CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-010

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

MAR 16 1999

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-010 **SUBMISSION DATES:** 01/05/99
PRODUCT: Lotrisone Lotion (clotrimazole/betamethasone dipropionate)
SPONSOR: Schering
2000 Galloping Hill Road
Kenilworth, NJ 07033
TYPE OF SUBMISSION: General Correspondence **REVIEWER:** Sue-Chih Lee, Ph.D.

Background:
NDA 20-010 was originally submitted on August 31, 1989 and the sponsor was sent an approvable letter on July 31, 1991. The sponsor has now accepted the Agency's recommendation to label this product as a high potency corticosteroid and is inquiring about the information needed in order for the product to be approved.

Comments:
It is noted that there was no formal pharmacokinetic review of this NDA before the approvable letter was sent to the sponsor. The sponsor did not determine the systemic absorption of clotriomazole nor did they conduct an acceptable HPA axis suppression study for this product. Since the NDA was considered approvable in 1991, lack of the above information will be reflected in the labeling. In addition, the sponsor will be required to conduct an HPA axis suppression study and determine the systemic exposure of clotrimazole as a Phase IV commitment.

Recommendation:
From the clinical pharmacology and biopharmaceutics standpoint, the application is approvable. The sponsor should conduct an HPA axis suppression study and determine the systemic exposure of clotrimazole as a Phase IV commitment. Until such time, the labeling should be revised to reflect the current state of knowledge.

/S/
Sue-Chih Lee, Ph.D.
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Dennis Bashaw, Pharm.D. /S/ 3/16/99

CC:
NDA 20-010
HFD-540 (Div.File)
HFD-540 (CSO/Cross)
HFD-880 (Bashaw)
HFD-880 (Lazor)
HFD-880 (Lee)

HFD-870 (attn: CDR. Barbara Murphy)
HFD-344 (Viswanathan)
AE

APPEARS THIS WAY
ON ORIGINAL

MAR 2 9 1999

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-010 **SUBMISSION DATES:** 10/07/99
PRODUCT: Lotrisone Lotion
(clotrimazole 1% / betamethasone dipropionate 0.05%)
SPONSOR: Schering Corp.
2000 Galloping Hill Road, Kenilworth, NJ 07033
TYPE OF SUBMISSION: Amendment **REVIEWER:** Sue-Chih Lee, Ph.D.

Background

This NDA was originally submitted on August 31, 1989 and the Agency issued an approvable letter dated July 31, 1991. On February 24, 1999, a teleconference took place between the sponsor and the Agency in which the sponsor was requested to update the label to current standards among other issues. The proposed product is [redacted]

Labeling Comments

1. Skin penetration and systemic absorption of clotrimazole for the 1% cream and 1% solution formulations are cited in the Clinical Pharmacology section of the label. Since formulation differences can result in changes in percutaneous absorption, the fact that no studies were conducted using the proposed Lotrisone Lotion should be indicated in the label.
2. Since the Biopharm Division was not included in the review of either the vasoconstrictor assay or HPA axis suppression study, the label related to these studies cannot be commented.
3. The pharmacokinetics section of the label is attached with the changes highlighted.

Recommendation

Labeling Comment #1 should be communicated to the sponsor.

/S/ 3/29/2000

Sue-Chih Lee, Ph.D.
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Dennis Bashaw, Pharm.D. 3/29/00 /S/

CC:
NDA 20-010
HFD-540 (Div.File)
HFD-540 (CSO/Cross)
HFD-880 (Bashaw)
HFD-880 (Lazor)
HFD-880 (Lee)
HFD-870 (attn: CDR. Barbara Murphy)
HFD-344 (Viswanathan)

Clotrimazole

Clotrimazole is a broad-spectrum, antifungal agent that is used for the treatment of dermal infections caused by various species of pathogenic dermatophytes, yeasts, and *Malassezia furur*. The primary action of clotrimazole is against dividing and growing organisms.

In vitro, clotrimazole exhibits fungistatic and fungicidal activity against isolates of *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, and *Microsporum canis*. In general, the *in vitro* activity of clotrimazole corresponds to that of tolnaftate and griseofulvin against the mycelia of dermatophytes (*Trichophyton*, *Microsporum*, and *Epidermophyton*.)

In vivo studies in guinea pigs infected with *Trichophyton mentagrophytes* have shown no measurable loss of clotrimazole activity due to combination with betamethasone dipropionate.

Strains of fungi having a natural resistance to clotrimazole have not been reported.

No single-step or multiple-step resistance to clotrimazole has developed during successive passages of *Trichophyton mentagrophytes*.

In studies of the mechanism of action in fungal cultures, the minimum fungicidal concentration of clotrimazole caused leakage of intracellular phosphorous compounds into the ambient medium with concomitant breakdown of cellular nucleic acids, and accelerated potassium efflux. Both these events began rapidly and extensively after addition of the drug to cultures.

Skin penetration and systemic absorption of clotrimazole following topical application of Lotrisone Lotion have not been studied. The following information was obtained using 1% clotrimazole cream and solution formulations. [redacted] Six hours after the application of radioactive clotrimazole 1% cream and 1% solution onto intact and acutely inflamed skin, the concentration of clotrimazole varied from 100 mcg/cm^3 in the stratum corneum, to 0.5 to 1 mcg/cm^3 in the stratum reticulare, and 0.1 mcg/cm^3 in the subcutis. No measurable amount of radioactivity (<0.001 mcg/mL) was found in the serum within 48 hours after application under occlusive dressing of 0.5 mL of the solution or 0.8 g of the cream.

Betamethasone Dipropionate

Like other topical corticosteroids, betamethasone dipropionate [redacted] has anti-inflammatory, anti-pruritic, and vasoconstrictive properties. The exact mechanism of the anti-inflammatory activity of topical steriods is unknown. Betamethasone

dipropionate, a corticosteroid, has been shown to have topical (dermatologic) and systemic pharmacologic and metabolic effects characteristic of this class of drugs.

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle, the integrity of the epidermal barrier and the use of occlusive dressings. (See DOSAGE AND ADMINISTRATION.)

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption of topical corticosteroids. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. (See DOSAGE AND ADMINISTRATION.)

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

Studies performed with betamethasone dipropionate formulated with propylene glycol indicate that it is in the high range of potency as compared with other topical corticosteroids.

2-1

JUN 27 1990

Clinical Review of Original NDA 20-010

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

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

Formulation:

Ingredient	mg/gram
Betamethasone Dipropionate	0.643*
Clotrimazole	10.0
White Petrolatum	
Mineral Oil	
Cetearyl Alcohol 70/30	
Ceteareth - 30	
Benzyl Alcohol	
[redacted]	
Phosphoric Acid	
Propylene Glycol	
Purified Water	q.s.
Sodium Hydroxide	

* Equivalent to 0.5 mg/gram of betamethasone. May contain up to a 5% manufacturing overcharge.

** Charged as a 1% (w/v) solution to adjust pH to 5.0 ± 0.2, if necessary.

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 [redacted] It is to be used twice daily.

Date of Submission: August 31, 1989. Amendment dated December 15, 1989.

Related Submissions: There are a number of NDA's approved which contain clotrimazole only (Lotrimin) and a number of others which contain betamethasone dipropionate only (Diprosone, Diprolene). Only one NDA has previously been approved which contains these ingredients in combination (NDA 18-827, Lotrisone Cream). The studies for this NDA were conducted under IND 18,274.

Chemistry: This is not yet available.

Pharmacology Review: In his pharmacology review dated November 29, 1989, the reviewing pharmacologist, Dr. Mainigi, found the application to be approvable.

Background: Lotrisone Cream was approved in 1984 for the same indications as are proposed for Lotrisone Lotion. 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, scaling, pruritus, etc) more quickly than did the Lotrimin product alone. There was no discernible difference between Lotrimin and Lotrisone at the end of the two-week study period (4 weeks for tinea pedis). The Lotrisone Cream application also contained the standard tests for irritation, sensitization, photoirritation and photosensitization.

On October 26, 1988, a meeting was held with Schering representatives concerning the clinical plan for Lotrisone Lotion. The principal focus of the meeting was that the lotion product was to be virtually identical to the cream product in terms of ingredients. The only ingredient which was changed was the substitution of an equal amount of Ceteareth-30 [redacted] These ingredients are both polyethylene glycol ethers of long-chain alcohols, with Ceteareth-30 having the longer chain. All other ingredients are identical, although the amounts of white petrolatum, mineral oil and cetearyl alcohol in the lotion are [redacted]

These revisions result in a product which is less stiff ("runnier") than the cream, and which may be suitably marketed as a lotion. The sponsors presented the idea that the clinical effectiveness of this product would not be expected to be less than the cream since the only real difference in the products would be consistency. They proposed that a suitable clinical program for the lotion would be:

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;

4. Results from a guinea pig model which purports to establish the the antifungal properties of the cream and lotion.

It was felt by the FDA representatives (Dr. Evans and Mr. Bostwick) that this was a reasonable approach to the clinical studies for this formulation. Further, since the antifungal properties of the lotion would theoretically be shown by the human clinical studies, it was felt that the guinea pig model data would not be necessary.

Clinical Studies:

A. Tinea pedis study

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:

[redacted]

[redacted]

Method: The investigators performed their studies under identical protocols as follows:

1. Study design: This was a parallel group, double-blind comparison of Lotrisone Lotion to its vehicle. Patients were assigned to the treatment groups in random fashion.

2. Patient selection: Patients 12 years of age and older were selected, who had a clinical diagnosis of moderate to severe tinea pedis that had been confirmed by direct examination of KOH mount and culture. In addition, it was necessary that at least moderately severe erythema be present.

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

4. Dosage and duration of treatment: Applications were made BID by the patients (this was an outpatient study) for 4 weeks. There was also a follow-up visit two weeks after the discontinuance of therapy.

5. Effectiveness parameters: One reference site was designated for clinical and mycological evaluations during the course of the study.

   a. Clinical assessments: The patient's clinical response to the medication was evaluated after 1, 2, 3, and 4 weeks of therapy and at the follow-up visit. The physician was to evaluate the clinical status of the infection according to the following scale:

      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.

      In addition, the following signs and symptoms were evaluated for presence and severity.

      a. Erythema
      b. Maceration
      c. Scaling
      d. Pruritus
      e. Vesicles
      f. Papules
      g. Pustules

      The severity of each sign/symptom was scored according the following criteria:

      0 = none
      1 = mild = slight
      2 = moderate = definitely present
      3 = marked or severe = intense

Finally, a 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 = Approximately 75% or more improvement, but less than complete improvement, from pre-treatment baseline.

3. Good = Approximately 50% or more improvement, but less than 75% improvement, from pre-treatment baseline.

4. Fair = Less than 50% improvement from pre-treatment baseline.

5. Poor = No detectable improvement from baseline.

6. Treatment Failure = Flare-up of lesions at the site being treated.

b. Mycology: KOH exams and cultures were done initially and at each return visit.

Results:

1. Evaluable patients: One hundred-twenty patients were enrolled in the study. One patient was an immediate dropout who never returned, and is not included in the safety or efficacy data. The other 119 patients were included in the safety analysis. Twenty-seven other patients were excluded from the efficacy analysis. Twenty-five of these had negative cultures at baseline, one had insufficient sign/symptom scores at baseline and the last was a protocol violation.

2. Distribution of patients by investigator: The following table shows the number of patients included in the safety and efficacy analysis by investigator. (The numbers represent no. efficacy/no. safety).

Investigator	Lotrisone	Vehicle
[redacted]	10/20	12/20
	19/20	20/20
	13/19	18/20
	42/59	50/60

3. Demographics: We have examined the demographic data presented by the applicant and conclude that the groups evaluated for efficacy were sufficiently comparable to exclude bias in the study for demographic reasons. The number of T. rubrum infections in each group was 32/42 = 76% in the Lotrisone group and 41/50 = 82% in the vehicle group. Other organisms present were T. mentagrophytes (8) and E. floccosum (10). The patients were aged 12-80 years.

4. Clinical assessments: We will present results at the end of the second week of therapy, at the end of therapy (week 4) and at the follow-up visit (week 6). We will present values only for those patients who were actually evaluated at each treatment visit (we have not done an intent-to-treat analysis). Therefore, it will be noted that varying numbers of patients were evaluated at each time period. We will discuss the reasons for the dropouts in the safety evaluation later in this review. In addition, since this was intended as a single study, pooled results from the three investigators are given. The conduct of the study justifies such pooling.

   a. Physician's evaluation of clinical status. Possible scores range from 0 to 3.

Physician's Overall Evaluation of Clinical Status
Mean Scale Value

Treatment	Baseline	(N)	Wk2	(N)	Wk4	(N)	Wk6	(N)
Lotrisone	2.2	(42)	1.5	(42)	1.1	(42)	0.7	(36)
Vehicle	2.3	(50)	1.6	(48)	1.6	(46)	1.5	(29)

Comment: These differences are significant to a level of $p < 0.01$ at week 4 and $p = 0.02$ at week 6.

   b. Symptoms. We will present the individual symptoms and signs followed by a total average score. Possible scores range from 0 to 3.

      i. Erythema

Mean Scale Value

Treatment	Baseline	(N)	Wk2	(N)	Wk4	(N)	Wk6	(N)
Lotrisone	2.2	(42)	1.2	(42)	0.7	(42)	0.6	(36)
Vehicle	2.2	(50)	1.4	(48)	1.5	(46)	1.1	(29)

      ii. Scaling

Mean Scale Value

Treatment	Baseline	(N)	Wk2	(N)	Wk4	(N)	Wk6	(N)
Lotrisone	2.3	(42)	1.5	(42)	1.1	(42)	0.8	(36)
Vehicle	2.3	(50)	1.7	(48)	1.7	(46)	1.8	(29)

iii. Pruritus

Mean Scale Value

Treatment	Baseline	(N)	Wk2	(N)	Wk4	(N)	Wk6	(N)
Lotrisone	1.8	(42)	0.6	(42)	0.2	(42)	0.2	(36)
Vehicle	1.7	(50)	0.9	(48)	0.8	(46)	1.0	(29)

iv. Maceration

Mean Scale Value

Treatment	Baseline	(N)	Wk2	(N)	Wk4	(N)	Wk6	(N)
Lotrisone	1.5	(42)	0.7	(42)	0.4	(42)	0.1	(36)
Vehicle	1.7	(50)	1.2	(48)	0.9	(46)	0.9	(29)

v. Vesicles

Mean Scale Value

Treatment	Baseline	(N)	Wk2	(N)	Wk4	(N)	Wk6	(N)
Lotrisone	0.5	(42)	0.2	(42)	0.0	(42)	0.0	(36)
Vehicle	0.3	(50)	0.1	(48)	0.2	(46)	0.2	(29)

vi. Papules

Mean Scale Value

Treatment	Baseline	(N)	Wk2	(N)	Wk4	(N)	Wk6	(N)
Lotrisone	0.3	(42)	0.1	(42)	0.1	(42)	0.1	(36)
Vehicle	0.3	(50)	0.1	(48)	0.2	(46)	0.2	(29)

vii. Pustules

Mean Scale Value

Treatment	Baseline	(N)	Wk2	(N)	Wk4	(N)	Wk6	(N)
Lotrisone	0.1	(42)	0.1	(42)	0.0	(42)	0.0	(36)
Vehicle	0.1	(50)	0.0	(48)	0.1	(46)	0.0	(29)

viii. Total Sign/Symptom Scores

Mean Scale Value

Treatment	Baseline	(N)	Wk2	(N)	Wk4	(N)	Wk6	(N)
Lotrisone	8.6	(42)	4.3	(42)	2.4	(42)	1.7	(36)
Vehicle	8.6	(50)	5.5	(48)	5.5	(46)	5.1	(29)

Comment: Lotrisone is statistically superior to its vehicle in relieving erythema, scaling, pruritus and maceration and in total signs and symptoms at week 4 ($p < 0.01$ or better). Lotrisone is superior to the vehicle at week 6 in scaling and in total signs and symptoms ($p = 0.02$) and is close to statistical significance in erythema ($p = 0.06$) and pruritus ($p = 0.07$). The higher p-values are due to the drop-out rate at week 6 rather than a regression of the symptoms in the Lotrisone group. It is interesting that the difference between the groups is not significant at week 2.

c. Global response evaluation

Status of Disease at Week 2 Compared to Baseline
Number of Patients and % of Total

Treatment	Complete	Excellent	Good	Fair	Poor	Failure	N
Lotrisone	0	12(28%)	13(31%)	6(14%)	10(24%)	1(2%)	42
Vehicle	1(2%)	4(8%)	12(25%)	13(27%)	18(38%)	0	48

Status of Disease at Week 4 Compared to Baseline
Number of Patients and % of Total

Treatment	Complete	Excellent	Good	Fair	Poor	Failure	N
Lotrisone	8(19%)	17(40%)	8(19%)	1(2%)	2(5%)	6(14%)	42
Vehicle	3(7%)	6(13%)	2(4%)	10(22%)	10(22%)	15(32%)	46

Status of Disease at Week 6 Compared to Baseline
Number of Patients and % of Total

Treatment	Complete	Excellent	Good	Fair	Poor	Failure	N
Lotrisone	14(39%)	14(39%)	4(11%)	3(8%)	1(3%)	0	36
Vehicle	2(7%)	7(24%)	2(7%)	3(10%)	13(45%)	2(7%)	29

Comment: Lotrisone is significantly superior to its vehicle in global response at both weeks 4 and 6.

5. Mycology: We will present results both separately and combined for culture and KOH mounts.

a. KOH results

Number of Patients and % of Total with Negative KOH Mount

Treatment	Week 2	Week 4	Week 6
Lotrisone	16/42 (38%)	27/42 (64%)	29/36 (81%)
Vehicle	12/48 (25%)	13/46 (28%)	10/29 (34%)

b. Culture results

Number of Patients and % of Total with Negative Culture

Treatment	Week 2	Week 4	Week 6
Lotrisone	29/42 (69%)	35/42 (83%)	28/36 (78%)
Vehicle	15/48 (31%)	20/46 (43%)	12/29 (41%)

c. Combined culture and KOH mount results

Number of Patients and % of Total with Negative KOH Mount and Culture

Treatment	Week 2	Week 4	Week 6
Lotrisone	13/42 (31%)	25/42 (60%)	25/36 (69%)
Vehicle	5/48 (10%)	8/46 (17%)	7/29 (24%)

Comment: Lotrisone is significantly superior to its vehicle in combined KOH mount and culture results at weeks 4 and 6 ($p = 0.02$).

6. Overall cure: This is defined as those patients with a negative KOH and culture as well as a "good", "excellent" or " complete" global response evaluation at both the end of treatment and two-week follow-up visit. These values were:

    Lotrisone: 22/36 (61%)
    Vehicle: 3/29 (10%)

Comment: Lotrisone is greatly superior to vehicle in this stringent method of testing effectiveness.

7. Relapse rate: In the context of this study, relapse rate is defined as those patients with an overall cure at week 4 who were not "cured" at week 6 (that is, they had a positive culture and/or KOH mount and/or global evaluation of less than good at week 6). These values were:

    Lotrisone: 4/36 (11%)
    Vehicle: 2/29 (7%)

Comment: This difference is not significant.

Safety Evaluation:

1. Dropouts: Aside from the immediate dropout and patients who were culture negative at baseline, there were 6 Lotrisone patients and 15 vehicle patients who failed to complete the study due to lack of efficacy. There were an additional 3 vehicle patients who were lost to follow-up and and may presumed to be failures. One Lotrisone patient was dropped as a protocol violation (specific problem not given).

2. Adverse reactions: Three (5%) of the 59 patients in the Lotrisone group and three (5%) of the 60 patients in the vehicle group experienced adverse reactions. These reactions were burning (2) and stinging in the Lotrisone group and pruritus (2) and stinging in the vehicle group.

Summary: This study establishes the superiority of Lotrisone Lotion to its vehicle in the treatment of tinea pedis. In all parameters examined (physician's evaluation of clinical status, signs and symptoms, global response, culture, KOH and overall cure), the active product was superior to vehicle at the end of treatment and at the follow-up visit. 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.

B. Tinea cruris study

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:

Method: The investigators performed their studies under identical protocols as follows:

1. Study design: This was a parallel group, double-blind comparison of Lotrisone Lotion to its vehicle. Patients were assigned to the treatment groups in a random fashion.

2. Patient selection: Patients 12 years of age and older were selected who had a clinical diagnosis of tinea cruris that had been confirmed by direct examination of KOH mount and culture. In addition, it was necessary that at least moderately severe erythema be present.

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

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

5. Effectiveness parameters: One reference site was designated for clinical and mycological evaluations during the course of the study. Visits were made for evaluation on the third day after initiation of therapy, at the end of 1 and 2 weeks of therapy and at 2 weeks after the end of therapy. The parameters observed were the same as are noted under section 5 of the tinea pedis study description.

Results:

1. Evaluable patients: One hundred thirty-two patients were enrolled in the study. Six were immediate dropouts who never returned; and they are not included in the safety or efficacy data. The other 126 patients are included in the safety analysis. Six other patients were excluded from the efficacy analysis because they either had negative cultures at baseline (5) or were a protocol violation (1).

2. Distribution of patients by investigator: The following table shows the number of patients included in the safety and efficacy analyses by investigator. (The numbers represent no. safety/no. efficacy).

Investigator	Treatment	
	Lotrisone	Vehicle
[redacted]	20/20	21/21
	21/21	21/21
	20/22	17/21
	61/63	59/63

3. Demographics: We have examined the demographic data presented by the applicant and conclude that the groups evaluated for efficacy were sufficiently comparable to exclude bias in the study for demographic reasons. The number of T. rubrum infections in each group was 44/61 = 72% in the Lotrisone group and 47/59 = 80% in the vehicle group. Other organisms present were T. mentagrophytes (20), E. floccosum (3), and T. tonsurans (2). Two of the vehicle patients were infected with Microsporum canis, but no active patients were. Since no M. canis patients were present in the tinea pedis study either, this organism has not been tested with Lotrisone Lotion. The patients were aged 16-88 years.

4. Clinical assessments: We will present results at Day 3 of therapy (in order to assess whether the signs/symptoms which would be affected by the steroid are improved early in the treatment cycle), at the end of therapy (week 2) and at the follow-up visit (week 4). Only data for the patients who were present for evaluation are given. Pooled data are presented.

a. Physician's evaluation of clinical status. Possible scores ranged from 0 to 3.

Physician's Overall Evaluation of Clinical Status
Mean Scale Value

Treatment	Baseline	(N)	Day 3	(N)	Wk 2	(N)	Wk 4	(N)
Lotrisone	2.2	(61)	1.6	(61)	0.8	(52)	0.7	(47)
Vehicle	2.3	(59)	2.0	(59)	1.3	(42)	1.4	(31)

Comment: These differences are significant at a p-value < 0.01 or better at all time periods.

b. Symptoms/signs. Possible scores range from 0 to 3.

i. Erythema

Mean Scale Value

Treatment	Baseline	(N)	Day 3	(N)	Wk 2	(N)	Wk 4	(N)
Lotrisone	2.3	(61)	1.5	(61)	0.8	(52)	0.7	(47)
Vehicle	2.3	(59)	1.9	(59)	1.1	(42)	1.1	(31)

ii. Scaling

Mean Scale Value

Treatment	Baseline	(N)	Day 3	(N)	Wk 2	(N)	Wk 4	(N)
Lotrisone	2.1	(61)	1.3	(61)	0.6	(52)	0.5	(47)
Vehicle	2.0	(59)	1.6	(59)	1.0	(42)	1.2	(31)

iii. Pruritus

Mean Scale Value

Treatment	Baseline	(N)	Day 3	(N)	Wk 2	(N)	Wk 4	(N)
Lotrisone	2.2	(61)	1.3	(61)	0.3	(52)	0.6	(47)
Vehicle	2.3	(59)	1.7	(59)	0.9	(42)	1.1	(31)

iv. Maceration

Mean Scale Value

Treatment	Baseline	(N)	Day 3	(N)	Wk 2	(N)	Wk 4	(N)
Lotrisone	0.8	(61)	0.6	(61)	0.1	(52)	0.0	(47)
Vehicle	0.8	(59)	0.6	(59)	0.2	(42)	0.3	(31)

v. Vesicles - the vehicle group exhibited no vesicles at baseline, so no comparison is possible.

vi. Papules

Mean Scale Value

Treatment	Baseline	(N)	Day 3	(N)	Wk 2	(N)	Wk 4	(N)
Lotrisone	0.4	(61)	0.2	(61)	0.0	(52)	0.1	(47)
Vehicle	0.4	(59)	0.2	(59)	0.1	(42)	0.0	(31)

vii. Pustules - the vehicle group exhibited no pustules at baseline, so no comparison is possible.

viii. Total Sign/Symptom Scores

Mean Scale Value

Treatment	Baseline	(N)	Day 3	(N)	Wk 2	(N)	Wk 4	(N)
Lotrisone	7.9	(61)	4.8	(61)	1.8	(52)	1.9	(47)
Vehicle	7.8	(59)	6.0	(59)	3.2	(42)	3.7	(31)

Comment: Lotrisone is statistically superior to its vehicle in relieving erythema, scaling and pruritus at all time periods at a p-value of 0.02 or less, except for erythema at week 4, where the p-value is 0.06. These symptoms are all treatable by the steroid component, so the effectiveness at Day 3 is an indication of early effectiveness of the steroid. Unfortunately, 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.

c. Global response evaluation

Status of Disease at Day 3 Compared to Baseline
Number of Patients and % of Total

Treatment	Complete	Excellent	Good	Fair	Poor	Failure	N
Lotrisone	0	1(2%)	25(41%)	21(34%)	11(18%)	3(5%)	61
Vehicle	0	1(2%)	5(8%)	26(44%)	23(39%)	4(7%)	59

Status of Disease at Week 2 Compared to Baseline
Number of Patients and % of Total

Treatment	Complete	Excellent	Good	Fair	Poor	Failure	N
Lotrisone	17(33%)	14(27%)	16(31%)	4(8%)	1(2%)	0	52
Vehicle	1(2%)	15(36%)	15(36%)	5(12%)	1(2%)	5(12%)	42

Status of Disease at Week 4 Compared to Baseline
Number of Patients and % of Total

Treatment	Complete	Excellent	Good	Fair	Poor	Failure	N
Lotrisone	23(49%)	7(15%)	7(15%)	9(19)	0	1(2%)	47
Vehicle	3(10%)	6(19%)	7(23%)	10(32%)	5(16%)	0	31

Comment: Lotrisone is significantly superior to its vehicle in global response at both weeks 2 and 4.

5. Mycology

a. KOH results

Number of Patients and % of Total with Negative KOH Mount

Treatment	Day 3	Week 2	Week 4
Lotrisone	21/61 (34%)	34/52 (65%)	30/47 (64%)
Vehicle	8/59 (13%)	18/42 (43%)	12/31 (39%)

b. Culture results

Number of Patients and % of Total with Negative Culture

Treatment	Day 3	Week 2	Week 4
Lotrisone	26/61 (43%)	36/52 (69%)	32/47 (68%)
Vehicle	10/59 (17%)	16/42 (38%)	13/31 (42%)

c. Combined culture and KOH mount results

Number of Patients and % of Total with Negative KOH Mount Culture

Treatment	Day 3	Week 2	Week 4
Lotrisone	19/61 (31%)	34/52 (65%)	30/47 (64%)
Vehicle	5/59 (89%)	15/42 (36%)	11/31 (35%)

Comment: Lotrisone is significantly superior to its vehicle in combined KOH mount and culture results at all time periods ($p = 0.02$). The early mycology conversion indicates that the symptomatic relief seen early in the study may be as much due to the antifungal component as to the steroid.

6. Overall cure:

Lotrisone: 26/47 = 55%
Vehicle: 10/31 = 32%

Comment: Lotrisone is superior to its vehicle in overall cure rate.

7. Relapse rate:

Lotrisone: 3/47 = 6%
Vehicle: 4/31 = 13%

Comment: This difference is not significant.

Safety Evaluation:

1. Dropouts: Aside from the immediate dropouts and patients who were culture negative at baseline, there were 7 Lotrisone patients and 15 vehicle patients who failed to complete the study due to lack of efficacy. One additional vehicle patient was lost to follow-up and may be presumed to be a failure.

2. Adverse reactions: Two (3%) of the 63 patients in the Lotrisone group and one (2%) of the 63 patients in the vehicle group experienced dry skin during the study.

Summary: This study establishes the superiority of Lotrisone Lotion to its vehicle in the treatment of tinea cruris. The active product was superior to the vehicle at day 3 of therapy, at the end of therapy, and 2 weeks after the end of therapy in all parameters which were examined. Adverse effects in both groups were inconsequential.

C. Vasoconstrictor study

Study Title: Formulation Screening Using the McKenzie Vasoconstrictor Assay.

Investigator: Not stated.

THIS SECTION WAS DETERMINED NOT TO BE RELEASABLE

3 pages

(H)

The labeling comments should be withheld until the application is complete in other respects.

/S/

David C. Bostwick
Chemist

/S/

C. Carnot Evans, M.D.
Group Leader/DERM

cc: Orig NDA
HFD-340
HFD-520
HFD-520/CCEvans
HFD-520/VCSickler
HFD-520/KMainigi
HFD-520/WDeCamp
HFD-520/DCBostwick:elp/06/20/90
5444m

/S/
6/27/90
I will discuss the statistical adequacy of the [redacted] study with Biostat.

APPEARS THIS WAY
ON ORIGINAL