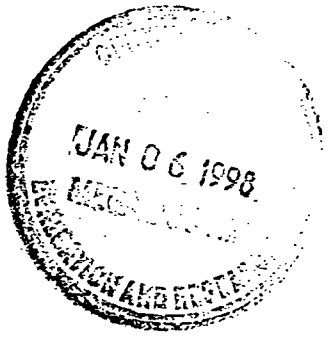
2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033
TELEPHONE: (908) 298-4000

AE & 7/31/91 /S/

January 5, 1999

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

NDA 20-010
LOTRISONE® Lotion



Attn: Ms. Mary J. Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatological and Dental Drug Product

SUBJECT: **GENERAL CORRESPONDENCE**
UPDATED CHEMISTRY, MANUFACTURING AND CONTROLS INFORMATION ON THE PENDING APPLICATION FOR LOTRISONE LOTION NDA 20-010

Dear Dr. Wilkin:

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 discussion with Ms. Mary J. Kozma-Fornaro on December 28, 1998. As discussed with Ms. Kozma-Fornaro, this General Correspondence summarizes Schering's proposal for updating our pending application with current CMC information. In addition, it contains a copy of the July 31, 1991 approvable letter along with Schering's acceptance of the Division's recommendation that this product be labeled as a high potency corticosteroid. Upon review of the information provided in this correspondence, we ask that Division contact us regarding its acceptability. If additional information is required prior to making this assessment, or if a discussion of the information would be beneficial, we request the opportunity to schedule a teleconference with the Division.

We would like to thank Ms. Fornaro for providing us with the guidance needed to begin discussions on this pending application and we look forward to working with the Division to achieve a rapid approval. Should you need additional information,