

Item 1 of your letter of December 31, 1990 posed a question concerning the greater vasoconstriction effect of Diprosone Ointment at the seven hour timepoint compared to all other formulations studied, even though each preparation contained the same amount of betamethasone dipropionate.

It should be noted that Diprosone Ointment was included in this study as a standard for the assay. The observation of a higher degree of skin blanching with betamethasone dipropionate in an ointment vehicle than in the cream or lotion vehicles was expected. This finding reflects the impact that vehicles are known to have on the bioavailability of topical corticosteroids. Ointments, being occlusive in nature, increase the penetration of the drug, thus increasing its blanching effect over non-occlusive creams and lotions. If our assay had failed to detect this expected difference, one would have had to question the sensitivity of the measurement.

The second question dealt with whether or not the results of the study supported a conclusion that Lotrisone Cream and Lotrisone Lotion (with — propylene glycol) demonstrated comparable vasoconstriction effect.

Our correspondence of July 20, 1990 provided raw data from a single vasoconstriction trial (C83-035-38) involving 24 subjects with 8 test sites per subject. No statistical evaluation of the data was provided at that time. Our response, including interpretive analysis and conclusions of this study, as well as two subsequent trials (C83-035-59 and C83-035-62/II), is presented in the following report. These additional studies resulted from our routine practice of including our marketed products or those projected for marketing in our ongoing vasoconstriction screening program.

Introduction

The use of in vivo vasoconstriction to evaluate the potency potential of topically applied corticosteroid formulations was first reported by McKenzie and Stoughton. A small amount of topically applied corticosteroid produces a visible blanching in fair-skinned subjects due to its local vasoconstrictive action. The application of several preparations to the forearms of normal volunteers and a visual quantitation of the degree of blanching at each test site allows a comparison of the vasoconstrictor potencies of the various preparations used. The results of this assay are used to evaluate the bioavailability of corticosteroids from various vehicles and test formulations and to screen the topical preparations for potency.

Methods

In our assay, test materials were applied to 8 pre-assigned test sites on the flexor surface of the forearms of 24 normal, healthy volunteer subjects, and the sites are covered by non-occlusive plastic shields. The test materials and shields are left in place for six and one half hours, at which time the shields are removed, and the sites washed with warm soap and water. At seven and twenty-four hours after the drug application, the treated sites are evaluated for vasoconstriction by assessing the degree of skin blanching. In this evaluation the traditional and generally employed grading system of 0 to 3 is employed in which 0=no blanching, and 1, 2, and 3 indicate mild, moderate, and strong blanching respectively. Half values are also used.

Study C83-035-38 included one site treated with Diprosone Ointment (as a standard), one treated with Lotrisone Cream, and two sites each for three test formulations of Lotrisone Lotion including the proposed commercial Lotrisone Lotion formulation (— propylene glycol). Raw data for this study is presented in Appendix 1 (A and B). Studies C83-035-59 and C83-035-62/II included both Lotrisone Cream and the proposed Lotrisone Lotion formulation (each at one test site) among the various treatments studied (raw data for these studies is presented in Appendices 2 and 3). Both seven and twenty-four hour scores were recorded in each study. As the degree of blanching seen at twenty-four hours was minimal (fewer than 25% of the subjects demonstrated mild or greater residual blanching with any test preparation), only seven hour data was subjected to statistical analysis.

Statistical Methods

To characterize the inherent variability of vasoconstriction skin blanching scores, differences between the measurements of the two test sites for each of the three test formulations (in study C83-035-38) were calculated and summarized. To compare Lotrisone Lotion to Lotrisone Cream (in each study), differences between their respective skin blanching scores were calculated for each subject. In study C83-035-38, where two test sites were treated with the proposed Lotrisone Lotion formulation, an average skin blanching score was first calculated and used to determine difference scores between Lotrisone Lotion and Lotrisone Cream. These "difference scores" were classified as favoring Lotrisone Lotion if a higher degree of blanching (at least one unit on the 0 to 3 scale) was seen at the lotion treated site than at the cream treated site, or as favoring Lotrisone Cream if the opposite was true. McNemar's test was used to compare the number (proportion) of subjects favoring one over the other.

Results

Three Lotrisone Lotion test formulations in study C83-035-38 were applied to two test sites each. Table 1 presents a tabulation of the degree of difference in skin blanching scores between the matching test sites for each formulation. As the table demonstrates, differences in skin blanching scores (between two measurements of the same preparation within a subject) of 0.5 was routine. As many as half of the subjects demonstrated differences of at least this degree.

TABLE 1

NUMBER OF SUBJECTS WITH DEGREE OF DIFFERENCE IN BLANCHING SCORES
(DIFFERENCE BETWEEN THE READINGS AT TWO SITES WITH THE SAME FORMULATION)

	DIFFERENCES BETWEEN MEASUREMENTS						
	-1.50	-1.00	-0.50	0.00	0.50	1.00	1.50
STUDY C83-035-38 (N=24)							
FORMULATION 1 — PROPYLENE GLYCOL)	1	1	7	12	2	0	1
FORMULATION 2 — PROPYLENE GLYCOL)	0	0	2	13	6	3	0
FORMULATION 3 — PROPYLENE GLYCOL -	0	4	3	12	4	1	0

NOTE: EACH SUBJECT APPLIED THE SAME FORMULATION AT TWO SITES. DIFFERENCES BETWEEN THE TWO MEASUREMENTS WERE CALCULATED (SITE 1 - SITE 2).

We conclude that differences in skin blanching scores of half a unit reflect the inherent variability of subjective visual measurement. Therefore, in our analysis of the comparison of two different formulations, differences in skin blanching scores have to exceed 0.5 units to be classified as favoring one treatment over another; if not, the treatments are considered clinically equivalent.

Three vasoconstriction studies were conducted which include comparisons of the proposed formulation for Lotrisone Lotion versus the marketed Lotrisone Cream formulation. Table 2 presents a summary of the number of subjects in each study who demonstrated differences in the degree of skin blanching between these two formulations, as well as the formulation which demonstrated the higher degree of skin blanching (i.e., the "favored" formulation).

TABLE 2

SUMMARY OF LOTRISONE LOTION VS LOTRISONE CREAM VASOCONSTRICTION STUDIES

	NUMBER OF SUBJECTS			MCNEMAR'S TEST EXACT P-VALUE
	FAVORING LOTRISONE CREAM	CLINICALLY EQUIVALENT	FAVORING LOTRISONE LOTION	
C83-035-38 (N=24)	4	18	2	.69
C83-035-59 (N=24)	2	22	0	.50
C83-035-62/II (N=24)	4	19	1	.38

NOTE: IN STUDY C83-035-38 TWO SITES RECEIVED LOTRISONE LOTION TREATMENT. SCORES FROM THESE SITES WERE AVERAGED $\{(SITE1 + SITE2)/2\}$ BEFORE CALCULATING DIFFERENCES BETWEEN LOTION AND CREAM.

No statistically significant differences between Lotrisone Cream and Lotrisone Lotion were detected in any of the three studies ($p \geq .38$). In study C83-035-38, 75% (18/24) of the subjects had skin blanching scores which were clinically equivalent, 17% (4/24) favored the cream, and 8% (2/24) favored the lotion. Similarly, in study C83-035-62/II 79% (19/24) of the subjects had skin blanching scores which were clinically equivalent, 17% (4/24) favored the cream, and 4% (1/24) favored the lotion. In study C83-035-59, 92% (22/24) of subjects demonstrated clinical equivalence between the two formulations, with only 8% (2/24) differing in the direction of favoring the cream.

These results support the conclusion that the vasoconstriction effect of betamethasone dipropionate, 0.05%, when applied in the proposed commercial Lotrisone Lotion formulation is similar to that of Lotrisone Cream. Furthermore, these results constitute a demonstration of the in vivo bioequivalence of the two formulations.

Q

Number of Pages
Redacted 4



Confidential,
Commercial Information

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ORIG

~~CONFIDENTIAL~~
Schering-Plough
Research

2000 Galloping Hill Road
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Telephone (201) 298-4000
Telex 6853298 SP KEN

January 9, 1991

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

Subject: NDA 20-010, Lotrisone Lotion
Samples For Methods Validation

Dear Dr. Lumpkin:

As requested on November 16, 1990 by your Dr. Katague, we have sent samples for methods validation to Dr. Larry Jones at the FDA testing laboratory in St. Louis, Missouri. Since several samples had passed their expiration date we replaced them with new samples. Included for your information is the updated list of samples and accompanying information we sent to the testing laboratory.

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

Sincerely,

Marion Ceruzzi, Ph.D.
Manager - Regulatory Affairs



cc: Dr. Katague
MC:lnm
Attachments

NDA 20-010

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

DEC 31 1990

Dear Dr. Given:

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

Reference is also made to the not approvable letter dated June 29, 1990 and to your additional correspondence of July 3 and 20, 1990.

We have completed the review of this application as amended and have concluded that the information presented is inadequate and that the application is not approvable.

Under section 505(d) of the Act and 21 CFR 314.125(b) of the FDA implementing regulations, you have failed to provide adequate evidence demonstrating the in vivo bioavailability of the drug product, as required under 21 CFR 320. Specifically, the vasoconstrictor study that was conducted to assess the availability of the steroid in the lotion formulation failed to demonstrate that the Lotrisone Cream and Lotion formulations were bioequivalent. In addition, there were inconsistencies in the data submitted.

The deficiencies regarding the vasoconstrictor study may be addressed by providing an explanation of the inconsistencies observed in the data submitted. The specific concerns are as follows:

1. The Diprosone Ointment product was observed to have a much greater vasoconstriction effect than the other formulations at the seven-hour time interval, even though all the preparations tested contained the same amount of betamethasone dipropionate.
2. The Lotrisone Lotion formulation that contains propylene glycol, ~~is~~ is similar to that of Lotrisone Cream. However, the Lotrisone Lotion formulation was observed to have a vasoconstriction effect comparable to 80% of the effect of Lotrisone Cream at both time intervals.

Alternatively, the deficiencies may be addressed by conducting an additional clinical study in tinea pedis or tinea cruris. It is recommended that the study include at least two test arms (the combination of clotrimazole and betamethasone dipropionate and clotrimazole alone) in order to evaluate the effect of the steroid in the formulation.

Please be advised that the establishment inspections have not yet been completed. We cannot approve this application until satisfactory Establishment Inspection Reports have been received for all facilities involved in the manufacture and packaging of the bulk drug and the drug product.

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

We reserve comment on the proposed labeling until the New Drug Application is found adequate in other aspects.

Within 10 days after the date of this letter, you are required to amend the application, or notify us of an intent to file an amendment, or follow one of the other alternatives under 21 CFR 314.120. In the absence of such action on your part, the FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. A partial response will not be processed as a major amendment, and, therefore, the review clock will not be activated.

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

**APPEARS THIS WAY
ON ORIGINAL**

cc: NWK-DO
ORIG. NDA 20-010
HFD-82
HFD-520
HFD-520/Div Dir/MLumpkir
HFD-520/MO/DBostwick
HFD-520/SUPV MO/CCEvans CHN
HFD-520/SUPV PHARM/Rosterberg
HFD-520/CHEM/DKatague DJC/12-28-90
HFD-520/SUPV CHEM/WDe Camr
HFD-521/PROJ MGR/RCook

S/ 12-31-90

S/ 12-28-90

S/ 12/28/90

12/28/90

S/ 12/28/90

12-28-90

NOT APPROVABLE

APPEARS THIS WAY
ON ORIGINAL



ORFG

Schering
Research

~~NEW DRUG APPLICATION~~

July 20, 1990

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

(A7A)

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



Subject: LOTRISONE Lotion NDA 20-010

Dear Dr. Lumpkin:

This is in response to your letter of June 29, 1990 concerning the above referenced New Drug Application.

As requested in your letter, the following information concerning the vasoconstrictor assay is submitted herewith:

- A complete protocol for the vasoconstrictor study (C83-035-38). (Attachment 1)
- The vasoconstrictor scores for each patient at each time point. (Attachment 2)
- The name and qualifications of the investigator and the name and location of the facility where this study was conducted. The investigator who conducted the study and where the study was conducted is as follows:

Elyane Lombardy, MD
Schering Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

Dr. Lombardy's Curriculum Vitae is included (Attachment 3).

This information supports the LOTRISONE Lotion formulation chosen for use in the clinical trials which are the basis of the above referenced NDA.

We look forward to the prompt approval of this product.

Sincerely,

Mary G. Given for

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

Desk Copies: Mr. Van Sickler
Mr. David Bostwick

MJN:lnm
Attachments



ORTK

ORIG NEW COUNTY

Schering-Plough
Research

2000 Galloping Hill Road
Kenilworth, New Jersey 07033
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Telex 6853298 SP KEN

July 3, 1990

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

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7-11-90
JUL 5 1990
HFD-520
EVALUATION AND RESEARCH

Subject: NDA 20-010 LOTRISONE Lotion

Dear Dr. Lumpkin:

This is in response to your letter of June 29, 1990 concerning the above referenced submission. We are in the process of compiling the data requested concerning the vasoconstriction study. This information will be submitted to you when it is available.

Sincerely,

Mary Ann Leiby for

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

MJN:lnm

Desk Copy: Mr. Van Sickler

2.1

NDA 20-010

1990

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

MAY 2 1990

Dear Dr. Given:

Reference is made to your New Drug Application (NDA), and to your amendment dated December 15, 1989, received by the Food and Drug Administration (FDA) on December 20, 1989, for Lotrisone Lotion.

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

A previous letter in this form, dated January 17, 1990, was sent to you, incorrectly giving the new due date as April 20, 1990. The correct new due date is June 18, 1990. We apologize for any inconvenience our error may have caused.

If questions arise concerning this NDA, please contact Van C. Sickler, of the Project Management Staff, at (301) 443-6797.

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-520
HFD-520/MO/DCBostwick
HFD-520/PHARM/RMainigi
HFD-520/CHEM/WDeCamp
HFD-521/EMS/VCSickler/sdj/4/25/90
HFD-521/EMS/JBona
F/T: 4/25/90

EXTENSION LETTER 2122u

Handwritten notes:
4/24/90
/S/
4/26/90
4/30
/S/acc/90
5/1/90
/S/

JAN 17 1990

Douglass B. Given, M.D., Ph.D.
Schering-Plough Research
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Given:

Reference is made to your New Drug Application (NDA), and to your amendment dated December 15, 1989, received by the Food and Drug Administration (FDA) on December 20, 1989, for Lotrisone Lotion (clotrimazole and betamethasone dipropionate).

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

The new due date is April 20, 1990.

If questions arise concerning this NDA, please contact Van Sickler, of the Project Management Staff, at (301) 443-6797.

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

~~HEP-520~~

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F/T: 1/3/90

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1-11-90

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ORIG

Schering-Plough
Research

December 15, 1989

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

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

~~EA~~ **ORIG. AMENDMENT**
(AM)

Subject: LOTRISONE[®] (clotrimazole 1%/
betamethasone dipropionate 0.05%) Lotion
NDA 20-010

Dear Dr. Lumpkin:

Submitted herewith is an amendment to our New Drug Application for LOTRISONE (clotrimazole 1%/betamethasone dipropionate 0.05%) Lotion. The original NDA for this product was submitted August 31, 1989, and contained information to support the use of this product in tinea cruris and corporis.

This amendment contains a clinical study in tinea pedis which would support the use of LOTRISONE Lotion in this indication. In reviewing this amendment, please refer to our meeting of October 26, 1988 with Mr. David Bostwick and Dr. Evans during which the clinical program for this product was discussed. At this meeting it was agreed that one clinical study in tinea pedis and one in t. cruris would be sufficient to gain approval in t. pedis, cruris and corporis.

During a December 14, 1989 conversation with Mr. Bostwick, it was established that review of the August 31, 1989 submission has not begun. Therefore, this submission should not adversely delay the review of this NDA.

Also, in accordance with 21 CFR 314.50(d)(5)(vi)(b), the safety summary has been updated to include the information from the clinical study. At this time, there are no ongoing studies with LOTRISONE Lotion.

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



Sincerely,

Mary Jane Kelly for

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

MJN:lnm
Encl.

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Douglas B. Given, M.D., Ph.D.
Vice President, Regulatory Affairs
Schering-Plough Research
2000 Galloping Hill Road
Kenilworth, NJ 07033

SEP 18 1989

Dear Dr. Given:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b) / 507 of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Lotrisone (clotrimazole, 1%/betamethasone dipropionate 0.05%) Lotion

Date of Application: August 31, 1989

Date of Receipt: September 5, 1989

Our Reference Number: NDA 20-010

Unless we find the application not acceptable for filing, the filing date will be November 5, 1989.

Please begin any communications concerning this application by citing the NDA number listed above. Should you have any questions concerning the NDA, please contact:

David Bostwick
Project Manager
(301) 443-6797

Sincerely yours,

Patricia L. DeSantis
Acting Chief, Project Management Staff
Division of Anti-Infective
Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Orig. NDA 20-010

HFD-520

HFD-520/MO

PH

CH

HFD-521/CSO/Bostwick/smc/9/11/89

ACKNOWLEDGEMENT LETTER

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20 9-15-89



ORIG

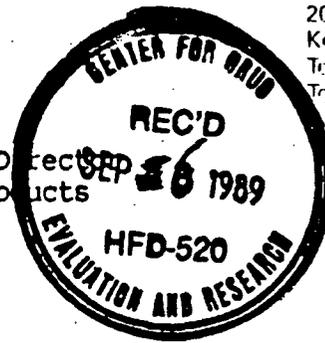
Schering-Plough
Research

N

August 31, 1989

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

Lillian Gavrilovich, M.D., Acting Director
Division of Anti-Infective Drug Products
Food and Drug Administration
CDER - II, HFD-520
Document Control Room 12B-45
5600 Fishers Lane
Rockville, Maryland 20857



20-010
520

Subject: LOTRISONE (clotrimazole 1%/
betamethasone dipropionate 0.05%) Lotion
NEW DRUG APPLICATION

Dear Dr. Gavrilovich:

Submitted herewith is our New Drug Application for LOTRISONE (clotrimazole 1%/
betamethasone dipropionate 0.05%) Lotion, as a prescription medication for the
treatment of Tinea cruris and T. corporis. This application is being submitted
in accordance with 21 CFR 314.50.

In reviewing this application, please refer to our meeting of October 26, 1988.
A copy of the meeting report is attached. At this meeting, the clinical program
for this product was discussed, and it was agreed that one clinical study in
T. cruris would be sufficient to gain approval in T. cruris and T. corporis.
The indication for T. pedis will be the subject of a subsequent submission.

We are also requesting a waiver of the requirement to submit evidence
demonstrating the in vivo bioavailability of the drug product under 21 CFR
320.22(b)(2) which exempts topically applied preparations for local therapeutic
effect.

The patent information (Item 13) for this product is attached to the application
form for your convenience.

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

We look forward to your approval.



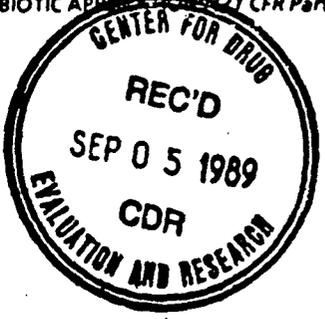
Sincerely,

Mary Jane Felty for

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

MJN:lnm
Attach.
Vol. 1.1 to 1.8

SEP 11 1989

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE <i>(Title 21, Code of Federal Regulations, 314)</i>		Form Approved: OMB No. 0910-0001 Expiration Date: August 31, 1989.	
		FOR FDA USE ONLY	
		DATE RECEIVED 5 SEP 89	DATE FILED
		DIVISION ASSIGNED 520	NDA/ANDA NO ASS 20-010
NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).			
NAME OF APPLICANT Schering Corporation		DATE OF SUBMISSION 8/31/89	
ADDRESS (Number, Street, City, State and Zip Code) 2000 Galloping Hill Road Kenilworth, NJ 07033		TELEPHONE NO. (Include Area Code) (201) 298-4000	
		NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (if previously issued)	
DRUG PRODUCT			
ESTABLISHED NAME (e.g., USPI/USAN) clotrimazole, USP 1%/ betamethasone dipropionate, USP 0.05%		PROPRIETARY NAME (if any) LOTRISONE ^R	
CODE NAME (if any) Sch 370		CHEMICAL NAME 1-[(2-chlorophenyl) diphenylmethyl]-1H-imidazole/Pregna-1,4-diene-3,20-dione,9-fluoro-11-hydroxy-16-methyl 1-17,21-bis(1-oxopropoxy)-, (11 β ,16 β)	
DOSAGE FORM Lotion	ROUTE OF ADMINISTRATION Topical	STRENGTH(S)	
PROPOSED INDICATIONS FOR USE 			
LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATION: See Attached			
			
INFORMATION ON APPLICATION			
TYPE OF APPLICATION (Check one)			
<input checked="" type="checkbox"/> THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) <input type="checkbox"/> THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)			
IF A V ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION			
NAME OF DRUG		HOLDER OF APPROVED APPLICATION	
STATUS OF APPLICATION (Check one)			
<input type="checkbox"/> PRESUBMISSION <input checked="" type="checkbox"/> ORIGINAL APPLICATION		<input type="checkbox"/> AN AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION	
<input type="checkbox"/> SUPPLEMENTAL APPLICATION			
PROPOSED MARKETING STATUS (Check one)			
<input checked="" type="checkbox"/> APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx)		<input type="checkbox"/> APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)	

CONTENTS OF APPLICATION

This application contains the following items: *(Check all that apply)*

1. Index	X
2. Summary (21 CFR 314.50 (c))	X
3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))	X
4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)	X
b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))	X
c. Labeling (21 CFR 314.50 (e) (2) (ii))	/ / / / /
i. draft labeling (4 copies)	X
ii. final printed labeling (12 copies)	
5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))	X
6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))	X
7. Microbiology section (21 CFR 314.50 (d) (4))	
8. Clinical data section (21 CFR 314.50 (d) (5))	X
9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))	
10. Statistical section (21 CFR 314.50 (d) (6))	X
11. Case report tabulations (21 CFR 314.50 (f) (1))	X
12. Case reports forms (21 CFR 314.50 (f) (1))	X
13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))	X
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. OTHER (Specify)	

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. 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.

NAME OF RESPONSIBLE OFFICIAL OR AGENT Douglass B. Civen, M.D., Ph.D. V.P., U.S. Regulatory Affairs	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Mary Gae Whyte for</i>	DATE 8/31/89
--	---	-----------------

ADDRESS (Street, City, State, Zip Code) 2000 Galloping Hill Road Kenilworth, NJ 07033	TELEPHONE NO. (Include Area Code) (201) 298-2780
---	---

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Schering

November 10, 1988

Lillian Gavrilovich, M.D., Acting Director
Division of Anti-Infective Drug Products
Food and Drug Administration
CDER - II, HFD-520
Document Control Room 12B-45
5600 Fishers Lane
Rockville, Maryland 20857

Subject: Lotrisone Lotion - IND 18,274 Serial No. 016
Elocon Lotion - NDA 19-796

Dear Dr. Gavrilovich:

This letter serves to confirm our understanding of the discussions and agreements reached at our October 26, 1988 meeting to discuss the requirements for an NDA program for LOTRISONE Lotion, and to discuss the requirement for an HPA study with ELOCON Lotion.

We hope you are in agreement with our summary of the meeting and would appreciate your comments should you disagree with our account of the meeting.

ATTENDEES

SCHERING

Ms. Bisbano
Ms. Nehring
Dr. Peets
Mr. Tkach

FDA

Dr. Carnot Evans
Mr. David Bostwick

LOTRISONE Lotion

Ms. Nehring reiterated our previous discussions with Drs. Evans and Casola which indicated that one clinical study would be required for an NDA approval. This was based on technical information showing that the formula for LOTRISONE Lotion is similar to the cream, in addition to the guinea pig dermatophyte model and McKenzie vasoconstrictor testing indicating similar results for the lotion and the cream.

The one clinical study that we chose to conduct was T. cruris. From this study we were requesting approval for all three Tinea indications (i.e., pedis, cruris and corporis).

Dr. Evans said that a T. pedis study would be required to obtain approval for this indication since it is the most difficult to treat. He noted that only one small study (number of patients to be determined by our statistician) in T. Pedis vs vehicle would be required. Therefore, we would receive an approved NDA for all three tinea indications based on the following:

- Results from the dermatophyte model showing equivalency between LOTRISONE Cream and Lotion
- Results from the McKenzie vasoconstrictor study showing equivalency between LOTRISONE Cream and Lotion
- Technical information indicating the similarity in formula between LOTRISONE Cream and Lotion
- Results from T. cruris study of LOTRISONE Lotion vs placebo
- Results from T. pedis study of LOTRISONE Lotion vs placebo

ELOCON Lotion

On August 30, 1988 we received a non-approvable letter from FDA requesting that we conduct a study to address HPA axis suppression under exaggerated conditions. A protocol was submitted on October 10, 1988 for Dr. Evans and Mr. Bostwick to review.

Mr. Bostwick indicated that they reviewed our protocol and the number of patients (4) is satisfactory. However, the study should be conducted in diseased patients in accordance with the guidelines for this type of study; 30 g (or 30 ml of lotion) should be applied per day, although two applications of 15 ml each would be acceptable.

We noted the impracticality of applying 30 ml of the lotion. Dr. Evans said that 5 ml can be applied to the diseased area on the scalp, and the remaining 10 ml applied to other areas of the body (i.e., the trunk), some of which he realized would be normal skin.

Dr. Evans explained that he is requesting that we use 30 ml since the FDA has standard requirements for the HPA test and that they do not want to depart from these requirements. However, if we felt strongly about using less than 30 ml in this study, we could, but the labeling would have to be adjusted accordingly to reflect a limit in dosing (i.e., safe usage of the drug has been studied up to X ml per week).

Lillian Gavrilovich, M.D., Acting Director
IND 18,274 NDA 19-796

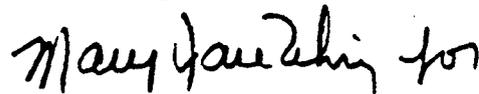
November 10, 1988
Page 3

Mr. Tkach noted that we will review their requests regarding the amount of lotion to be used in this study, and will respond to Dr. Evans shortly.

POST-MEETING NOTE: We will use 30 ml of lotion for this study
(15 ml twice a day).

Mr. Bostwick then confirmed that they would expedite their review of the HPA study once it was submitted, and we could receive approval based on draft labeling when it is agreed upon.

Sincerely,



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

MJN:lnm

APPEARS THIS WAY
ON ORIGINAL

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: December 6, 2000 Number of Pages (including cover sheet) – 1

TO: Elin Krhoun, Manager, Regulatory Affairs
COMPANY: Schering-Plough Corporation
FAX #: 908-740-6500

MESSAGE: Please commit to the following Post-Marketing Commitment for NDA
20-010, LOTRISONE[®] (clotrimazole and betamethasone dipropionate)
Cream and Lotion.

Evaluate the efficacy of Schering's educational campaign by monitoring the pediatric use of Lotrisone Lotion and Lotrisone Cream in age 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 performed annually. A baseline evaluation, i.e., before the labeling change (e.g., 1999 or 2000) should be submitted within three months of approval."

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: December 6, 2000 Number of Pages (including cover sheet) - 18

TO: Elin Krohn, Manager, Regulatory Affairs
COMPANY: Schering-Plough Corporation
FAX #: 908-740-6500

MESSAGE: For your review/concurrence please find attached to this facsimile transmission, draft labeling for NDA 20-010, LOTRISONE® (clotrimazole and betamethasone dipropionate) Cream and Lotion. To facilitate your review, please note the following:

1. Under the **ADVERSE REACTIONS** Section, page 8, numbers of patients experiencing parasthesia and rash, edema, and secondary infection have been replaced by percentages.
2. Under the **DOSAGE AND ADMINISTRATION** Section, page 9, dosing information for LOTRISONE Cream has been included.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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(y)

Number of Pages
Redacted 18



Draft Labeling
(not releasable)

**Division of Dermatologic and Dental Drug Products**

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: November 24, 2000. Number of Pages (including cover sheet) - 2
TO: Elin Krhoun/Michael Belman, Regulatory Affairs
COMPANY: Schering Plough Corp.
FAX#: 908-740-6500

MESSAGE: NDA 20-010, Lotrisone Lotion

Please note that we have not received your acceptance of the following commitment, requested in our telecon of 10/3/2000 (see our 10/12 fax to you):

- "b. To monitor the particle size of the product, and report the results to the Agency as they become available.
- c. To add the homogeneity test (00370-211B-003-02.01) to the proposed marketing stability program for all future stability batches tested....

The first three post-approval batches will be placed on stability and the results will be submitted to the agency for information. If the results of particle size or homogeneity testing indicate a problem, then the Applicant will submit a Prior Approval Supplement to revise the specifications."

For clarification, please note that this standard post-marketing stability commitment is not considered to fall within the Agency's definition of a "Phase 4" commitment for tracking purposes, and should not have been referred to as a Phase 4 commitment.

Furthermore, we wish to restate the following from our memorandum of the 10/3 telecon:

"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."

Note that storage under the ICH intermediate and accelerated conditions is considered to be outside the labeled storage conditions.

IN 0-3

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: November ^{22 06}~~21~~, 2000 Number of Pages (including cover sheet) - ^{17 06}~~21~~

TO: Mike Belman, Regulatory Fellow, Regulatory Affairs
COMPANY: Schering-Plough Corporation
FAX #: 908-740-6500

MESSAGE: For your review/concurrence please find attached to this facsimile transmission, draft labeling for NDA 20-010, LOTRISONE® (clotrimazole, USP and betamethasone dipropionate, USP) Cream and Lotion.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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Number of Pages
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Draft Labeling
(not releasable)



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Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: November 22, 2000. Number of Pages (including cover sheet) - 1
TO: Elin Krhoun,/Michael Belman, Regulatory Affairs
COMPANY: Schering Plough Corp.
FAX #: 908-740-6500

MESSAGE: Please commit to the following Phase 4 commitment for NDA 20-010, Lotrisone Lotion

Clinical:

Evaluate the efficacy of Schering's educational campaign by monitoring the pediatric use of Lotrisone Lotion and Lotrisone Cream in the treatment of pediatric patients in age groups: 0-1, 1-2, 2-4, 4-8, and 8-12 years, and also for the treatment of patients with diaper dermatitis, using the IMS Health databases: National Prescription Audit (NPA) and National Disease and Therapeutic Index (NDTI), and one additional prescription use database. Such evaluations 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.

FROM: Olga Cintron, R.Ph. for CDR Frank Cross
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

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Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
2921 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: November 9, 2000 Number of Pages (including cover sheet) - 1

TO: Elin Krhoun, Manager, Regulatory Affairs
COMPANY: Schering-Plough Corporation
FAX #: 908-740-6500

MESSAGE: Please find attached to this facsimile transmission, a labeling revision comment from our review of your submission dated October 13, 2000, to NDA 20-010, LOTRISONE® (betamethasone dipropionate, USP and clotrimazole, USP) Cream and Lotion:

With reference to your October 13, 2000, submission and item 2a of our October 30, 2000, facsimile transmission, please be advised that your request to delete "Brand of" before "clotrimazole and betamethasone dipropionate" and to add parentheses to "clotrimazole and betamethasone dipropionate" for your proposed labeling for this NDA is acceptable.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: October 12, 2000 Number of Pages (including cover sheet) - 4

TO: Elin Krhoun, Manager, Regulatory Affairs

COMPANY: Schering-Plough Corporation

FAX #: 908-740-6500

MESSAGE: Please find attached to this facsimile transmission, minutes of our teleconference of October 3, 2000, for NDA 20-010, LOTRISONE® (betamethasone dipropionate, USP and clotrimazole, USP) Lotion:

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR

TITLE: Senior Regulatory Management Officer

PHONE #: 301-827-2063

FAX #: 301-827-2075/2091

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**APPEARS THIS WAY
ON ORIGINAL**

Meeting Date: October 3, 2000

Time: 1125

Location: N229

CMC Discussion of NDA 20-010, LOTRISONE® (betamethasone dipropionate, USP and clotrimazole, USP) Cream and Lotion:

Applicant: Schering-Plough Research Institute

Meeting Chair: Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII

Meeting Recorder (Project Manager): Frank Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-540

Saleh Turujman, Ph.D., Chemistry Reviewer, DNDCIII, HFD-540

Frank Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

Schering-Plough Research Institute

Joel Sequeira, Ph.D., Senior Associate Director, Pharmaceutical Research and Development

Donald Chambers, Ph.D., Director, Analytical Development

Edward A. Mularz, Ph.D., Principal Scientist

Elin Krhoun, M.S., Regulatory Affairs Manager

Elaine Potomski, Regulatory Affairs Manager

Applicant:

The Applicant clarified the following items from the September 28, 2000, Teleconference:

1. Issue # 13: "Regarding the Applicant's proposal Stability Protocol..."

Agency:

The Applicant was informed that

2. Issue # 12: "The Applicant will be asked to commit to the following Phase 4 Commitments in the near future:
 - b. To monitor the particle size of the product, and report the results to the Agency as they become available.
 - c. To add the homogeneity test (00370-211B-003-02.01) to the proposed marketing stability testing program for all future stability batches tested, including the Phase 4 commitment tests."

The first 3 post-approval batches will be placed on stability and the results will be submitted to the Agency for information. If the results of the particle size or homogeneity testing indicate a problem then the Applicant will submit a Prior Approval Supplement to revise the specifications.

3. Request # 3. "Remove the decimal point and terminal zero from the expression of the quantity of the active ingredient, clotrimazole, in all labeling, i.e., 10 mg instead of 10.0 mg, as per USP 24, General Notices page 11 (under 'labeling')."

Applicant:

The Applicant asked if this request still applies since quantities of the active ingredients will now be expressed in terms of volumetric measurements, per the September 28, 2000, teleconference.

Agency:

The Agency concurred.

4. Regarding Request # 6 from the September 28, 2000, Minutes of Teleconference – "Ascertain that the established names must be at least half the size of the trade name (all labels and principal display panel of cartons)."

The Applicant desires clarification of font size with respect to combination products and in particular to 21CFR 201.10(h).

Agency:

The Agency advised the Applicant that the requirement for the established name to be at least half as large as the proprietary name, and to have equal prominence, is described in 21CFR 201.10(g)(2).

5. Regarding Request # 8 - "Ascertain that the wording in the 'Use' statement on the cartons and the labels matches the wording in the patient insert." - from the September 28, 2000, Minutes of Teleconference and Issue #10 - "The description may also need to be revised to include the cream."

Applicant:

The Applicant cited a problem with implementing these recommendations due to labeling space constraints on the 10-mL bottle label.

Agency:

The Agency advised the Applicant that if they are unable to get a legible font on the 10-mL bottle label then a waiver can be requested in accordance with 21CFR 201.15. Regarding NDA 18-827, Lotrisone Cream, the Agency also advised the Applicant that a Request for Labeling Supplement will be issued at the same time the Action Letter is issued for NDA 20-010.

6. Regarding Issue # 12 - "The Applicant will be asked to commit to the following Phase 4 Commitments in the near future:

a. _____

Agency:

The Agency advised the Applicant _____ If the Applicant
desires expiration dating of 24 months _____ the Applicant may develop a testing program and
submit the results for our review.

The Applicant was also advised that out of specification results at 12 months at the intermediate
and accelerated stability testing ranges are not usually cited as reasons for withdrawal of the drug
from the market.

The teleconference ended amicably.

Signature, minutes preparer: _____

JSI

Concurrence Chair (or designated signatory): _____

JSI
10/15/00

**APPEARS THIS WAY
ON ORIGINAL**

cc:

NDA 20-010

NDA 18-827

HFD-540/DIV DIR/Wilkin

HFD-540/CHEM TL/DeCamp

HD-540/CHEM/Turujman SAT 10/11/00

HFD-540/DERM TL/Okun

HFD-540/MO/Luke

HFD-540/PM/Cross

Drafted by: fnc/October 4, 2000

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Initialed by:

final:

MEMORANDUM OF TELECONFERENCE

**APPEARS THIS WAY
ON ORIGINAL**



Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: October 2, 2000 Number of Pages (including cover sheet) **4**
TO: Elin Krhoun, Manager, Regulatory Affairs
COMPANY: Schering-Plough Corporation
FAX #: 908-740-6500

MESSAGE: Please find attached to this facsimile transmission, minutes of our teleconference of September 28, 2000 for NDA 20-010, LOTRISONE® (betamethasone dipropionate, USP and clotrimazole, USP) Lotion:

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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**APPEARS THIS WAY
ON ORIGINAL**

Meeting Date: September 28, 2000

Time: 1545

Location: N225

CMC Discussion of NDA 20-010, LOTRISONE® (betamethasone dipropionate, USP and clotrimazole, USP) Cream and Lotion:

Applicant: Schering-Plough Research Institute

Meeting Chair: Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII

Meeting Recorder (Project Manager): Frank Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-540

Saleh Turujman, Ph.D., Chemistry Reviewer, DNDCIII, HFD-540

Frank Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

Schering-Plough Research Institute

Joel Sequeira, Ph.D., Senior Associate Director, Pharmaceutical Research and Development

Donald Chambers, Ph.D., Director, Analytical Development

Edward A. Mularz, Ph.D., Principal Scientist

Elin Khoun, M.S., Regulatory Affairs Manager

Elaine Potomski, Regulatory Affairs Manager

Agency:

The Agency reiterated items 1 through 10 faxed to the Applicant earlier today:

1. "Delete [REDACTED] from all components on the patient insert and all labels.
2. "Remove caps from chemical names that do not appear at the beginning of a sentence (e.g., 'chloro-', not 'Chloro-'). Chemical names take caps only at the beginning of a sentence."
3. "Delete [REDACTED] wherever it appears."
4. [REDACTED]
5. [REDACTED]
6. "Ascertain that the established names must be at least half the size of the trade name (all labels and principal display panel of cartons)."
7. "The Patient Insert instructs the user to 'store upright' in 'How Supplied'; the term 'upright' should be added to the bottle label and to the carton."

8. "Ascertain that the wording in the 'Use' statement on the cartons and the labels matches the wording in the patient insert."
9. "Remove the decimal point and terminal zero from the expression of the quantity of the active ingredient, clotrimazole, in all labeling, i.e., 10 mg instead of 10.0 mg, as per USP 24, General Notices page 11 (under 'labeling')."
10. "The description may also need to be revised to include the cream."

Agency:

The Agency also gave the following recommendations:

Regarding item 10 above, the labeling for the Lotrisone Cream product should be revised to include: 'FOR TOPICAL USE ONLY, NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE, NOT RECOMMENDED FOR PATIENTS UNDER THE AGE OF 12 YEARS AND NOT RECOMMENDED FOR DIAPER DERMATITIS.' This change may be forwarded to the Applicant via a Request for Labeling Supplement in the near future.

11. The Applicant's proposed expiration date of 24 months with an excursion to 30°C is acceptable with the following Phase 4 commitments, which the Applicant has acknowledged (amendment dated July 21, 2000 and the submission dated October 7, 1999):

a.

12.

a.

b.

c.

13. The Applicant's proposal [redacted] in their Stability Protocol for Lotrisone Lotion is unacceptable. Therefore, the sampling methodology should not [redacted] prior to placing the samples on stability. The Applicant is advised to establish a temporary protocol in which 12 bottles are sampled through the tip and 12 bottles are sampled with the tips removed and compare the stability results obtained from both sets of bottles. The data obtained from this study should be presented to the Agency for its review and concurrence prior to implementation of a replacement Stability Protocol.
14. The Applicant's proposal to [redacted] in its Stability Protocol is unacceptable at this time. At the appropriate time, the Applicant may submit a request to change the sample size.

Applicant:

The Applicant asked if the Agency would allow volume units only rather than volume and weight units, in the labeling.

Agency:

The Agency concurred with the Applicant's request.

Action Items:

The Applicant expressed its desire for additional discussion of the following issues during the October 2, 2000, teleconference:

6. The Applicant desires clarification of font size with respect to combination products.
- 8/10. The Applicant cited a problem with implementing these recommendations due to labeling space constraints on the 10-mL bottle label.
12. The Agency will rediscuss: "The Applicant will be asked to commit to the following Phase 4 Commitments in the near future:
[redacted]
13. The Applicant needs guidance as to the appropriate regulatory route of submission of the data collected from the study proposed above.
14. The Applicant requested additional discussion and guidance for [redacted]

The teleconference ended amicably.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

NDA 20-010, LOTRISONE® (betamethasone dipropionate, USP
and clotrimazole, USP) Cream and Lotion
CMC Discussion
Page 4

cc:

NDA 20-010

NDA 18-827

HFD-540/DIV DIR/Wilkin

HFD-540/CHEM TL/DeCamp

HD-540/CHEM/Turujman

HFD-540/DERM TL/Okun

HFD-540/MO/Luke

HFD-540/PM/Cross

Drafted by: fhc/September 29, 2000

c:\word\lotrisone\nda20010\nda20010tcon.doc

Initialed by:

final:

MEMORANDUM OF TELECONFERENCE

**APPEARS THIS WAY
ON ORIGINAL**



Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: March 14, 2000 Number of Pages (including cover sheet) - 3

TO: Ellen Krone, Manager, Regulatory Affairs

COMPANY: Schering-Plough Corporation

FAX #: 908-740-6500

MESSAGE: Additional information needs from the Chemistry Reviewer concerning
NDA 20-010 follow:

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.
2. 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" number is not adequate without specifying what constitutes a "sufficient" number).
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.
4. We have received the three month stability data for only one of the three batches placed on stability. Please provide the three month stability data for the remaining two batches.
5. With reference to our March 9, 2000, teleconference:
 - a. Please provide the formulation disclosure statement for the dispenser tips.

b. An example of the type of information that should be included in the packaging portion of an NDA submission is as follows:

i. DESCRIPTION

◆ General Description:

◆ Closure Components:

➤ Plastic Closure/Cap:

- Name:
- Product Code:
- Manufacturer:
- Physical Description:
- Materials of Construction:
- Description of Additional Treatments:

➤ Liners:

- Name:
- Product Code:
- Manufacturer:
- Physical Description:
- Materials of Construction:
- Description of Additional Treatments:

➤ Colorant:

- Name:
- Product Code:
- Manufacturer:
- Physical Description:
- Materials of Construction:
- Description of Additional Treatments:

ii. SUITABILITY

◆ Protection Studies:

- Moisture Vapor Transmission per USP23/NF18 <671>.
- Weight Loss/Water Vapor Permeation per USP23/NF8 <661>*

- Safety:
- Compatibility:
- Performance:
 - Removal Torque:
 - Closure Dimensions:
 - Physical Properties Comparison :

iii. QUALITY CONTROL

- ◆ Applicant's Acceptance Specifications
- ◆ Acceptance Testing for Finished Closure:
- ◆ Quality Control Testing Finished Closure:

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

cc: Aichin (I/h)
Div F.1E
Turnjmer
DeComp
Cross
Wilk.

FACSIMILE TRANSMISSION

DATE: March 3, 2000 Number of Pages (including cover sheet) - 2

TO: Ellen Krone, Manager, Regulatory Affairs

COMPANY: Schering-Plough Corporation

FAX #: 908-740-6500

MESSAGE: Information Needs from the Chemistry Reviewer concerning NDA 20-010 follow:

1. Please provide the three month stability data for the other two manufactured batches (stability data for only one of the three manufactured batches was provided in the submission), as well as the 6-month and 9-month stability data for all three batches, previously requested on February 11, 2000.
2. Formulation:
 - a. Please confirm that the three batches manufactured and tested are identical to those used in the pivotal clinical studies
 - b. Please reconfirm that "overage" of betamethasone dipropionate is no longer being used in the formulation of Lotrisone Lotion.
3. Specifications:
 - a. **Clotrimazole Degradation Products:** [REDACTED]

The sponsor does not provide a specification for [REDACTED] which is a potential impurity in clotrimazole (see NDA 18-813 NC, dated 3/10/99). The sponsor has identified Lotrimin Lotion (NDA 18-813) as the repository for Clotrimazole in NDA 20-010. The sponsor is requested to answer how much [REDACTED] has been historically found in clotrimazole.

b. Packaging:

The sponsor refers to _____

_____). The
Letter of authorization for FDA is access dated June 24, 1999.
However, this is a Type I DMF. The sponsor is requested to provide
the appropriate Type III DMF citation.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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