CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-010

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

PATENT INFORMATION

Under the patent provisions of the Drug Price Competition and Patent Term Restoration Act of 1984, we call you attention to U.S. Patent No. 4,289,604 (expiration date 10/06/2000) which claims a pharmaceutical composition of the captioned drug (clotrimazole and betamethasone dipropionate), and with respect to such patent a claim of patent infringement could reasonably be asserted against any person, not licensed under such patent, who engaged in the manufacture, use or sale of the inventions claimed therein.

EXCLUSIVITY SUMMARY FOR NDA # 20-010

Trade Name: Lotrisone Lotion Generic Name: clotrimazole and betamethasone dipropionate

Applicant Name Schering-Plough Research Institute

Approval Date December 8, 2000

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?

YES /_X_/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X_/

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

YES /_X_/ NO /___/

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

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

d) Did the applicant request exclusivity?

YES /__/ NO /_X_/

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

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

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

YES /__/ NO /_X_/

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

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

YES /___/ NO /_X_/

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

Clotrimazole Active Ingredient

NDA 17-613, Lotrimin Solution
NDA 17-619, Lotrimin Cream
NDA 18-052, Gyne-Lotrimin Vaginal Cream
NDA 18-182, Mycelex-7 Vaginal Inserts
NDA 18-230, Mycelex-G Cream
NDA 18-713, Mycelex Troche
NDA 18-813, Lotrimin Lotion
NDA 19-069, Mycelex-G Vaginal Tablets
NDA 20-289, Gyne-Lotrimin
NDA 20-389, Mycelex-7
NDA 20-525, Gyne-Lotrimin 3, 200 mg Vaginal Inserts
NDA 20-526, Gyne-Lotrimin 3, 3-Day Vaginal Inserts
NDA 20-574, Gyne-Lotrimin, 3/3 Day Vaginal Cream
NDA 20-888, Lotrimin AF Cream, 1%
NDA 20-889, Lotrimin AF Solution, 1%
NDA 20-890, Lotrimin AF Solution, 1%
NDA 21-143, Clotrimazole Cream, 2%

Betamethasone Dipropionate Active Ingredient

NDA 19-408, Diprolene Gel
NDA 19-716, Diprolene Lotion
NDA 19-555, Diprolene AF Cream
NDA 18-741, Diprolene Ointment

NDA 17-781, Diprosone Lotion

2. Combination product.

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

YES /_X_/ NO /__/

NDA 18-827, Lotrisone (betamethasone dipropionate, USP and clotrimazole, USP) Cream

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

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

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

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

YES /_X_/ NO /__/

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

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

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

YES /_X_/ NO /___/

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

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

YES /_X_/ NO /___/

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

YES /___/ NO /_X_/

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

YES /___/ NO /_X_/

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

Investigation #1, Study # S-88-067

Investigation #2, Study # S-87-024

Investigation #3, Vasoconstrictor Study C83-0538 - submitted 7/20/90

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

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

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

Investigation #1,	Study # S-88-067	YES /___/	NO /_X_/
Investigation #2,	Study # S-87-024	YES /___/	NO /_X_/
Investigation #3,	Vasoconstrictor Study C83-0538	YES /___/	NO /_X_/

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

Investigation #1,	Study # S-88-067	YES /___/	NO /_X_/
Investigation #2,	Study # S-87-024	YES /___/	NO /_X_/
Investigation #3,	Vasoconstrictor Study C83-0538	YES /___/	NO /_X_/

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

Investigation #1,	Study # S-88-067	YES /_X_/	NO /__/
Investigation #2,	Study # S-87-024	YES /_X_/	NO /__/
Investigation #3,	Vasoconstrictor Study C83-0538	YES /_X_/	NO /__/

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

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

Investigation #1, IND 18,274, Study # S-88-067	YES /_X_/	NO /__/
Investigation #2, IND 18,274, Study # S-87-024	YES /_X_/	NO /__/
Investigation #3, ———	YES /_X_/	NO /__/

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

N/A

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

YES /___/ NO /_X__/

/S/ 10/3/00
Signature of Project Manager Date

/S/ for 12/08/00
Signature of DDDDP Division Director Date
JONATHAN K. WILKIN

cc: Original NDA 20-010 HFD-540 Division Files HFD-90 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

FDA Links Tracking Links Check Lists Searches Reports Help

Edit Pediatric Information for Submission N020010 - N/000

Indication

Topical treatment of symptomatic inflammatory tinea pedis, tinea cruris, and tinea corporis due to Epidermophyton floccosum, Trichophyton mentagrophytes, and Trichophyton rubrum.

Adequacy of Proposed label: Other - See Comments

Formulation Status: NO NEW FORMULATION is needed

Decision Date: 2000-12-07

Comments & Recommendations (please date):

Not recommended for patients under the age of 12 years and not recommended for diaper dermatitis.

Related Applications:

Enter Pediatric Ranges Below

Application Range	Current Status/Due Date	Final Status/Action Date
Min. 0 Max. 11 ☐ kg ☐ mo. ☑ yr. ☐ kg ☐ mo. ☑ yr.	Status: Waived Due Date: 1991-07-3	Status: Waived Action Date: 2000-12-0
Reasons for Waivers and Deferrals/Comments: NDA 20-010 was submitted 8/31/89 and is a pre-PDUFA Application. Pediatric studies are waived below the age of 12 years, because the use of Lotrisone Cream and Lotion is not recommended in patients below the ag		
Min. 12 Max. 17 ☐ kg ☐ mo. ☑ yr. ☐ kg ☐ mo. ☑ yr.	Status: Deferred Due Date: 1991-07-3	Status: Deferred Action Date: 2002-12-3
Reasons for Waivers and Deferrals/Comments: NDA 20-010 was submitted 8/31/89 and is a pre-PDUFA Application.		
Min. 18 Max. Adult ☐ kg ☐ mo. ☑ yr. ☐ kg ☐ mo. ☐ yr.	Status: Completed Due Date: 1991-07-3	Status: Completed Action Date: 2000-12-0
Reasons for Waivers and Deferrals/Comments:		

Add New Range | New Indic. (Copy) | New Indic. (Blank) | Finished

Cancel Changes/Exit

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements) View Word Document

NDA Number:	020010	**Trade Name:**	LOTRISONE TOPICAL LOTION
Supplement Number:	000	**Generic Name:**	CLOTRIMAZOLE/BETAMETHASONE DIPROPIONATE
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	NA	**COMIS Indication:**	TINEA CRURIS AND TINEA CORPORIS & Tinea pedis
Action Date:	6/29/90		

Indication # 1 Topical treatment of symptomatic inflammatory tinea pedis, tinea cruris, and tinea corporis due to Epidermophyton floccosum, Trichophyton mentagrophytes, and Trichophyton rubrum.

Label Adequacy: Other - See Comments

Forumulation Needed: NO NEW FORMULATION is needed

Comments (if any): Not recommended for patients under the age of 12 years and not recommended for diaper dermatitis.

	Lower Range	Upper Range	Status	Date
	0 years	11 years	Waived	12/7/00
Comments: NDA 20-010 was submitted 8/31/89 and is a pre-PDUFA Application. Pediatric studies are waived below the age of 12 years, because the use of Lotrisone Cream and Lotion is not recommended in patients below the age of 12 years.				
	12 years	17 years	Deferred	12/31/02
Comments: NDA 20-010 was submitted 8/31/89 and is a pre-PDUFA Application.				
	18 years	Adult	Completed	12/7/00

This page was last edited on ~~12/7/00~~

/S/ 12/7/00

Signature Date

NCE 12/1/2000

/S/ - for

JONATHAN K. WILKIN 12/08/00

Debarment Certification

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

APPEARS THIS WAY
ON ORIGINAL

This NDA 20-010, Lotrisone (betamethasone dipropionate, USP and clotrimazole, USP) Lotion, is a pre-PDUFA New Drug Application originally submitted on August 31, 1989 and issued Not Approvable Letters on June 29 and December 31, 1990, and issued an Approvable Letter on July 31, 1991. A complete response to the December 31, 1990, was received on October 7, 1999.

NDA 20010
LOTRISONE LOTION

30 July 1991

DIVISION DIRECTOR'S MEMORANDUM

In 1988 the Division agreed with the sponsor of this NDA that - if the sponsor demonstrated that Lotrisone Lotion was superior to its vehicle in the treatment of *tinea pedis*, that Lotrisone Lotion was superior to its vehicle in the treatment of *tinea cruris*, and that the steroid activity of Lotrisone Lotion and Lotrisone Cream as measured by cutaneous vasoconstrictor assay methodology was deemed equivalent - then the sponsor would have met its obligation to demonstrate safety and efficacy of this line extension of this topical combination of clotrimazole and betamethasone. As documented in the medical officer's review, the sponsor conducted studies which indeed have documented that the Lotion formulation is superior to its vehicle in the treatment of *tinea cruris* and *pedis*. The study design does not allow one to make conclusions regarding the effects each component makes to the claimed effect. The study simply reaffirms the satisfactory anti-fungal clinical and microbiologic efficacy of the product in this new formulation.

I believe the thought process in 1988 was that vasoconstrictor assay results, which established equivalence in steroid activity of the approved Cream formulation and the proposed Lotion formulation, would, by inference, establish the clinical steroid equivalence of the two products. The Cream formulation formally established in 1984 that the combination resulted in improved clinical results (time to relief of symptoms) as opposed to the results with the individual components alone. As such, the Cream formulation met the requirement of 21 CFR 300.50. The Divisional belief was that - with anti-fungal efficacy and clinical steroid equivalence to the approved Cream formulation established, there would be no need to formally establish that the Lotion formulation line extension met the combination requirements itself.

The results of the vasoconstrictor assay submitted by the sponsor demonstrate once again that the assay methodology has observer differences as great as ± 0.5 - 1 (on a 1 - 4 scale) when comparing blanching on the same person with the same drug formulation. Adding the anti-fungal drug to the formulation is questionably further eroding this margin of error inherent in this methodology.

Nonetheless, the results of the vasoconstrictor assay demonstrate that at 24 hours, the mean blanching scores were equivalent and that at 7 hours, 13/24 subjects had identical blanching scores (comparing Cream and Lotion formulations), 6 subjects exhibited Lotion blanching scores 0.5 to 1 units greater than the Cream formulation, and 5 subjects demonstrated Lotion blanching scores 0.5 - 1.5 less than the Cream formulation. Overall the mean blanching score for the Cream was approximately 1.0 and for the Lotion (two simultaneous tests) 0.9 and 0.8. As such, the vasoconstrictor could be said to establish steroid activity "equivalence" by divisional interpretative criteria.

As such, I feel the sponsor has met the standard espoused by the Division at the time this product was originally developed. There is nothing in the NDA to make me believe that this product is not safe or effective as labeled, or that there is sufficient reason to renege on the original Divisional agreement at this time.

However, I feel that we have learned a great deal from this first experience with a topical combination product line extension. Most importantly, we have learned the vasoconstrictor assay is a poor method for establishing steroid activity equivalence when a the steroid is combined with another product. I would maintain that in the future, sponsors should establish the equivalence of their topical combination line extensions by either conducting one three-armed study (combination, anti-fungal, and steroid) using the same (i.e., lotion, cream, etc) formulation for all three arms. For approval, this study would be expected to demonstrate that each component of the combination makes a contribution to the claimed effects. Alternative study designs to demonstrate equivalence to the approved original product formulation would, of course, be considered on an individual basis, should a sponsor wish to undertake an alternative development approach.

/S/

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

APPEARS THIS WAY
ON ORIGINAL

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

NDA # 20-010 Drug: Lotrisone (clotrimazole and betamethasone dipropionate) Lotion
Applicant: Schering-Plough Research Institute Chem/Ther/other Types: 3,4S
PM: Cross Phone: 827-2020 HFD- 540
USER FEE GOAL DATE: pre-PDUFA DATE CHECKLIST COMPLETED: 12/1/00

Arrange package in the following order (include a completed copy of this CHECKLIST):	Check or Comment
1. ACTION LETTER with supervisory signatures Are there any Phase 4 commitments?	AP_X__ AE__NA___ Yes_X_ No____
2. Have all disciplines completed their reviews? If no, what review(s) is/are still in draft?	Yes __X__ No_____
3. LABELING (package insert and carton and container labels). (If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.)	Draft_____ Revised Draft_____ Final____X _____
4. PATENT INFORMATION	_____X_____
5. EXCLUSIVITY CHECKLIST	_____X_____
6. PEDIATRIC PAGE (all NDAs)	_____X_____
7. DEBARMENT CERTIFICATION (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992).	_____X_____
8. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status. If no audits were requested, include a memo explaining why.	____N/A____

9. REVIEWS & MEMORANDA:

DIVISION DIRECTOR'S MEMO GROUP LEADER'S MEMO MEDICAL REVIEW	If more than 1 review for any discipline, separate reviews with a sheet of colored paper.	_____ _____ 6/27/90, 10/9/90, 7/18/91, 2/2/92, 4/16/99, 87/11/00 9/13/00 (2), 9/28/00
SAFETY UPDATE REVIEW STATISTICAL REVIEW	Any conflicts between reviews must have resolution documented	_____ 6/22/90
BIOPHARMACEUTICS REVIEW		3/16/99, 3/29/00
PHARMACOLOGY REVIEW (Include pertinent IND reviews)		11/29/89, 3/13/00
Statistical Review of Carcinogenicity Study(ies)		N/A
CAC Report/Minutes		N/A
CHEMISTRY REVIEW		12/28/90, 6/27/91, 12/15/94, 4/5/00, 4/25/00, 9/12/00, 12/1/00
Labeling and Nomenclature Committee Review Memorandum		8/24/00
Date EER completed _6/12/00_ (attach signed form or CIRTS printout)		YES
FUR needed ___No_____ FUR requested __N/A_____		
Have the methods been validated?		Yes (attach)____ No__X____
Environmental Assessment Review /FONSI		Acceptable
MICROBIOLOGY REVIEW		2/13/00, 10/3/00
What is the status of the monograph?		N/A

10. CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes	_____X_____
11. MINUTES OF MEETINGS	_____ X _____
Date of End-of-Phase 2 Meeting:	_____N/A_____
Date of pre-NDA Meeting:	_____N/A_____
12. ADVISORY COMMITTEE MEETING MINUTES _____X_____ or, if not available, 48-Hour Info Alert or pertinent section of transcript.	Minutes___ Info Alert_____ Transcript__X___ No mtg__ __

13. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS _____N/A_____

14. If approval letter, has ADVERTISING MATERIAL been reviewed? Yes_____ No_____X_____
    If no and this is an AP with draft labeling letter, has advertising material already been requested? Yes, documentation attached_____
    No, included in AP Letter __X_____

15. INTEGRATED SUMMARY OF EFFECTIVENESS (from NDA) _____N/A _____

16. INTEGRATED SUMMARY OF SAFETY (from NDA) _____ N/A _____

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

TELEPHONE: (908) 298-4000

December 6, 2000

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

NDA 20-010
LOTRISONE LOTION

SUBJECT: RESPONSE TO FDA REQUEST-LABELING AND POST MARKETING COMMETMENT

Dear Dr. Wilkin:

Reference is made to the facsimile transmissions dated December 6, 2000 from the Division of Dermatologic and Dental Drug Products regarding the Post-Marketing Commitment and labeling for NDA 20-010, LOTRISONE® (clotrimazole and betamethasone dipropionate) Cream and Lotion.

We commit to the Post-Marketing Commitment as stated in the December 6, 2000 facsimile transmission.

We concur with the labeling provided the December 6, 2000 facsimile transmission. with inclusion of the correction in the betamethasone dipropionate chemical name to "...11β,17, 21-trihydroxy...".

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
Desk Copy (via fax): Frank Cross

J:\OPS\SUBMIT\USRA\NDA\20010\LETTERS\120600Wilkin.doc

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	December 6, 2000
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(908) 740-2628	(908) 740-2982

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:

[redacted]

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 — 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
Response to FDA Request-Labeling and Post Marketing Commetment

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)

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))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Response to FDA Request

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
/for Dr. Lamendola	Joseph F. Lamendola, Ph.D. Vice President, U.S. Regulatory Affairs	12/06/00

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2000 Galloping Hill Road, Kenilworth, NJ 07033	(908) 740-2628

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)

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

TELEPHONE: (908) 298-4000

November 29, 2000

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

NDA 20-010
LOTRISONE LOTION

SUBJECT: RESPONSE TO FDA REQUEST REGARDING LABELING AND PHASE 4 COMMENTS

Dear Dr. Wilkin:

Reference is made to the 11/22/00 FAX from the Division of Dermatological and Dental Drug Products as well as a teleconference which took place on 11/29/00 between the Agency's CMD. Frank Cross and Schering's Ms. Elin Krhoun regarding the Phase 4 clinical commitment for Lotrisone Lotion NDA 20-010. Schering agrees to monitor the efficacy of the educational campaign according to the following plan. As discussed, it has been modified slightly to more clearly describe the activities.

> "Evaluate the efficacy of Schering's educational campaign by monitoring the pediatric use of Lotrisone Lotion and Lotrisone Cream groups: 0-1, 1-2, 2-4, 4-8 and 8-12 years for; 1) all uses and 2) uses in diaper dermatitis. Usage will be estimated by utilizing the IMS Health databases; physician survey data from the National Disease and Therapeutic Index (NDTI) should be used to estimate the percentage of total use in these specified populations then multiplied by the total Lotrisone usage available through the National Prescription Audit (NPA) to derive the estimated Lotrisone use in the above specified age groups. A second database, estimating prescription use through any means in the above populations, will be utilized to support the IMS estimate. Such evaluations are to be are to be performed annually. A baseline evaluation, i.e., before the labeling change (e.g., 1999 or 2000), should be submitted within three months of approval."

Reference is made to the 11/22/00 FAX from the Division of Dermatological and Dental Drug Products as well as the teleconference which took place on 11/29/00 between the Agency's CMD. Frank Cross and Schering's Ms. Elin Krhoun regarding the labeling for Lotrisone Lotion NDA 20-010. Schering agrees to the text of the product insert (PI) and patient package insert (PPI) labeling as provided. However, as discussed and agreed, the PI and PPI could be formatted as a single sheet separated by perforations to enable the healthcare provider to separate the PPI and give it to the patient with the product. Directions for the pharmacists/healthcare provider will be added to the 10-mL and 30-mL cartons. See attached copies with the additions indicated.

In addition, as discussed several minor typos will be corrected.

- Generic Name on PI: Parentheses will be added and the "C" in clotrimazole and "B" in betamethasone will be lower case to be consistent with the labels and cartons. This was agreed as noted in the FAX from CMD. Frank Cross on 11/9/00.

- In **PRECAUTIONS - Pregnancy Category C**, two paragraphs will be used for description of the Segment II (teratology studies).

- In **Nursing Mothers** section of the PI, 5th line, "product" should be "produce", i.e., "...insufficient systemic absorption to produce detectable quantities...".

- In the **How Supplied** section for LOTRISONE Lotion, "to" will be changed to "between", i.e., "...excursions permitted between 15°C and 30°C...".

- In the PPI, 1st page, 5th paragraph, "message" should be "massage", i.e., "Gently massage...".

Also, several other minor grammatical corrections will be made:

- In **PRECAUTIONS General**, 6th paragraph, the cross-reference should be bolded, i.e., (See **PRECAUTIONS – Pediatric Use**).

- In **PRECAUTIONS Carcinogenicity, Mutagenicity, Impairment of Fertility** and **Pregnancy Category C**, dashes will be added to numbers preceding "fold", e.g., "5- and 38- fold".

- In **PRECAUTIONS – Pediatric Use**, 4th line, "cream" will be capitalized, i.e., "LOTRISONE Cream" and " and in the PPI, 1st paragraph, 7th line, "Lotrisone" will be all capitals, i.e., "LOTRISONE".

- In several places, periods will be placed at the end of the sentence rather than at the end of the cross-reference parentheses.

- In last sections identifying the company, etc., the date of PI and PPI, "Revised 11/20/2000" will be changed to "Rev. 11/00" and the "®" symbol will be

changed to "©". "Rights" will be changed to "rights", i.e., "All rights reserved." This section in the PPI will be made the same as that in the PI.

- In the PPI, 2nd paragraph, in the question, "Work" will be lower case, "work".
- In the PPI, 8th section, the storage statements will be bolded.

Reference is also made to the 11/24/00 FAX from the Division of Dermatological and Dental Drug Products as well as a teleconference which took place on 11/29/00 between the Agency's CMD. Frank Cross and Schering's Ms. Elaine Potomski regarding Phase 4 CMC commitments for Lotrisone Lotion NDA 20-010.

Schering agrees to monitor the particle size of the product, and report the results to the Agency on a quarterly basis as well as in the annual stability report.

Schering also agrees to perform Homogeneity testing on all future stability batches and report the results of the first three production batches to the Agency, on a quarterly basis as well as in the annual stability report. As agreed to during the 11/29/00 teleconference, if results of the homogeneity testing do not indicate a problem, Schering will request the opportunity to discuss withdrawing the commitment from the application.

Schering also acknowledges the statement on the 11/24/00 FAX that "The Applicant was also advised that out of specification results at 12 months at the intermediate and accelerated testing ranges are not usually cited as reasons for withdrawal of the drug from the market." All stability testing results will be submitted in the product's Annual Report.

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 (via fax)

Number of Pages Redacted 2

❖❖❖

Draft Labeling
(not releasable,

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: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY
APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Schering Corporation	November 29, 2000
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(908) 740-2628	(908) 740-2982
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
2000 Galloping Hill Road Kenilworth, New Jersey 07033	Joseph F. Lamendola, Ph.D. Vice President, U.S. Regulatory Affairs 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:

[redacted]

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

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

IF AN ANDA, OR 505(b)(2), 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 ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING, AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

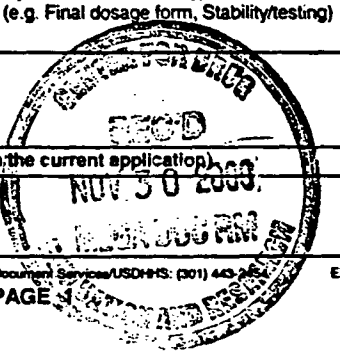
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Response to FDA Request

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 (Full establishment information should be provided in the body of the Application.)
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)

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

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

5. DOES 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
20-010

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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Elaine Potanski /for Dr. Lamendola	Vice President U.S. Regulatory Affairs	October 7, 1999

FORM FDA 3397 (12/93)

This NDA 20-010, Lotrisone (betamethasone dipropionate, USP and clotrimazole, USP) Lotion, is a pre-PDUFA New Drug Application originally submitted on August 31, 1989 and issued Not Approvable Letters on June 29 and December 31, 1990, and issued an Approvable Letter on July 31, 1991. A complete response to the December 31, 1990, was received on October 7, 1999.

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

NDA ORIG AMENDMENT

October 13, 2000

Dr. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
N216 (Document Control Room)
9201 Corporate Blvd
Rockville, MD 20850

NDA 20-010
LOTRISONE LOTION

BL

SUBJECT: RESPONSE TO FDA REQUEST FOR INFORMATION

Dear Dr. Wilkin:

Reference is made to the October 2, 2000 teleconference in which the labeling submitted on September 27, 2000 was discussed. At the teleconference it was agreed that we could send our views on the use of the [redacted] or other graphics to indicate "Not recommended for use under the age of 12 years and not recommended for diaper dermatitis", as they would affect policy issues.

Our position regarding the use of a graphic symbol to supplement product labeling is attached.

As discussed at the teleconference, we proposed that the Division issue the Action Letter for the Lotrisone Lotion NDA. Schering believes that labeling symbols should be a joint industry/FDA project, and not imposed upon one company in the interim.

The proposed labeling sent to Schering on October 3, 2000 is acceptable in other aspects except for the inclusion of the [redacted] and the exceptions listed below for the package insert, patient package insert, cartons and 30-mL bottle label.

- Package and Patient Package Inserts Headers, Cartons and Bottle Labels: [redacted] was deleted before "clotrimazole and betamethasone dipropionate" and parentheses added, to make more room for additional "use" text.

DUPLICATE

- Package Insert, Page 2, lines 16 and 23, and Bottle labels and Cartons: [redacted] as requested by Dr. DeCamp in the October 3, 2000 teleconference.
- Package Insert, Page 4, line 19: It appears in the fax copy that the "I" in "Information Is" are caps; they should be lower case.
- Package Insert, P. 19, line 20, add "-" to "30 mL", to be "30-mL".
- Package Insert, P. 19, line 21 delete "only" when referring to storage conditions.

As discussed a sample of the 10-mL bottle label will be submitted shortly.

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

Z

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

2 pages (2)

III. Addressing the Need for Appropriate Labeling of Lotrisone Products.

Schering-Plough requests approval of Lotrisone Lotion. We believe that our mutual agreement to implement the several alternative measures recommended by the Agency and the Advisory Committee described below will ensure appropriate labeling of this product.

A. Labeling for Lotrisone products would be as agreed to in the October 2, 2000 teleconferences,

B. The agreed upon prominent, bolded wording is being added to the carton, container label (on the lotion bottle) and patient package insert;

> **"NOT RECOMMENDED FOR PATIENTS UNDER THE AGE OF 12 YEARS AND NOT RECOMMENDED FOR DIAPER DERMATITIS"**

These words provide appropriate precautions for use of the product according to current regulatory policies and practices.

C. A patient package insert has been developed and will been placed in each Lotrisone carton, as requested by the Agency.

D. We have initiated an educational campaign directed at informing pediatric physicians on the proper-labeled use of Lotrisone Cream. In September, we began making personal sales representative visits to physicians of Lotrisone emphasizing the need to avoid the use of the product in patients under 12 years of age and in the use of diaper dermatitis.

we plan

We have been receiving positive feedback from physicians expressing their pleasure with our efforts to eliminate inappropriate use of Lotrisone. The new labeling of the product is a prominent part of our promotional material and is being highlighted on every call (see the attached). We believe that this has been an effective way to inform physicians on how to safely and appropriately use our products.

E. Applicable adverse event reports for patients under 12 years of age will be submitted as expedited reports to the Agency.

Schering-Plough Research Institute

2000 Galloping Hill Road
Kenilworth, New Jersey 07033

TELECOPIER TRANSMITTAL SHEET

Please deliver the following 8 pages (including cover page)

If transmittal is incomplete or illegible, please call: 908-740-5434

DATE:	November 29, 2000
TO:	CMD. Frank Cross
FAX NUMBER:	301-827-2075

FROM:	Elin R. Krhoun
LOCATION:	K-6-1 1635
FAX NUMBER:	908-740-6500
SUBJECT:	Lotrisone Lotion - NDA 20-010

MESSAGE:

Attached is a copy of the response on the labeling and Phase 4 commitments.

Regards,

Elin Krhoun
Reg. Affairs Manager

J:\Shared\KRHOUN\Diprolene\OGD Fax.doc

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 0703

September 29, 2000

BC

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®
(betamethasone dipropionate, USP and clotrimazole, USP)
Lotion

SUBJECT: 12-MONTH STABILITY REPORT

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 correspondences dated March 3, 2000, March 13, 2000, April 5, 2000, April 13, 2000, May 5,2000 and June 30, 2000.

An updated stability report containing 12-months of data on three batches of Lotrisone Lotion manufactured at our Kenilworth facility is being sent to NDA 20-010 today (September 29, 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 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

Nicholas J. Pelliccione, Ph.D.
Vice President, CMC
Worldwide Regulatory Affairs

EP/sa

APPEARS THIS WAY
ON ORIGINAL

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

NDA ORIG AMENDMENT

September 27, 2000

BL

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

SUBJECT: RESPONSE TO FDA REQUEST
REVISED DRAFT LABELING

Dear Dr. Wilkin:

We refer you to your September 15, 2000 fax with the proposed draft labeling for Lotrisone Cream and Lotion.

We are providing our proposed Lotrisone Cream and Lotion Revised Draft Labeling. The following revisions are proposed:

Package Insert (PI):

The [redacted] was deleted. This graphic is a pictorial representation which indicates **"DO NOT USE..."** and is not consistent with **"NOT RECOMMENDED FOR ..."**. **"NOT RECOMMENDED FOR PATIENTS UNDER THE AGE OF 12 YEARS AND NOT RECOMMENDED FOR DIAPER DERMATITIS"** is included prominently at the beginning of the PI and two times in the text portion. At the June 29, 2000 DODAC Committee meeting, the Advisory Committee and the Agency agreed that **"NOT RECOMMENDED..."** was appropriate wording rather than **"NOT FOR USE..."**. Pictorial warnings such as this for topical drugs containing corticosteroids are unprecedented.

DESCRIPTION:

For LOTRISONE Cream, "70/30" was added after cetearyl alcohol to be consistent with the listing of ingredients for the Lotion.

ORIGINAL

Number of Pages Redacted 1

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Draft Labeling
(not releasable,

(U)

[redacted]

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,

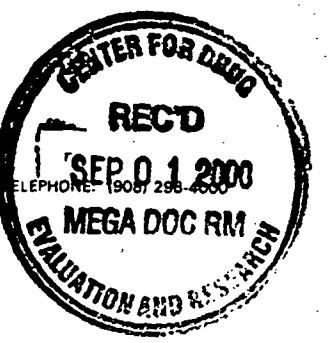
Ellen R. Kirkorian for

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

EK/js
Enclosure
Desk Copy: Frank Cross, HFD-540

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 0703



August 30, 2000

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

NDA 17-781 (Diprosone® Lotion)

NDA 18-741 (Diprolene® Ointment)
NDA 19-408 (Diprolene® Gel)
NDA 19-555 (Diprolene® AF Cream)
NDA 18-827 (Lotrisone® Cream)
NDA 20-010 (Lotrisone® Lotion)

SUBJECT: **NOTIFICATION OF GENERAL CORRESPONDENCE TO NDA 19-716– ADDITIONAL ANALYTICAL METHODS FOR BETAMETHASONE DIPROPIONATE**

Dear Dr. Wilkin,

Reference is made to our approved application for Diprolene Lotion (NDA 19-716) which serves as the central repository for all chemistry, manufacturing and controls information pertaining to the drug substance betamethasone dipropionate for each of the NDAs referenced above in this letter. Reference is also made to our August 30, 2000 general correspondence notifying FDA that we have developed a method for determining Estimation of Chromatographic Impurities. A copy of the analytical procedure for determining Estimation of Chromatographic Impurities was provided to NDA 19-716.

During the next 12 months, we will be generating a database using the method for Estimation of Chromatographic Impurities in order to develop an appropriate specification. In November 2001, following the review of the database and subsequent specification development, we will submit a prior approval supplement to establish this additional method and specification as the regulatory method with final specification.

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,

Dennis Flanagan for

Nicholas J. Pelliccione, Ph.D.
Vice President, CMC
Worldwide Regulatory Affairs

BM/sa

APPEARS THIS WAY
ON ORIGINAL

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

TELEPHONE: (908) 298-4000

NDA ORIG AMENDMENT

August 16, 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
NDA 18-827
LOTRISONE CREAM

NC

SUBJECT: RESPONSE TO FDA REQUEST

Dear Dr. Wilkin:

Reference is made to the August 16, 2000 telephone call to Elin Khroun from Frank Cross in which he requested a disk with a WORD file with the labeling for the Patient Information Leaflet (Patient Package Insert) for Lotrisone Lotion and Lotrisone Cream submitted on August 15, 2000.

In response to Mr. Cross's request, a disk with a WORD file with the labeling the Patient Information Leaflet (Patient Package Insert) for Lotrisone Lotion and Lotrisone Cream is being provided. A hard copy of the text is also included. The disk is attached to Mr. Cross's desk copy.

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

Sincerely,

Yvette Henderson for

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

YH/it
Enclosure

ORIGINAL

Desk Copy: Frank Cross (WORD disk attached)

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Number of Pages Redacted 6

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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: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY
APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Schering Corporation	September 27, 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):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
2000 Galloping Hill Road Kenilworth, New Jersey 07033	Joseph F. Lamendola, Ph.D. Vice President, U.S. Regulatory Affairs 2000 Galloping Hill Road Kenilworth, NJ 07033

BL

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:
[redacted]

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

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

IF AN ANDA, OR 505(b)(2), 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 ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING, AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

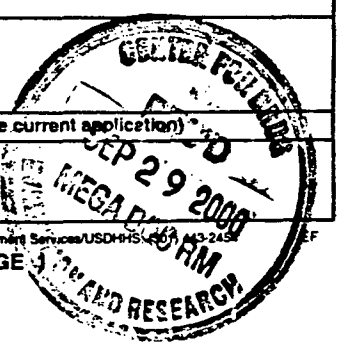
REASON FOR SUBMISSION
Response to FDA Request - Revised Draft Labeling

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 (Full establishment information should be provided in the body of the Application.)
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)



DUPLICATE

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))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Response to FDA Request - Revised Draft Labeling

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 Parts 210 and 211, or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Part 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 FD&C Act Section 506A, 21 CFR 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
/for Dr. Lamendola	Joseph F. Lamendola, Ph.D. Vice President, U.S. Regulatory Affairs	9/27/00

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2000 Galloping Hill Road, Kenilworth, NJ 07033	(908) 740-2628

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:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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

Number of Pages Redacted 26

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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	October 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

BL

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 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 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

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

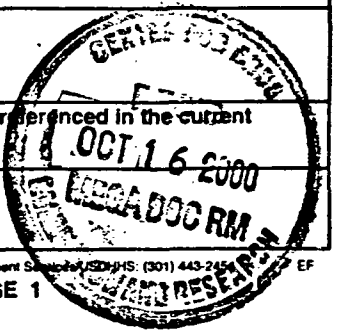
NUMBER OF VOLUMES SUBMITTED_____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

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)

DUPLICATE



SCHERING CORPORATION

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

NDA ORIG AMENDMENT

August 15, 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

BL

SUBJECT: RESPONSE TO FDA REQUEST

Dear Dr. Wilkin:

Reference is made to the August 10, 2000 telephone call to Elin Krhoun from Frank Cross in which he requested a draft Patient Information Leaflet (Patient Package Insert) for Lotrisone Lotion.

In response to Mr. Cross's request, 2 copies of the proposed draft Patient Information Leaflet are being submitted.

A separate letter and copies of the proposed draft Patient Information Leaflet have been sent for Lotrisone Cream, NDA 18-827.

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

Sincerely,

Yvette Henderson for

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

YH/it
Enclosure
Desk Copy: Frank Cross, HFD-540
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ORIGINAL

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Draft Labeling
(not releasable,

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SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

TELEPHONE: (908) 298-4000

AMENDMENT

BC

August 2, 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®
(betamethasone dipropionate, USP and clotrimazole, USP)
Lotion

SUBJECT: RESPONSE TO FDA REQUEST: CLINICAL TRIAL BOTTLE INFORMATION.

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 CMC correspondences dated March 3, 2000, March 13, 2000, April 5, 2000, April 13, 2000, May 5, 2000, June 30, 2000 and July 21, 2000.

In a telephone conversation on 7/13/00 and again on 7/20/00, between FDA's Mr. Frank Cross, CSO and Schering's Ms. Potomski, it was requested that Schering provide certain information regarding bottles used in the clinical trials submitted in the original submission dated August 31, 1989.

The requested information is as follows:

The nominal bottle size as well as the minimum fill is 30 mL. The bottle's overflow capacity is [redacted]

Regarding the area of application in the two Lotrisone Lotion studies, subjects were to treat only the infection under study. In other words, subjects in the tinea pedis study (S88-067) were permitted to treat both feet if affected, but not the groin if tinea cruris was present. This was also true for tinea cruris subjects (study no. S87-024) were not permitted to treat tinea pedis infections.

ORIGINAL

The amount of product used during the trials was not recorded as part of the case report form, nor was it captured as part of the database. However, subjects were given a 30-mL bottle (28.9 g) of the medication each week. Therefore, subjects in the tinea pedis trial received no more than 120 mL (115.6 g) of lotion and tinea cruris received no more than 60 mL (57.8 g) of lotion.

Based on the publication 'Manual of Dermatolgic Therapeutics, 5th edition', on page 247 (edited by Kenneth A. Arndt, 1995, Little Brown and Company, Boston MA) it is stated that for the "anogenital area" twice daily applications for one week would require 28 grams of topical medication. Although the feet are not specifically listed, we would anticipate a similar amount of medication would be used.

In accordance with 21 CFR 314.70(a), we are concurrently submitting a field copy of this submission to our home FDA 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 Patomski for

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

EP/sa

APPEARS THIS WAY
ON ORIGINAL

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A copy of the transcripts of the June 29, 2000, Dermatologic and Ophthalmic Advisory Committee Meeting are available in a separate binder in the Division Files and on the Internet.