

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-010

MEDICAL REVIEW(S)

BEST POSSIBLE COPY

Date Review Begun: September 10, 1990

Date Review Completed: September 12, 1990

Clinical Review of Amendment to NDA 20-010

Sponsor: Schering-Plough Research
Kenilworth, N.J. 07033

Drug: Lotrisone (clotrimazole 1% and betamethasone dipropionate 0.05%) Lotion.

Category: This is a combination product containing an antifungal and a topical corticosteroid which is intended for use in tinea pedis, tinea cruris, and tinea corporis due to Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, and _____ it is to be used twice daily.

Date of Submission: The original application was dated August 31, 1989. The amendment reviewed here is dated July 20, 1990.

Background: In the original review of this NDA dated June 20, 1990, Mr. Bostwick and Dr. Evans recommended that the application not be approved because more specific information concerning the vasoconstrictor assay was required. The NDA was subsequently made "not approvable" on June 29, 1990. It was also noted that the chemistry review was not yet complete.

Chemistry Review: This is not yet available. Presumably Dr. DeCamp will reassign this NDA, since he was the original reviewer of it.

Material Reviewed: The following information has been submitted concerning the vasoconstrictor assay:

Investigator: Elyane Lombardy, M.D.
Schering Corporation
Kenilworth, N.J. 07033

Dr. Lombardy is well-qualified to conduct vasoconstrictor assays.

Method: This was a study in 24 healthy subjects. The reference products were Lotrisone Cream and Diprosone Ointment (betamethasone dipropionate, 0.05%). Three test lotion products were examined. One of the three is the Lotrisone Lotion product proposed for marketing which contains _____ propylene glycol. The other two test lotion formulations contained _____ propylene glycol. 10 mg. of each formulation was applied to test sites 2 cm in diameter on the volar forearm in a random fashion. Each test lotion formulation was tested twice in each subject and each reference formulation was tested once, for a total of eight readings for each subject.

The test sites were covered with non-occlusive plastic shields for 6 1/2 hours. The shields were removed, the test sites washed with soap and water, and vasoconstriction estimated one-half hour later (7 hours after drug application). The sites were evaluated a second time 24 hours after drug application.

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NDA 20-010

- 2 -

The degree of blanching was graded as follows:

- 0 = No blanching
- 1 = Mild blanching
- 2 = Moderate blanching
- 3 = Strong blanching

Readings at 0.5 intervals were also allowed.

Results: There are twice as many readings for the test lotion products as for the reference products.

H. Seven-hour readings

Drug	Number of Patients per Blanching Score							Mean
	0	0.5	1	1.5	2	2.5	3	
Lotrisone Cream	3	5	9	2	4	1	0	1.04
Diprosone Ointment	2	0	3	1	10	5	3	1.92
Lotion with 10% PG	16	7	13	0	12	0	0	0.84
Lotion with 15% PG	16	7	9	4	10	2	0	0.91
Lotion with 20% PG	12	6	15	3	9	3	0	1.00

Handwritten notes: "24", "48", "48", "48"

B. Twenty-four hour readings

Drug	Number of Patients per Blanching Score					Mean
	0	0.5	1	1.5	2	
Lotrisone Cream	17	3	4	0	0	0.23
Diprosone Ointment	13	10	1	0	0	0.25
Lotion with 10% PG	32	14	2	0	0	0.19
Lotion with 15% PG	29	13	5	1	0	0.27
Lotion with 20% PG	30	12	2	3	1	0.30

Handwritten notes: "24", "48", "48", "48"

These data are interesting for a number of reasons. Although all the products tested contained the same amount of betamethasone dipropionate, the "plain" Diprosone product, which contains no propylene glycol, performed much better in terms of vasoconstrictor ability than did the other products. In addition, it is not clear why Lotrisone Cream performed better than the Lotion product which contains 10% propylene glycol, since their formulations are virtually identical. The Lotion product with 20% propylene glycol is more comparable to the Cream product in terms of vasoconstriction effect.

Comment: These data fail to establish that the Cream and Lotion products are bioequivalent. It may be that the propylene glycol impedes the vasoconstriction effect of the steroid. Other vasoconstriction studies which have been reviewed concerning the Diprosone products, all of which contain propylene glycol, suggest that this may be the case. This does not explain, however, why the Cream and 10% Lotion Products are 20% different in vasoconstriction effect at both time frames.

It is felt that this study was competently performed, so it is unlikely that a repeat will produce markedly different results. The sponsor should be given a chance to explain the inconsistencies seen in the data, or they may wish to perform another clinical study to serve as the corroborative study for this NDA.

Labeling Review: Final labeling comments will be made when this NDA is complete in other respects. Reference is made to the concurrent review of NDA 18-827/S-007 for Lotrisone Cream, which will be applicable to this NDA if a decision is made to approve it.

Summary and Evaluation: The vasoconstrictor study submitted in support of this application is not satisfactory. The sponsor may address the deficiencies present in one of two ways:

1. An explanation in the vasoconstrictor data may be offered. If this is done, the following specific questions should be addressed:
 - A. Why does the Diprosone Ointment product perform so much better than the other formulations at the seven-hour time interval?
 - B. Why does the Lotion product with 10% propylene glycol perform only 80% as well as the Cream product at both time intervals, even though the formulations are so similar?
2. Another clinical study in tinea pedis or tinea cruris may be performed. If this is done, the protocol should consider the effect of the steroid in the formulation. That is, there should be three test arms in the study: the combination, the steroid alone and the anti-fungal alone.

IS/

 David C. Eastwick

IS/

 Wiley Chambers, M.D.

- cc: Orig NDA
- HFD-340
- HFD-520
- HFD-520/CCEvans
- HFD-520/CHEM/WHDeCamp
- HFD-520/PHARM/KMainigi
- HFD-520/CSU/RLOOK
- HFD-520/WAChambers
- HFD-520/DCEastwick/llm/9/18/90
- N18827.S007

IS/
 10/09/90

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Date of Review: April 22, 1991

Clinical Review of Amendment to NDA 20-010

Sponsor: Schering-Plough Research
Kenilworth, N.J. 07033

Drug: Lotrisone (clotrimazole 1% and betamethasone dipropionate 0.05%) Lotion.

Category: This is a combination product containing an antifungal and a topical corticosteroid which is intended for use in

Date of Submission: The original application was dated August 31, 1989. The amendment reviewed here is dated March 19, 1991.

Background: This NDA has been made "not approvable" twice (the last time on December 31, 1990), because of deficiencies in the vasoconstrictor assay submitted in support of the application. The March 19, 1991 amendment addresses these deficiencies. The NDA is otherwise approvable (pharmacology, chemistry) with the exception of the Establishment Inspection Reports.

Material Reviewed: In the not approvable letter of December 31, 1990, the sponsor was asked to comment on the following:

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, 10% 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.

Concerning the first item, the sponsor's explanation is that since the Diprosone product is an ointment, and ointments are in general more occlusive than other topical dosage forms, it would be expected to cause more vasoconstriction than a cream or lotion. However, since the Lotrisone Cream and Lotion products both contain propylene glycol, a skin penetrant, it is logical that they would be more potent than Diprosone Ointment, which contains only petrolatum and mineral oil. In fact, the Lotrisone products appear to be much more potent in practice than Diprosone Ointment, and so would be expected to react better in the vasoconstrictor assay.

A complicating factor is that the Lotrisone products also contain an antifungal, making a "pure" comparison between the products impossible. It may be that the antifungal in some way compromises the performance of the steroid in the vasoconstrictor assay. Given this circumstance, we are not inclined to push this issue further. It should be noted that vasoconstrictor assays are probably not suitable for establishing the bioequivalence of topical antifungal/steroid combinations.

Concerning the second item, the sponsor maintains that a difference in skin blanching which averages 0.5 on a scale of 0-3 is not significant because of evaluator error. They also note that there are no statistically significant differences between Lotrisone Cream and Lotrisone Lotion.

While the products may not be different statistically, it is disturbing that two products which have such similar formulations (see the Background section of the original M.O.R. for details) could have such different results in the vasoconstrictor assay. Once again, the explanation offered by the sponsor is not entirely satisfactory, but it does not seem to be a sufficiently important point to pursue further. This is principally because the clinical study submitted which compares the active product to the vehicle establishes the effectiveness of the product.

The sponsor should be informed that vasoconstrictor assays will not be accepted as proof of bioequivalence for products which contain a steroid in combination with another ingredient.

Labeling Review: A review of NDA 18-827/S-007 and S-009 for Lotrisone Cream has been completed. A copy of the label in that review has been attached. It should be used as a basis for labeling Lotrisone Lotion.

(A)

**Number of Pages
Redacted** 6



Draft Labeling
(not releasable)

NDA 20-010

Date of Review: October 4, 1991

Clinical Review of Amendment to NDA 20-010

Sponsor: Schering-Plough Research
Kenilworth, N.J. 07033

Drug: Lotrisone (clotrimazole 1% and betamethasone dipropionate 0.05%) Lotion.

Category: This is a combination product containing an antifungal and a topical corticosteroid which is intended for _____

_____ It is to be used twice daily.

Date of Submission: The original application was dated August 31, 1989. The amendment reviewed here is dated September 16, 1991.

Background: This NDA was made "approvable" on July 31, 1991. The approvable letter requested submission of FPL which conformed to the label which had been suggested by FDA for Lotrisone Cream (NDA 18-827). See also the previous reviews of this NDA dated June 20, 1990, September 10, 1990 and April 22, 1991. The approvable letter also requested safety update reports and advertising copy.

Material Reviewed:

A. Labeling. The sponsor has taken exception to some portions of the draft labeling which was included with the approvable letter. These items will be discussed individually below. It may be assumed that the sponsor has agreed to comply with any labeling recommendations which are not specifically discussed below.

- ii. The sponsor disagrees with the FDA suggestion in the last paragraph of this section that betamethasone dipropionate when formulated with propylene glycol is a high to super-high potency steroid. They have presented side-by-side formulations for Diprosone Cream (NDA 17-536) and Lotrisone Cream which establish that the products are quite similar, basically differing only by the addition of 1% clotrimazole and benzyl alcohol to the Lotrisone product.

The most striking thing about this comparison is the fact that Diprosone Cream contains propylene glycol. When FDA made the decision to grant the "augmented betamethasone dipropionate" generic name to the Diprosone products to differentiate them from the Diprosone products, it was assumed that the addition of propylene glycol (a skin penetrant) was the key ingredient which caused the potentiation of betamethasone dipropionate.

Some research into the Diprosone formulations seems relevant. The following points should be made:

- a. Apparently the cream is the only Diprosone product which contains propylene glycol.
- b. The Diprosone Cream package insert claims that the propylene glycol is present as a preservative only. The Diprosone package inserts do not make any mention of a preservative property for propylene glycol.
- c. When Diprosone Cream was originally approved in 1975, it did not contain propylene glycol. The original package insert noted that the preservative in the product was chlorocresol.

In 1980, a supplement was submitted which added propylene glycol to the formulation and claimed it as a preservative. No clinical review of this supplement was done, and no clinical data (adrenal suppression, etc) was submitted to support it. The supplement was approved in October, 1981.

The sponsor states that the actual difference between the Diprosone and Diprolene products is that the inactive ingredients in the Diprolene products cause the active ingredient to be in solution in the formulation, while in the Diprosone products the active ingredient is in suspension. This difference in formulation quality then causes potency distinctions.

This is an interesting theory, but is unproven. A review of the ingredients in the Diprosone and Diprolene products does not suggest an obvious pattern of substitution, except for propylene glycol. Further, no adrenal suppression studies have ever been performed, to the knowledge of the reviewers, with Diprosone Cream. In the absence of such information, the most relevant data available is for Diprolene Cream which contains propylene glycol and has been shown by adrenal suppression and clinical studies to be a high to super-high potency steroid.

Further, the sponsor's proposed statement concerning the relative potency of Lotrisone Cream leans heavily on results of vasoconstrictor studies which suggest that Diprosone Cream and Lotrisone Cream are similar in vasoconstrictor activity. As noted in the clinical review for this NDA, and in the approvable letter, vasoconstrictor studies will no longer be accepted as the only proof of the relative potency of products containing both an antifungal and a corticosteroid.

The vasoconstrictor data submitted in support of Lotrisone Lotion are useful as an indication that the activity of the steroid is not greatly different in the Lotion formulation than in the Cream formulation.

In summary, the following items are relevant:

- The sponsor's contention that the active ingredient is in solution in Diprolene and in suspension in Diprosone is unproven. Information should be submitted which establishes this fact, as well as the relevancy of this information to the relative clinical potency of the Diprosone and Diprolene products.

- Until such information is available, the most relevant data available suggests that betamethasone dipropionate, when formulated with propylene glycol, is a high to super-high potency steroid.

- A rationale should be presented for claiming propylene glycol as a preservative in the Diprosone product but not in the Diprolene products.

- Vasoconstrictor studies will not be accepted as a basis for evaluating the clinical potency of combination topical steroid/antifungal products.

- The possibility must be considered that Diprosone Cream is not a mid-potency steroid as claimed by the sponsor, but is in fact a high or super-high potency steroid. An adrenal suppression study using the present Diprosone Cream formulation would answer this question.

2. In the INDICATIONS AND USAGE section:

i. The sponsor has added _____ to the list of indicated organisms. This organism is approved in the Lotrisone Cream label, but may not be _____

**Number of Pages
Redacted** 11



Draft Labeling
(not releasable)

B

In addition, the following recommendations are pertinent:

1. A copy of this review should be sent to Mr. William Purvis of Drug Advertising in reference to the comments above under "C. Advertising."
2. When this label has been finally approved, the revisions as they relate to this product and Lotrisone Cream should be publicized through the FDA Medical Letter.

 /S/
David C. Bostwick

 /S/
Susan Alpert, M.D.

1/30/92

Orig. NDA
HFD-520
HFD-520/MO/Alpert
~~HFD-520/CSO/Cook~~
HFD-520/Chem/Katague
HFD-520/Pharm/Mainigi
HFD-240/W Purvis
HFD-520/Bostwick/PWise
NDA20010

Rev'd 1/31/92
2/2/92

/S/

**APPEARS THIS WAY
ON ORIGINAL**

Medical Officer Review of 20-010 NC
New Correspondence

NDA 20-010
Serial Number: NC
HFD540 #: 992414

Correspondence date: January 5, 1999
CDER Stamp date: January 6, 1999
Review date: March 26, 1999

Drug: Lotrisone (Clotrimazole and Betamethasone Dipropionate) Lotion
Sponsor: Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

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

Pharmacological Category: Topical Steroid/Anti-Fungal

Background

In a related NDA, 18-827, Lotrisone Cream, a combination drug product with clotrimazole and betamethasone dipropionate was approved on July 10, 1984 and is indicated for the topical treatment of the following dermal infections: tinea pedis, tinea cruris, and tinea corporis due to *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, and *Microsporum canis*.

The Applicant makes reference in its current correspondence to an NDA originally submitted on August 31, 1989 and FDA's Approvable letter dated July 31, 1991. It appears from the correspondence that various issues regarding CMC needed to be addressed and will be addressed in future correspondence. The last correspondence from the Applicant was dated 12/94, an interim of about 4 years.

Regulatory Intent

The Applicant wishes to further pursue its Approvable status and address unresolved issues in order to garner an Approved NDA. A telephone conference was held on February 24, 1999 to discuss with the Applicant current issues of concern (Please refer to Mr. Frank Cross' meeting minutes). These concerns included CMC issues, Pediatric Rule issues, and issues regarding the labeling.

A Post-Marketing Safety Evaluation of Lotrisone Cream was pending at the time. The Evaluation on Lotrisone Adverse Events, dated March 9, 1999 evaluated reports on adverse events from 1992 to 1997, as well as an evaluation of pediatric use (see consult from the Division of Postmarketing Drug Risk Assessment I, HFD-736).

Chemistry

Please see Chemistry's review.

Pharmacology/Toxicology

Please refer to Pharm/Tox review.

Clinical

Considering the relatively significant clinical use of Lotrisone Cream in children below the age of 12 (roughly 20% of prescriptions written, see Table below), the Medical Reviewer would like to propose additional studies to support the use of this Lotrisone Lotion in that age group.

Table: Lotrisone Total Number of Drug Appearances by Age and Year*

Lotrisone Total Number of Drug Appearances by Age and Year (numbers in thousands)								
	Total	% from Total	1992	1993	1994	1995	1996	1997
Lotrisone (All)	9101	100	1673	1518	1585	1530	1498	1296
000-001 years	651	7.2	134	137	125	123	92	40
002-006 years	620	6.8	99	100	122	105	128	67
007-012 years	562	6.2	106	85	81	91	98	101
013-018 years	645	7.1	101	105	110	121	120	88
019+ years	6205	68.2	1202	1015	1053	996	990	949
Unspecified	417	4.6	31	76	95	95	70	51

* National Disease and Therapeutic Index, IMS HEALTH

Via the Adverse Event Reporting System (AERS) we have learned that about 17 percent (53 out of 315) of adverse events are reported for the pediatric age group. About 50% of those adverse events result from use of the product beyond the recommended treatment period of 2 weeks. Of great significance are reports via AERS that the drug is ineffective or the condition was aggravated (174 out of 761 cases = 22.9%). Also significant were 48 out of 761 cases (or 6.3%) that reported atrophy of the skin, atrophy nos, or skin striae. Even though these side effects are non-serious, they do raise concern as there are products on the market to treat cutaneous fungal infections (the only labeled uses of Lotrisone are for tinea) without these side effects.

Additionally, a significant number of prescriptions are being written for diaper dermatitis – an off-label indication. The label under pediatric use specifically states the following: “The use of LOTRISONE Cream in diaper dermatitis is not recommended.” Lotrisone has been prescribed for diaper dermatitis at a high rate despite this warning (at least _____ prescriptions between 1992 and 1997).

IS
Markham C. Luke, MD PhD
Medical Officer/Dermatology

- cc: HFD-540
- HFD-540/CSO/ Cross
- HFD-540/Chemist/Decamp
- HFD-540/PharmTox/Brown
- HFD-540/Biostats TL/Srinivisan
- HFD-540/Biopharm/Bashaw
- HFD-540/Dermatology TL/Walker
- HFD-540/DivDir/ Wilkin
- NDA 18-827
- NDA 20-010

*Labeling to be determined
at Division level. Should
be consistent with current thinking
on corticosteroid labels.
sw 4/9/99*

IS - 4/16/99

**APPEARS THIS WAY
ON ORIGINAL**

Medical Officer's Review of NDA 20-010 BC
NDA Supplement Amendment

JUL 11 2000

NDA 20-010
Serial # BC
HFD-540 # 005421

Correspondence Date: March 13, 2000
CDER Stamp Date: March 15, 2000
Review Date: March 30, 2000

Drug: LOTRISONE (betamethasone dipropionate and clotrimazole) LOTION

Sponsor: Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07053

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

Pharmacologic Category: Topical Combination Anti-Fungal/Corticosteroid

Regulatory Intent:

The Applicant provides this correspondence regarding chemistry issues for its resubmission to an Approvable NDA (new manufacturing site). The Applicant appears to have made a determination that it had a specification failure [REDACTED] for an inverted 30 mL bottle of (Batch 75242-063-A) at the six month 30°C/60% RH condition. The Applicant proposes [REDACTED]

Background:

Please see review of NDA 20-010 AZ dated January 28, 2000 for Background information regarding this NDA. Also see review of NDA 20-010 NC dated March 16, 2000. Please refer to Chemistry reviews of NDA 20-010 regarding stability issues for this drug product.

Regulatory Recommendation (may be conveyed to Applicant)

- 1) The Applicant should consider reformulating its product to allow greater stability rather than propose a change in labeling which would inconvenience the patient.
- 2) The Dosage and Administration section of the label should not be used to circumvent failed stability testing of a given batch of drug product.

15/1

Markham C. Luke, M.D., Ph.D.
Medical Officer, Dermatology

cc: HFD-540
 HFD-540/PM/Cross
 HFD-540/ChemistryTL/DeCamp
 HFD-540/Pharm/Brown
 HFD-880/Biopharm/Bashaw
 HFD-540/MO/Luke
 HFD-540/Clinical TL/Okun
 HFD-540/DIVDIR/Wilkin
 NDA 20-010
 NDA 18-827
 IND 18,274

Team Leader Addendum

Submitted to DF 3/30/2000

15/1

15/1

7/07

Medical Officer's Review of NDA 20-010 AZ and SU SEP 13 2000
Original Amendment (Response to AE Letter) and Safety Update

NDA 20-010

Serial # (AZ) 6.1-6.3
HFD-540 # 994357Correspondence Date: October 7, 1999CDER Stamp Date: October 13, 1999Serial # (SU) A 8.1
HFD-540 # 005803Correspondence Date: May 10, 2000CDER Stamp Date: May 11, 2000

Preliminary Review Completed: January 21, 2000
(Submission Incomplete due to lack of Safety Update)

Final Review Date: August 10, 2000

Drug: LOTRISONE (betamethasone dipropionate and clotrimazole) LOTION

Sponsor: Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07053

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

Pharmacologic Category: Topical Combination Anti-Fungal/Corticosteroid

Regulatory Intent:

This amendment is provided to updated labeling and CMC information. Reference is made to the "pending" NDA submitted on August 31, 1989 and FDA's approvable letter of July 31, 1991 for this NDA.

Background:

NDA 20-010 was submitted on August 31, 1989. An approvable action was taken per the letter dated July 31, 1991 with outstanding CMC and labeling issues to be resolved.

A telecon was held on February 24, 1999 between the Applicant and the Division regarding CMC issues. At that meeting, the Applicant was informed that it must update labeling which was nine years old to current standards. With this submission, the Applicant has provided updated drafts of the labeling. No new clinical studies were submitted for review.

The studies for this NDA were conducted under IND 18,274. Only one other NDA has been approved which contains betamethasone dipropionate and clotrimazole in combination (NDA 18-827, Lotrisone Cream). Lotrisone Cream was approved in 1984 for the same indications as proposed for Lotrisone Lotion. Lotrisone Cream was the reference product for the Lotrisone Lotion line extension.

A Brief Summary of the Lotrisone Cream NDA

The Lotrisone Cream NDA contained single studies in tinea pedis, tinea corporis and tinea cruris which were of parallel group design and compared the combination to Lotrimin Cream and Diprosone Cream alone (no vehicle group was tested). Approval was granted on the basis that the combination relieved the symptoms (erythema, maceration, scaling, pruritus, vesicles, papules, and pustules) more quickly than did the Lotrimin product alone. There was no discernable difference between Lotrimin and Lotrisone at the end of the two-week study period (4 weeks for tinea pedis).

Studies submitted to NDA 18-827 (Lotrisone Cream) – Data as obtained from Clinical Review of this NDA (original data was not available):

1) Tinea Cruris study

7 sites, only 6 used in analysis (one site had only two enrollees and data was not included in review)

Signs and Symptoms Day3-5 – Patients with Excellent Response (Improved – No Mycology)

	#excellent/total	%excellent
Lotrisone Cream	22/50	44%
Lotrimin Cream	4/50	8%
Diprosone Cream	14/49	29%

Overall Evaluation Day26-32 (Includes Mycology)

	#complete cure/total	%complete cure
Lotrisone Cream	19/51	37%
Lotrimin Cream	9/51	18%
Diprosone Cream	1/49	2%

2) Tinea Pedis study

6 sites

Signs and Symptoms Day 6-10 – Patients with Excellent Response (Improved – No Mycology)

	#excellent/total	%excellent
Lotrisone Cream	10/78	13%
Lotrimin Cream	7/78	9%
Diprosone Cream	19/78	24%

Overall Evaluation Day40-46 (Includes Mycology)

	#complete cure/total	%complete cure
Lotrisone Cream	8/78	10%
Lotrimin Cream	7/78	9%
Diprosone Cream	3/79	4%

3) Tinea Corporis study

6 sites

Signs and Symptoms Day 3-5 – Patients with Excellent Response (Improved – No Mycology)

	#excellent/total	%excellent
Lotrisone Cream	14/45	31%
Lotrimin Cream	2/48	4%
Diprosone Cream	15/47	32%

Overall Evaluation Day 24-34 (Includes Mycology)

	#complete cure/total	%complete cure
Lotrisone Cream	17/51	33%
Lotrimin Cream	5/53	9%
Diprosone Cream	4/48	8%

The Lotrisone Lotion line extension results in a product that is more liquid than Lotrisone Cream. The Agency had apparently accepted a clinical program for development of the lotion as follows:

- 1) A parallel-group comparison of active lotion and vehicle in tinea pedis;
- 2) A parallel-group comparison of active lotion and vehicle in tinea cruris which would qualify the drug for approval in both tinea cruris and tinea corporis;
- 3) A vasoconstrictor assay which would compare the cream and lotion products and confirm the availability of the steroid.

Additionally, the Applicant was to provide _____

but the Agency felt at that time that such a study would not be necessary as the antifungal properties of the lotion would theoretically be shown by the human clinical studies.

It is important to note that no comparison to either of the actives plus vehicle alone were required by the Agency at that time.

Clinical Review:

The original NDA 20-010 had a clinical review dated June 27, 1990 which reviewed the two clinical studies submitted (these are excerpted below):

A. Tinea pedis study

Title – A multicenter, double-blind comparison study of Lotrisone Lotion and its Vehicle in Patients with Tinea Pedis (Schering Study No. S-88-067).

Investigators - _____

Study design – Parallel group, randomized, double-blind comparison of Lotrisone Lotion to its vehicle.

Patient selection - Patients were 12 years of older with a clinical diagnosis of moderate to severe tinea pedis that had been confirmed by direct examination of KOH mount and culture with moderately severe erythema.

Patient exclusions - Pregnant or nursing women, patients seeking pregnancy, Patients receiving conflicting concomitant therapy, and patients with known hypersensitivity to the drug were excluded.

Dosage and duration – Applications were BID by the patients for 4 weeks. There was also a follow-up visit two weeks after the discontinuance of therapy.

Effectiveness parameters – One reference site was designated for clinical and mycological evaluations during the course of the study. The patients clinical response was evaluated after 1, 2, 3, and 4 weeks of therapy and at the follow-up visit (2 weeks after the end of therapy) with the following criteria:

1) Physician's scoring of clinical status of the infection

0 = none

1 = mild: Lesions are confined to interdigital spaces. Erythema and itching are slight.

2 = moderate: Lesions are confined to interdigital spaces. Erythema and itching are definite. Maceration and scaling may be present.

3 = severe: Lesions are interdigital and also extended to other areas of the foot. Erythema is conspicuous. Itching is intense and may be accompanied by sensations of burning or pain. Maceration and scaling are present. Vesicles are present.

2) In addition, the following ^{signs (s.o)} signs and symptoms were evaluated for presence and severity: erythema, maceration, scaling, pruritus, vesicles, papules, and pustules. These were scored as 0 = none, 1 = mild or slight, 2 = moderate or definitely present, 3 = marked or severe and intense.

3) Global evaluation of the clinical response to treatment compared to the baseline condition was made according to the following scale:

- 1 Complete = 100% improvement from pre-treatment baseline.
2. Excellent = 75% or more improvement, but less than complete
3. Good = 50% or more improvement, but less than 75% improvement
4. Fair = Less than 50% improvement
5. Poor = No detectable improvement from baseline
6. Treatment failure = flare-up of lesions at the site being treated.

4) KOH exams and cultures were done initially and at each return visit.

Results -

Evaluable patients – One hundred twenty (120) patients were enrolled in the study. One patient was an immediate dropout and was not included in the safety or efficacy data. The other 119 patients were included in the safety analysis.

27 patients were excluded from the efficacy analysis. 25 had negative cultures at baseline, 1 had insufficient signs/symptoms scores at baseline and 1 was a protocol violation.

The original clinical review from June 30, 1990 stated that the demographic data for both arms were comparable enough to exclude bias for demographic reasons. The patients were aged 12-80 years. The organisms treated were *T. rubrum* (about 80 %), *T. mentagrophytes*, and *E. floccosum*.

Lotrisone was shown to be statistically superior to vehicle in relieving symptoms of erythema, scaling, pruritus, and maceration and in total signs and symptoms at week 4 ($p < 0.01$ or better). Lotrisone Lotion was also shown to be better than vehicle with regard to mycological culture and KOH results at weeks 4 and 6.

Lotrisone was superior to vehicle for both anti-inflammatory effect at an early timepoint and for anti-fungal effect at the end of the study:

S88-067 – Tinea Pedis

4 week treatment period

Total Signs and Symptoms (=anti-inflammatory effect)

	Baseline	Week2	N
Lotrisone Lotion	8.6	4.3	42
Vehicle	8.6	5.5	48

Mycological Cure Week6 (=anti-fungal effect)

	#improved/total	% improved
Lotrisone Lotion	25/36	69%
Vehicle	7/29	24%

Overall Cure Week6= negative KOH and good, excellent, or complete global response (=anti-fungal effect)

	#improved/total	% improved
Lotrisone Lotion	22/36	61%
Vehicle	3/29	10%

Thus, this study established the superiority of Lotrisone Lotion to its vehicle in the treatment of tinea pedis according to the standards of the time when this product was found Approvable. The relapse rates for the active and vehicle groups were not significantly different. Adverse reactions in both groups were relatively infrequent and local in effect according to the original clinical review.

B. Tinea Cruris Study

Title – A Double-Blind Efficacy and Safety Study of Lotrisone Lotion and its Vehicle in Patients with Tinea Cruris (Schering Study No. S-87-024).

Investigators -

Study design – Parallel group, randomized, double-blind comparison of Lotrisone Lotion to its vehicle.

Patient selection - Patients were 12 years ^{of (m.o.)} older with a clinical diagnosis of tinea cruris that had been confirmed by direct examination of KOH mount and culture with moderately severe erythema.

Patient exclusions - Pregnant or nursing women, patients seeking pregnancy, Patients receiving conflicting concomitant therapy, and patients with known hypersensitivity to the drug were excluded.

Dosage and duration – Applications were BID by the patients for 2 weeks. There was also a follow-up visit two weeks after the discontinuance of therapy.

Effectiveness parameters – One reference site was designated for clinical and mycological evaluations during the course of the study. The patients clinical response was evaluated after 3 days, after 2 weeks of therapy, and at the follow-up visit (2 weeks after the end of therapy) with the following criteria:

1) Physician's scoring of clinical status of the infection
1 = mild; 2 = moderate; 3 = severe

2) In addition, the following ^{signs (m.o.)} signs and symptoms were evaluated for presence and severity: erythema, maceration, scaling, pruritus, vesicles, papules, and pustules. These were scored as 0 = none, 1 = mild or slight, 2 = moderate or definitely present, 3 = marked or severe and intense.

3) Global evaluation of the clinical response to treatment compared to the baseline condition was made according to the following scale:

1. Complete = 100% improvement from pre-treatment baseline.
2. Excellent = 75% or more improvement, but less than complete
3. Good = 50% or more improvement, but less than 75% improvement
4. Fair = Less than 50% improvement
5. Poor = No detectable improvement from baseline
6. Treatment failure = flare-up of lesions at the site being treated.

4) KOH exams and cultures were done initially and at each return visit.

Results -

Evaluable patients – One hundred thirty-two (132) patients were enrolled in the study. 6 patients were immediate dropouts and were not included in the safety or efficacy data. The other 126 patients were included in the safety analysis.

6 patients were excluded from the efficacy analysis. 5 had negative cultures at baseline, 1 was a protocol violation.

The original clinical review from June 30, 1990 stated that the demographic data for both arms were comparable enough to exclude bias for demographic reasons. The patients were aged 16-88 years.

The organisms treated were *T. rubrum* (about 75%), *T. mentagrophytes*, *T. tonsurans* and *E. floccosum*. Two of the vehicle patients were infected with *M. canis*, but no active patients were. Since no *M. canis* patients were present in the tinea pedis study either, this organism was not tested with Lotrisone Lotion.

Lotrisone was shown to be statistically superior to vehicle in relieving symptoms of erythema, scaling, and pruritus at all time points measured ($p \leq 0.02$ or better). The reviewer made a comment that "the symptoms which are more affected by the antifungal component were at a low level of incidence, so it is difficult to state that the steroid actually made a difference."

Lotrisone Lotion was also shown to be better than vehicle with regard to mycological culture and KOH results at all time periods.

S87-024 - Tinea Cruris
2 week treatment period

Total Signs and Symptoms

	Baseline	Day3	N
Lotrisone Lotion	7.9	4.8	61
Vehicle	7.8	6.0	59

Mycological Cure Day29

	#improved/total	% improved
Lotrisone Lotion	30/47	64%
Vehicle	11/31	35%

Overall Cure Day29

	#improved/total	% improved
Lotrisone Lotion	26/47	55%
Vehicle	10/31	32%

Thus, this study established the superiority of Lotrisone Lotion to its vehicle in the treatment of tinea cruris according to the standards of the day. The relapse rates for the active and vehicle groups were not significantly different. Adverse reactions in both groups were "inconsequential" according to the original review.

Vasoconstrictor Assays:

The review dated June 27, 1990 stated the vasoconstrictor assay data provided in the original submission was incomplete and it was recommended that the NDA be not approved pending receipt of such data. The original review also made note of reports of toxicities in children with Lotrisone Cream, namely skin atrophy, steroid induced acne, and Cushingoid symptoms.

As a response to the NA issues, the study data and protocol were submitted for the vasoconstrictor assay and reviewed on September 12, 1990. This study was conducted in 24 healthy subjects with Lotrisone Cream and

Diprosone Ointment (betamethasone dipropionate) 0.05% was the reference products. The Lotrisone Lotion product intended for marketing contains propylene glycol (P.G.). Additional test formulations containing propylene glycol were also included.

10 mg of each formulation was applied to test sites 2 cm in diameter on the volar forearm in a random fashion. Each test lotion formulation was tested twice and each reference formulation was tested once. The test sites were evaluated at 7 hours and 24 hours after drug application with the degree of blanching measured on a scale from 0 to 3.

DRUG	7 HOUR READING (MEAN BLANCHING SCORE)	24 HOUR READING (MEAN BLANCHING SCORE)
Lotrisone Cream	1.04	0.23
Diprosone Ointment	1.92	0.25
Lotrisone Lotion – 10% P.G.	0.84	0.19
Lotrisone Lotion – 15% P.G.	0.91	0.27
Lotrisone Lotion – 20% P.G.	1.00	0.30

The original reviewers of this data stated the following "These data fail to establish that the Cream and Lotion products are bioequivalent." The Lotrisone Cream appears to be more potent than the Lotrisone Lotion with propylene glycol (to be marketed product). A second non-approvable letter was sent on December 31, 1990.

Reviewer's Comment - As the study did not bracket with a lower strength reference product it is difficult to know where the Lotion would fall in terms of potency using a vasoconstriction assay. This vasoconstriction assay may not have been adequately powered to detect a difference between the reference products and Lotrisone Lotion.

The Applicant replied (March 19, 1991) to the second NA letter stating that "there are no statistically significant differences between Lotrisone Cream and Lotrisone Lotion." An alternative way of evaluating the vasoconstrictor data and additional vasoconstrictor data was submitted:

**APPEARS THIS WAY
ON ORIGINAL**

STUDY	NUMBER OF SUBJECTS			McNemar's Test Exact P- value
	Favoring Lotrisone Cream	No Difference Detected	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

The reviewer of the March, 1991 submission stated "While the products may not be different statistically, it is disturbing that two products which have such similar formulations ... could have such different results in the vasoconstrictor assay. Once again, the explanation offered by the sponsor is not entirely satisfactory, but it does not seem to be a sufficiently important point to pursue further. This is principally because the clinical study submitted which compares the active product to the vehicle establishes the effectiveness of the product."

The reviewers (Mr. David Bostwick and Dr. C.C. Evans) further comment that the Agency "will not accept vasoconstrictor assays in the future as proof of the bioequivalence of topical products which contain steroids in combination with another active ingredient." Written by the then Division Director (Dr. Murray Lumpkin) above his signature (July 18, 1991) is the following comment: "I question whether the decreased mineral oil and petrolatum in the lotion formulation resulted in less "occlusion" than with the cream formulation, thus decreased vasoconstrictor results. Nonetheless, steroid activity was documented in this formulation. Because the sponsor has 2 A&WC studies which demonstrate superiority of this product to its vehicle, I agree with approval. In the future, I think the policy for line extensions of fungal/steroid combinations should require one 3-armed study (combo, fungal alone, vehicle) with analysis of rates of resolution of signs and symptoms... [and] anti-fungal activity."

Review of Current Submission:

The current submission attempts to address the "high" potency classification, Pediatric Use, and some previous labeling recommendations made for Lotrisone Cream. The Sponsor also inserts the CLINICAL PHARMACOLOGY section to describe the clinical studies of the combination product, Lotrisone Cream.

The Applicant has ~~_____~~ (see above review of tinea cruris study as to the reason this was not originally included in the indications for Lotrisone Lotion).

Reviewer's Comment - Please also refer to the article by Rosen and Elewski, 1995 regarding the "Failure of clotrimazole-betamethasone

dipropionate cream in treatment of *Microsporum canis* infections" (J. of Amer. Acad. Dermatol., June 1995, pp. 2050-2051).

It is submitted that the indication for short-term use of this product in the INDICATIONS AND USAGE section is removed. The ADVERSE REACTIONS section of the label has some significant AERs deleted. The label will need to be further reviewed in the Labeling Review.

Safety Update

A safety update of this product and related products is not included with the original submission. A report of clinical safety of this product will need to be assured before approval.

The Applicant was asked to submit a detailed safety report regarding this product (in any foreign marketing), and its related product (Lotrisone Cream).

Pediatric Use

The Applicant has revised the PEDIATRIC USE section so as to read, in part:

"LOTTRISONE Cream

Reviewer's Comments - We note that the Applicant will have studies underway in the pediatric population down to age 12 for Lotrisone Cream as a Pediatric Written Request. The results from those studies will impact the labeling for this product as well.

Advisory Committee Recommendations

In order to remedy and clarify the nature of the indications for this combination product and certain safety concerns that were raised for this product, NDA 20-010, Lotrisone Lotion was presented to the Dermatologic and Ophthalmic Drugs Advisory Committee on June 29, 2000.

The Advisory Committee made several recommendations regarding future combination anti-fungal/corticosteroid drug products for treatment of tinea.

These recommendations (as grounded in 21 CFR 300.50) are as follows:

- 1) A distinction can be made in labeling for such products between "minimally inflamed tinea not requiring a corticosteroid component" and "sufficiently inflamed tinea warranting a corticosteroid component."
- 2) Four-armed studies should be conducted:
 - a) Combination Antifungal + Corticosteroid
 - b) Antifungal Alone
 - c) Corticosteroid Alone
 - d) Vehicle

These studies should compare anti-inflammatory effect (early reduction of signs and symptoms) and anti-fungal effect (clinical and mycological cure). The presence of the corticosteroid should be justified by a better anti-inflammatory effect with the combination as compared to the Anti-fungal alone.

- 3) If the presence of corticosteroid in the combination product does not reduce the antifungal activity (as compared to Antifungal alone), then the product could be labeled for all tinea.

With NDA 20-010, the Applicant had demonstrated superiority in efficacy for treatment of tinea with its combination product vs. vehicle. However, no studies were conducted to compare antiinflammatory effect or antifungal effect of the combination with corticosteroid and antifungal alone arms. Based on the rationale as recommended by the DODAC, Lotrisone Lotion (and Lotrisone Cream) should only be used for symptomatic and inflamed tinea. Thus, the recommended Indications and Usage section for labeling for Lotrisone Lotion is as follows:

Additional recommendations that were conveyed at the June 29, 2000 DODAC meeting include several safety concerns. These included more obvious warnings regarding Pediatric Use of this high potency corticosteroid-containing product and sterner and more obvious warnings to deter use of this product for treatment of diaper dermatitis. These issues will need to be addressed with labeling.

CMC Issues

Please refer to the CMC review by Dr. Saleh Turujman regarding CMC issues with this NDA. Various issues including stability and packaging remain outstanding at the time of this review.

Review of Safety Update:

On May 11, 2000, the Sponsor submitted the requested Safety Update for this NDA.

- 1) Clinical Trials Data: Several Clinical trials have been conducted with Lotrisone Cream since the 1991 AE letter for Lotrisone Lotion. Results from these studies include cases of skin atrophy and telangiectasia in patients using Lotrisone Cream. In HPA Axis suppression studies, one of the patients (out of 8) demonstrated borderline abnormal response to Cortrosyn stimulation.
- 2) Spontaneous Adverse Event Reporting: Multiple cases of Skin Atrophy (23 cases listed in the submission), cases of hypertrichosis, telangiectasias, and other local site of application adverse events have been reported.

The Sponsor states that "The data in the PSUR report do not reveal any significant new safety issues or trends. No changes to the labeling are recommended at this time." The Sponsor also stated that "The data...do not permit a comparison of the safety profile of adults vs. children."

A more complete review of the safety issues with Lotrisone Cream (also applicable to Lotrisone Lotion) was provided by the FDA Office of Post-marketing Drug Risk Assessment. At the request of this reviewer, a review of Lotrisone Adverse Events was conducted for the years 1984 to 1999. A more complete review of Adverse Event Reporting and IMS Health national prescribing data provided information that confirms widespread off-label use of Lotrisone Cream including use in children and for diaper dermatitis. Significant adverse events have been reported including growth retardation, HPA Axis suppression, and local cutaneous events. About 25% of all cases of adverse events with use of Lotrisone Cream were reported for patients aged 12 or less.

Conclusions:

This amendment/response to Approvable Letter provides additional CMC information and proposed updated labeling for Lotrisone Lotion, a combination product that was originally found Approvable in the year 1991 on the basis of two clinical studies (vs. vehicle) and a vasoconstriction assay.

The Approvable status of this application carries over intact due to Agency commitments made in 1991. The Indications and Usage section of labeling will be impacted due to lack of information of whether this product has improved efficacy for early improvements of signs and symptoms vs. antifungal alone. There is also no information as to whether the corticosteroid detracts from anti-fungal efficacy.

A detailed safety update of the Lotrisone products was submitted on May 11, 2000. Additional safety concerns were addressed at the June 29, 2000 DODAC meeting. DODAC recommendations should be incorporated into labeling.

It is incumbent upon the Sponsor to demonstrate efficacy of Lotrisone Lotion in adequate and well-controlled studies in order to garner an indication for broader use in a wider range of patients than inflammatory tinea alone. Thus, the Applicant may wish to support labeling for — through two-armed studies demonstrating non-inferiority of the Combination to its anti-fungal alone in the same vehicle.

Regulatory Recommendation

Based on the current submission and data submitted to date, this reviewer would recommend maintaining the Approval decision of July 31, 1991 due to regulatory commitments made at that time. However, it would be appropriate to modify labeling of Lotrisone to reflect current information or lack of information. It should be noted in labeling that health care providers should consider using topical anti-fungal agents without corticosteroid in tinea without a symptomatic and inflammatory component.

As part of the Approval, it is recommended that the Applicant include an educational campaign for both Lotrisone Cream and Lotion products to educate all physicians regarding proper use of these products (i.e. not recommended for

use in patients 12 years and younger and not recommended for use in diaper dermatitis). A Dear Doctor letter regarding Lotrisone Cream should be part of that educational campaign.

ISI
8/11/2000
Markham C. Luke, M.D., Ph.D.
Medical Officer, Dermatology

- cc: HFD-540
- HFD-540/PM/Cross
- HFD-540/Chemistry/Turujman
- HFD-540/ChemistryTL/DeCamp
- HFD-540/Pharm/Brown
- HFD-880/Biopharm/Bashaw
- HFD-540/MO/Luke
- HFD-540/Clinical TL/Okun
- HFD-540/DIVDIR/Wilkin
- NDA 20-010
- NDA 18-827
- IND 18,274

**APPEARS THIS WAY
ON ORIGINAL**

OFS 8/11/2000
no OFS copy identified on 9/13/00
ISI
9/13/00

Medical Officer's Review of NDA 18-827 and NDA 20-010**Combined Labeling Review and PPI**

NDAs 18-827 and 20-010
HFD-540 #s 006409, 006411,
006410, and 006398

Correspondance Date: August 15, 2000
CDER Stamp Date: August 17, 2000
Review Date: August 25, 2000
Revised Date: September 12, 2000

Drug: LOTRISONE Cream and Lotion
Applicant: Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033
(908) 298-4000

Pharmacologic Category: Topical Anti-dermatophyte

Labeling Review:

According to the June 29, 2000 Advisory Committee recommendation, the committee voted unanimously that the Lotrisone Cream and Lotion labels should be the same. One way of achieving this sameness in an expeditious fashion is to combine the two labels. Hence the labels for NDA 18-827 and NDA 20-010, which is a line extension of 18-827, are combined in this review.

Also at the June 29, 2000 Advisory Committee, a recommendation that was publicized by the news media was the inclusion of a pictorial representation of the statement "Not Recommended for Use in Patients Less than 12 years of Age and Not Recommended for Use in Diaper Dermatitis." This recommendation was given with thought to the non-English-speaking U.S. population. It was recommended that the picture and warning be placed on tube and container packaging, as well as on the package insert. Thus,  is included on the package insert and should be used on tube and carton labeling as well.

The available data for Lotrisone Lotion from the studies was added to labeling to generate a Clinical Studies Section. In addition, a Geriatric Use section is incorporated. Data from the AERS Datamart is included.

Changes to the labeling as suggested at the August 17, 2000 labeling meeting are incorporated into this package insert.

The Sponsor's proposed Patient Package Insert has been modified. Changes to the PPI from the labeling meeting held on August 17, 2000 are incorporated.

Microbiology changes of September 11, 2000 are included.

Recommendations: It is recommended that the labeling as attached to this review be used for the Lotrisone Cream and Lotion. The label is derived from information contained in the review of original NDA 20-010 and its amendments. Recommendations given by the Dermatologic and Ophthalmic Drugs Advisory Committee, June 29, 2000 are included. In addition, the attached revision to the Applicant proposed Patient Package Insert should be used in labeling.

C

Number of Pages
Redacted 26



Draft Labeling
(not releasable)

C

ISI
Markham C. Luke, M.D., Ph.D.
Medical Officer, Dermatology

9/12/2000

cc: HFD-540
HFD-540/CSO/Cross
HFD-540/Chem TL/DeCamp
HFD-540/Chemist/Hathaway
HFD-540/Chemist/Turujman
HFD-540/Pharm/Brown
HFD-540/BioPharm/Bashaw
HFD-590/Silver
HFD-540/MO/Luke
HFD-540/Clinical TL/Okun
HFD-540/DIVDIR/Wilkin

NDA 18-827

NDA 20-010

ISI

9/12/00

No DFS

✓

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9/13/00

REQUEST FOR CONSULTATION

Division/Office: OPDRA, HFD-400, Sammie Beam, Room
wn 15B08

FROM: HFD-540 (Division of Dermatologic and Dental Drug
Products) Frank Cross

DATE:
March 20, 2000

IND NO.:

NDA NO.:
20-010

TYPE OF DOCUMENT :
Original NDA

DATE OF DOCUMENT:
10/13/99

NAME OF DRUG:
Lorisonone Lotion

PRIORITY CONSIDERATION:
S

CLASSIFICATION OF DRUG:
3,4

DESIRED COMPLETION DATE:
4/10/00

NAME OF FIRM: Schering-Plough

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL
 PROGRESS REPORT
 NEW CORRESPONDENCE
 DRUG ADVERTISING
 ADVERSE REACTION REPORT
 MANUFACTURING CHANGE/ADDITION
 MEETING PLANNED BY

PRE-NDA MEETING
 END OF PHASE II MEETING
 RESUBMISSION
 SAFETY/EFFICACY
 PAPER NDA
 CONTROL SUPPLEMENT

RESPONSE TO DEFICIENCY LETTER
 FINAL PRINTED LABELING
 LABELING REVISION
 ORIGINAL NEW CORRESPONDENCE
 FORMULATIVE REVIEW
 OTHER (SPECIFY BELOW):
Tradename Consult

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
OTHER:

CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER:

III. BIOPHARMACEUTICS

DISSOLUTION
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
 DRUG USE e.g. POPULATION EXPOSURE,
ASSOCIATED DIAGNOSES
 CASE REPORTS OF SPECIFIC REACTIONS (List below)
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
 SUMMARY OF ADVERSE EXPERIENCE
 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review the Applicant's proposed Tradename for this NDA and provide us with your feedback. Please note that the name "Lorisonone" has been approved for some time and that this pending NDA is a response to the July 31, 1991, Approvable Letter. Thanks, Frank (7-2063)

cc: Original NDA 20-010
HFD-540/Div. Files
HFD-540/Cross

SIGNATURE OF DELIVERER: *[Signature]*

METHOD OF DELIVERY (Check one):
 MAIL HAND

SIGNATURE OF RECEIVER:

SIGNATURE OF DELIVERER:

M E M O R A N D U M

**DEPARTMENT OF HEALTH AND
HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION
AND RESEARCH**

DATE: May 5, 2000 MAY 8 2000

FROM: Lois LaGrenade, M.D., M.P.H., Epidemiologist

THROUGH: Julie Beitz, M.D., Director
Division of Postmarketing Drug Risk Assessment I,
HFD-430

SUBJECT: Advisory Committee Meeting June 29/30, 2000
Lotrisone Lotion NDA 20010
Possible options for Lotrisone labeling re safety

TO: Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
HFD-540

PID # D000309

Introduction

This consult is part of OPDRA's contribution to preparations for the advisory committee meeting on Lotrisone Lotion NDA 20010, and presents our proposal for labeling and other options to address safety concerns.

Background

In March, 1999 at the request of HFD-540, Division of Dermatologic and Dental Drug Products, we reviewed all adverse events to Lotrisone reported to the agency's Adverse Events Reporting System (AERS), with special emphasis on pediatric adverse events and whether there was an association between adverse events and duration of use longer than indicated on the label.

Of 315 unduplicated cases of adverse events to Lotrisone in the AERS database, 37 percent were pediatric. Of the 153 cases for whom complete data were available, 41(27%) were less than 12 years old. Thirteen of these were between the ages of 5 months and 2.5 years and in 10 of them the stated indication for use was diaper dermatitis. In 64% of these infants the duration of therapy exceeded 2 weeks (range 4 – 80 weeks). Adverse events reported in this age group included hirsutism, benign intracranial hypertension, skin atrophy, growth retardation, application site reaction,

aggravation of the condition and ineffectiveness of the cream. Drug use data showed that Lotrisone was widely used in the pediatric age group, in spite of product labeling stating that "safety and efficacy have not been established in children under 12" and "the use of Lotrisone in diaper dermatitis is not recommended". Adverse pediatric events appeared to be associated with off-label use of the drug with respect to age group, indication and duration of treatment.

In view of these findings we were requested to present the postmarketing experience with Lotrisone cream at the June 2000 advisory committee meeting to consider NDA 20010, Lotrisone lotion, and to make recommendations aimed at improving the safety of this drug.

Recommendations

Label

We recommend the following options for strengthening the labels of both Lotrisone cream and Lotrisone lotion, if the latter is approved for marketing:

Box/tube

Educational campaign

Since usage data and published reports^{1,2} indicate that Lotrisone cream continues to be widely used in children under age 12 years, despite the 1991 label change, we recommend that the sponsor be required to undertake an educational campaign aimed at pediatricians and non-dermatologists to increase awareness of these safety issues with Lotrisone cream and lotion. Evaluation of the educational program should be undertaken by the sponsor at 6- and 12-month periods after completion to determine effectiveness of the program and the need for its continuation.

As part of this program a "Dear Healthcare Practitioners" letter should be strongly considered to alert non-dermatologists to the labeling change.

Postmarketing surveillance

We further recommend that the sponsor be required to submit to the agency all reports of potential corticosteroid related adverse events connected to Lotrisone lotion/cream in children under age 12 years as expedited reports for the foreseeable future, with assessment of the need to continue based on the results of the sponsor's educational program.

Question for the Advisory Committee

Should the educational campaign against use of Lotrisone cream and lotion products in children and diaper dermatitis, be separate from the launch of Lotrisone lotion?

**APPEARS THIS WAY
ON ORIGINAL**

Medical Officer's Review of NDA 20-010 NC
New Correspondence

SEP 28 2000

NDA 20-010
Serial # NC
HFD-540 # 005377Correspondence Date: March 3, 2000
CDER Stamp Date: March 6, 2000
Review Date: March 16, 2000**Drug: LOTRISONE (betamethasone dipropionate and clotrimazole) LOTION****Sponsor:** Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07053**Contact:** Joseph F. Lamendola, Ph.D.,
Vice President, U.S. Regulatory Affairs**Pharmacologic Category:** Topical Combination Anti-Fungal/Corticosteroid**Regulatory Intent:**

The Applicant provides this correspondence regarding safety issues for its resubmission to an Approvable NDA. Reference is made to FDA's approvable letter of July 31, 1991.

Background:

Please see review of NDA 20-010 BZ dated January 28, 2000 for Background information regarding this NDA.

Safety Update

A safety update of this product and related products was not included in the resubmission/response to an Approvable letter dated October 7, 1999. In the current submission, the Applicant states the following: "No additional studies have been conducted since the original NDA. Therefore, there is no safety update to submit.

The Applicant is referred to 21 CFR 314.50(d)(5)(vi)(a) and (b). The regulations state that a safety update to an NDA submission should include "data from epidemiological studies of related drugs" and that "the applicant shall submit these reports ... following receipt of an approvable letter, and at other times as requested by FDA."

The Applicant should submit information so that an adequate and up-to-date determination of safety can be made for this new drug product.

Regulatory Recommendation (may be conveyed to Applicant)

- 1) The Applicant is referred to 21 CFR 314.50(d)(5)(vi)(a) and (b) regarding the filing of a Safety Update following receipt of an approvable letter.
- 2) The Applicant should submit a detailed safety update of the Lotrisone products (Cream and Lotion) including a summary of all adverse events reported since 1991. Significant foreign adverse events should also be

reported. The Safety Update submission to NDA 20-010 should include the following sections:

- a) Epidemiological Data from Lotrisone Cream Spontaneous Adverse Event Reporting.
- b) Data from Foreign Marketing of Lotrisone Cream and/or Lotion
- c) A Integrated Summary of Safety for Lotrisone Lotion taking into account Adverse Event Reporting for Lotrisone Cream (a summary of Safety of the Lotion in the studies submitted to NDA 20-010 should be included).

The safety data should be presented by gender, age, and racial subgroups as per 21 CFR 314.50 (d)(5)(vi)(a).

ISI
 3/16/2000
 Markham C. Luke, M.D., Ph.D.
 Medical Officer, Dermatology

cc: HFD-540
 HFD-540/PM/Cross
 HFD-540/ChemistryTL/DeCamp
 HFD-540/Pharm/Brown
 HFD-880/Biopharm/Bashaw
 HFD-540/MO/Luke
 HFD-540/Clinical TL/Okun
 HFD-540/DIVDIR/Wilkin
 NDA 20-010
 NDA 18-827
 IND 18,274

ISI
 3/30/00

✓ Entered on DFS
 3/16/2000

Sponsor has submitted Safety Update
 requested by P.M. since this review.
 As of 9/25/2000 *ISI* *On*
ISI 9/25/00 / /

ISI 9/28/00
 DFS ✓