CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 020193/S003

Trade Name : LAMISIL CREAM 1%

Generic Name: Terbinafine Hydrochloride Cream 1%

Sponsor : Sandoz Pharmaceutical Co.

Approval Date: January 21, 1997

JAN 21 1997

NDA 20-192/S003

Sandoz Pharmaceuticals Corporation
Attention: Stephanie Barba
59 Route 10
East Hanover, NJ 07936-1080

Dear Mrs. Barba:

Please refer to your September 28, 1993, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamisil (terbinafine hydrochloride cream) Cream, 1%.

Please also refer to the approvable letters dated September 27, 1994, and July 25, 1996.

We acknowledge receipt of your additional communications dated July 31, October 10, 22, and 30, 1996, and January 10, 1997.

This supplemental new drug application provides for the treatment of plantar tinea pedis (moccasin type).

We have completed the review of this application as amended, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed revised draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed revised draft labeling. The enclosed revised draft labeling was stated to be acceptable to you in the facsimile of your letter dated January 10, 1997. Marketing the product with FPL that is not identical to the enclosed revised draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-192/S-003. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Dermatologic and Dental Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Frank H. Cross, Jr., M.A., LCDR
Project Manager
(301) 827-2023

Sincerely yours,

1/21/97

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and
Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

cc:

Orig NDA 20-192/S-003
HFD-540/DIV FILE
HFD-340
HFD-105/Weintraub (with labeling)
HFD-2/Lumpkin (with labeling)
HFD-735 (with labeling)
HFD-222
HFD-92 (with labeling)
District Office
HF-2/Medwatch (with labeling)
HFD-40 (with labeling)
HFD-613 (with labeling)
HFD-540//DIV DIR/Wilkin
HFD-540/CHEM/Higgins
HFD-540/PHARM/Mainigi
HFD-540/PM/Cross/rev1-10.8.96/rev2-11.7.96/rev3-1.8.97/rev4-1.10.97

Concurrences:
HFD-540/SPM/Kozma-Fornaro/11.7.96
HFD-540/MO/Huene/10.31.96
HFD-540/DEP DIR/Katz/11.5.96

APPROVAL

NDA 20-192/S-003

Hedy M. Ries
Executive Director
Drug Registration and
Regulatory Affairs
Sandoz Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936

SEP 27 1994

Dear Ms. Ries:

Reference is made to your supplemental New Drug Application (NDA) dated September 28, 1993, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamisil (terbinafine hydrochloride cream), 1%

This supplemental New Drug Application provides for the addition of plantar tinea pedis (moccasin type) to the INDICATIONS AND USAGE section of the labeling for the drug product.

We have completed the review of this supplemental New Drug Application, and it is approvable. Before the application may be approved, however, we request that the proposed draft labeling be revised as follows:

Should additional information relating to the safety and effectiveness of this drug product become available, further revision of the labeling may be required.

Please submit a revised package insert for the drug product that incorporates the specified revisions, but that is otherwise identical to draft labeling submitted on September 28, 1993.

Within 10 days of the date of this letter, you are required to amend the supplemental New Drug Application, or notify us of an intent to file an amendment, or follow one of the other alternatives described in 21 CFR 314.110. In the absence of such action, on your part, the FDA may proceed to withdraw the supplemental New Drug Application.

Should you have any questions concerning this supplemental New Drug Application, please contact Maria Rossana R. Cook at 301-594-0466.

Sincerely yours,

[signature] MD 9/27/94

For

Jonathan K. Wilkin, M.D.
Director
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Orig NDA 20-192/S-003
HFC-130
HFD-82
HFD-500
HFD-638
HFD-735
HFD-540
HFD-540/MO/Huene [signature] 9/26/94
HFD-540/PHARM/Mainigi
HFD-540/CHEM SUPV/De Camp
HFD-540/PROJ MGR/Turtil

Concurrence:
HFD-540/MO SUPV/Chambers [signature] 9/26/94
HFD-540/PROJ MGT SUPV/Cook [signature] 9/28/94

APPROVABLE

CROSS
540

JUL 25 1996

NDA 20-192/SE1-003

Sandoz Pharmaceuticals Corporation
Attention: Roy Dodsworth
59 Route 10
East Hanover, NJ 07936-1080

Dear Mr. Dodsworth:

Please refer to your September 28, 1993, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamisil Cream (terbinafine hydrochloride cream), 1%. Please also refer to the approvable letter dated September 27, 1994.

We acknowledge receipt of your additional communications dated November 29, 1994; and February 24, March 8, July 10, and August 2, 1995.

This supplemental new drug application provides for the treatment of plantar tinea pedis (moccasin type).

We have completed the review of this supplemental new drug application as amended, including the revised draft labeling dated August 2, 1995, and it is approvable. Before this supplement may be approved, however, it will be necessary for you to submit draft labeling that incorporates the revisions specified below:

5. In the Clinical Studies section, there are a number of factual and typographical errors in the text and tables under Tinea Pedis (Interdigital type). These include:

   a. The numbers and percentages reflect patients with a total clinical score of The table should be revised to reflect the text.

   b. The division (/) symbols are missing.

   c. The number should be

   d. The term should be

   e. A close parenthesis is missing following

   f. The table is referred to both as and in the text; one of these terms should be consistently used.

   There are similar errors in the tabulation under Tinea Corporis/Cruris.

   In the table under Plantar Tinea Pedis (Moccasin type), the numbers and percentages also appear to reflect patients with a total clinical score of The table should be revised to reflect the text.

1 Page deleted

Revised Labeling

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, please submit a safety update report in accordance with section 314.50(d)(5)(vi)(b) of Title 21 of the Code of Federal Regulations.

Within 10 days after the date of this letter, you are required to amend this supplemental new drug application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw this supplemental new drug application.

The changes proposed in this application may not be implemented until you have been notified in writing that this supplemental new drug application is approved.

Should you have any questions, please contact:

Frank Cross, Jr, MA, LCDR
Project Manager
Telephone: (301) 827-2020

Sincerely yours,

7/24/96

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and
Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:

Orig NDA 20-192/SE1-003
HFD-540
HFD-340
HFD-540//DIV DIR/Wilkin
HFD-540/MO/Huene
HFD-540/CHEM/Higgins
HFD-540/PHARM/Mainigi
HFD-540/PM/Cross/rev1-4.5.96/rev2-4.26.96/rev3-5.8.96/rev3-5.17.96

Concurrences:
HFD-540/PROJ MGT SUPV/Cook/5.16.96
HFD-725/BIOSTAT SUPV/Srinivasan
HFD-540/MO/Huene
HFD-540/DEP DIR/Katz

APPROVABLE

SECTION 13: Patent Information

Lamisil® (Terbinafine HCL), and pharmaceutical compositions containing the drug, including Lamisil® 1% Cream, and its use as an antimycotic agent are claimed in USP 4,755,534, which has a statutory expiration date of July 5, 2005.

SECTION 14: Patent Certification

Not Applicable.

Lamisil® (terbinafine HCl) Cream, 1%
Supplimental New Drug Application

SANDOZ CERTIFICATION
IN COMPLIANCE WITH THE
GENERIC DRUG ENFORCEMENT ACT OF 1992

SANDOZ PHARMACEUTICALS CORPORATION certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with the supplemental application.

9/27/93
Date

M. J. Finkel
Marion J. Finkel, M.D., Vice President
Drug Registration and Regulatory Affairs

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-192 Supplement # S-003 Circle one: (SE1) SE2 SE3 SE4 SE5 SE6

HFD-540 Trade (generic) name/dosage form: Lamisil (terbinafine hydrochloride), 1% Cream Action: AP (AE) NA

Applicant Sandoz Pharmaceuticals Corp. Therapeutic Class _____

Indication(s) previously approved T. pedis, T. corporis/cruris, interdigital T. pedis
Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application Plantar tinea pedis (moccasin type)
(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
___ (1) Studies are ongoing,
___ (2) Protocols were submitted and approved.
___ (3) Protocols were submitted and are under review.
___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

[signature] PM L. Weese, M.D. 5/17/96
Signature of Preparer and Title (PM, CSO, MO, other) Date

[signature] 7/12/96

cc: Orig NDA/PLA # 20-192
HFD-540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

95

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-192 Supplement # SE1-003 Circle one: (SE1) SE2 SE3 SE4 SE5 SE6

HF D-540 Trade (generic) name/dosage form: Lamisil (terbinafine hydrochloride cream) Cream, 1% Action: (AP) AE NA

Applicant Sandoz Pharmaceuticals Therapeutic Class 1S

Indication(s) previously approved Interdigital T. pedis, T. corporis/cruris

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application Plantar tinea pedis (moccasin type)

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing,

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

Children do not have plantar tinea pedis except rarely.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

[signature] PM [signature] M.D. 10/8/96

Signature of Preparer and Title (PM, CSO, MO, other) Date

[signature] 1/3/97

cc: Orig NDA/PLA # 20-192
HF D-540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

E: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

5/95

MAR 23 1994

21

MEDICAL OFFICER'S REVIEW OF SUPPLEMENT TO NDA 20-192
S-003

December 13, 1993

SPONSOR: Sandoz Pharmaceuticals
East Hanover, New Jersey

DRUG: Lamisil (terbinafine HCl) cream 1%

PROPOSED CLINICAL INDICATION: Plantar tinea pedis (moccasin type)

APPROVED INDICATIONS: Interdigital tinea pedis (athlete's foot), tinea cruris (jock itch), tinea corporis (ringworm).

PROPOSED DOSAGE AND ADMINISTRATION: Applications BID for two weeks.

DATE OF SUBMISSION: September 28, 1993

Clinical studies

The sponsor has conducted two double-blind, vehicle controlled multicenter studies under an identical protocol in patients with tinea pedis of the mocassin type. These studies are designated Study 2509-01 and Study 2509-02.

The investigators for Study 2509-01 were as follows.

Paul Bergstresser, M.D.
University of Texas
Dallas, Texas

Norman Levine, M.D.
University of Arizona
Tuczon, Arizona

H. Earl Jones, M.D.
Fairhope, Alabama

Ronald Savin, M.D.
New Haven, Conn.

Boni Elewski, M.D.
Case Western Reserve University
Cleveland, Ohio

The investigators for Study 2509-02 were as follows.

James Leyden, M.D.
University of Pennsylvania
Philadelphia, Pa.

Gerald Weinstein, M.D.
University of Calif.
Irvine, Ca.

Jerome Shupack, M.D.
NYU Medical Center
New York, N.Y.

Nardo Zaias, M.D.
Miami Beach, Fla.

Eduardo Tschen, M.D.
Albuquerque, N.M.

The protocol for Studies 2509-01 and 2509-02 was as follows.

1) Study objective: The objective of the study was to compare the safety and efficacy of two weeks treatment with Lamisil cream to that with the Lamisil cream vehicle in the treatment of tinea pedis of the mocassin type, and to detect continual clearing during a six week followup period.

2) Study design: This was a double-blind, randomized, parallel group comparison of Lamisil cream with the cream vehicle in patients with tinea pedis of the mocassin type, with applications BID for two weeks.

3) Patient selection: Those selected were males and females aged 5 years or more, with a clinical diagnosis of plantar tinea pedis of the mocassin type and a positive KOH exam, confirmed by a positive culture for a dermatophyte. On a scale of 0-none, 1-mild, 2-moderate, and 3-severe, the condition was to have a baseline score of at least 2 for scaling/hyperkeratosis, and one or more of the clinical symptoms or signs fissuring, erythema, or pruritus, to make a total score of 4. At least one-third of the plantar surface of the foot was to be involved.

4) Patient exclusions: Among the patient exclusions were the following:

a. Pregnant or breast feeding women, or women of childbearing potential not using reliable methods of contraception.

b. Those with superficial white or proximal subungual onychomycosis or severe distal subungual onychomycosis of the toenails.

c. Those who had received immunosuppressive medication or radiation therapy within three months prior to the study, or systemic antifungal or anti-inflammatory therapy within one month prior to the study, or topical antifungal or anti-inflammatory therapy within two weeks prior to the study.

5) Treatment regimen: Applications of Lamisil cream or the vehicle cream were made BID for two weeks.

6) Effectiveness parameters: After the baseline evaluation, return visits were made at weeks 1, 2, 4, 6, and 8. The following procedures and evaluations were done:

a. Mycological examinations: Skin scrapings from the same site on a target foot were taken at each visit for KOH exams and mycological cultures.

b. Clinical signs and symptoms: The symptoms/signs erythema, scaling/hyperkeratosis, fissuring, and pruritus were scored for the target foot at each visit on a scale which was defined as follows:

0 = none - complete absence of any signs or symptoms
1 = mild - obvious but minimal involvement
2 = moderate - something that is easily noted
3 = severe - quite marked

c. Physician's evaluation of overall disease severity: The overall disease severity of all lesions on both feet was scored at each visit according to the scale under b.

d. Physician's rating of global clinical response: Global clinical response was rated at each return visit according to categories defined as follows:

Clinical cure: Complete improvement from baseline

Marked improvement: Approximately 75% or more improvement, but less than complete improvement.

Moderate improvement: Approximately 50% or more improvement, but less than 75% improvement.

Slight improvement: Less than 50% improvement.

No change: No detectable improvement.

Exacerbation: Increase in overall severity of condition.

e. Patient evaluation: At each return visit the patient rated the overall response to treatment as 0 - poor, 1 - fair, 2 - good, 3 - very good, or 4 - excellent.

f. Cures: The sponsor considered effective treatment to be either a 'complete cure' or a 'mycological cure' of the target area; these terms were defined as follows:

Complete cure - a negative KOH and culture with no residual signs and symptoms.

Mycological cure - a negative KOH and culture with some residual signs and/or symptoms; these were not to exceed a total score of 2 for erythema, scaling/hyperkeratosis, pruritus, and fissuring, nor exceed individual scores of 1 for erythema, scaling, or pruritus.

The results for Study 2509-01 were as follows.

1) Patient enrollment and demographic characteristics: 109 patients were entered into the study, of which 96 patients were evaluable for efficacy. The demographic characteristics of all patients enrolled were as follows.

Demographic characteristics		
	Lamisil	Vehicle
# pts	54	55
Age (years) Mean Range	43	43
Sex Male Female	40 (74%) 14 (26%)	43 (78%) 12 (22%)
Race Caucasian Black Asian Hispanic	39 (72%) 10 (19%) 1 (2%) 4 (7%)	36 (65%) 14 (25%) 1 (2%) 4 (7%)

The baseline disease characteristics of the evaluable patients were as follows.

Baseline disease characteristics		
	Lamisil	Vehicle
# pts	49	47
Scaling/hyperkeratosis		
None	0	0
Mild	2 (4%)	1 (2%)
Moderate	22 (45%)	22 (47%)
Severe	25 (51%)	24 (51%)
Fissuring		
None	20 (41%)	19 (40%)
Mild	11 (22%)	14 (30%)
Moderate	14 (29%)	11 (23%)
Severe	4 (8%)	3 (6%)
Erythema		
None	2 (4%)	1 (2%)
Mild	12 (24%)	11 (23%)
Moderate	32 (65%)	31 (66%)
Severe	3 (6%)	4 (9%)
Pruritus		
None	3 (6%)	2 (4%)
Mild	7 (14%)	12 (26%)
Moderate	23 (47%)	19 (40%)
Severe	16 (33%)	14 (30%)
Overall severity		
Mild	0	2 (4%)
Moderate	31 (63%)	23 (49%)
Severe	18 (37%)	22 (47%)
Organism		
T.rubrum	47 (96%)	44 (94%)
T. mentagrophytes	1 (2%)	2 (4%)
E. floccosum	1 (2%)	1 (2%)

There were no statistically significant differences between the treatment groups in the severity of the signs and symptoms of the target lesions, the overall disease severity, or in the proportion of patients with T. rubrum infections. Of all patients enrolled, 35 (65%) of the Lamisil group and 43 (78%) of the vehicle group had onychomycosis of the toenails.

2) Patient discontinuations: The reasons for discontinuations were as follows.

Patient discontinuations		
	Lamisil	Vehicle
Negative culture	5	7
Non-compliance	1	0
Lost to followup	1	2
Personal reasons	0	1
Treatment failure	0	3
Illness	1	0
Total	8	13

Only those patients who were lost to followup and those with a negative culture were excluded from the efficacy analysis.

3) Deviations from the protocol: There were a number of missed applications, which did not differ significantly between the treatment groups; no other protocol deviations were reported.

4) Effectiveness parameters.

a. Mycological examinations: The percentages of patients with negative KOH exams and cultures at each return visit and at endpoint were as follows.

Percentage of patients with negative mycology			
	Lamisil (n=49)	Vehicle (n=47)	p value
Week 1	12/48 (25%)	4/46 (9%)	0.053
Week 2	18/47 (38%)	4/45 (9%)	0.001
Week 4	25/46 (54%)	2/45 (4%)	< 0.001
Week 6	30/46 (65%)	2/44 (5%)	< 0.001
Week 8	32/46 (70%)	6/42 (14%)	< 0.001
Endpoint	33/49 (67%)	6/47 (13%)	< 0.001

b. Clinical signs and symptoms: The mean change and the percentage change in scores from baseline at endpoint for the clinical signs and symptoms of the target lesions were as follows.

Clinical signs and symptoms Mean change from baseline			
	Lamisil	Vehicle	p value
Scaling/hyperkeratosis Mean change Percent change	- 1.3 52%	- 0.5 20%	< 0.001
Fissuring Mean change Percent change	- 0.9 90%	- 0.5 50%	0.099
Erythema Mean change Percent change	- 1.2 71%	- 0.4 22%	< 0.001
Pruritus Mean change Percent change	- 1.7 81%	- 0.7 35%	< 0.001
Total signs/symptoms Mean change Percent change	- 5.1 70%	- 2.2 32%	< 0.001

c. Overall disease severity: The overall disease severity at week 2 (the end of treatment), at followup weeks 4, 6, and 8, and at endpoint was as follows.

Overall Disease Severity Week 2			
	Lamisil (n=47)	Vehicle (n=45)	p value
None	1 (2%)	1 (2%)	0.43
Mild	19 (40%)	14 (31%)	
Moderate	22 (47%)	27 (60%)	
Severe	5 (11%)	3 (7%)	

Overall Disease Severity Week 4			
	Lamisil (n=46)	Vehicle (n=45)	p value
None	4 (9%)	1 (2%)	0.037
Mild	17 (37%)	12 (27%)	
Moderate	24 (52%)	29 (64%)	
Severe	1 (2%)	3 (7%)	

Overall Disease Severity Week 6			
	Lamisil (n=46)	Vehicle (n=44)	p value
None	9 (20%)	0	< 0.001
Mild	26 (57%)	13 (30%)	
Moderate	10 (22%)	22 (50%)	
Severe	1 (2%)	9 (20%)	

Overall Disease Severity Week 8			
	Lamisil (n=46)	Vehicle (n=42)	p value
None	11 (24%)	0	< 0.001
Mild	24 (52%)	8 (19%)	
Moderate	10 (22%)	27 (64%)	
Severe	1 (2%)	7 (17%)	

Overall Disease Severity Endpoint			
	Lamisil (n=49)	Vehicle (n=47)	p value
None	11 (22%)	0	< 0.001
Mild	25 (51%)	9 (19%)	
Moderate	12 (24%)	28 (60%)	
Severe	1 (2%)	10 (21%)	

d. Global clinical response: The physician's assessment of the global clinical response at week 2 (the end of treatment), at followup weeks 4, 6, and 8, and at endpoint was as follows.

Global Clinical Response Week 2			
	Lamisil (n=47)	Vehicle (n=45)	p value
Cleared	1 (2%)	1 (2%)	0.053
Marked improvement	9 (19%)	6 (13%)	
Moderate improvement	14 (30%)	7 (16%)	
Slight improvement	16 (34%)	21 (47%)	
No change	7 (15%)	9 (20%)	
Exacerbation	0	1 (2%)	

Global Clinical Response Week 4			
	Lamisil (n=46)	Vehicle (n=45)	p value
Cleared	3 (7%)	1 (2%)	0.001
Marked improvement	15 (33%)	4 (9%)	
Moderate improvement	14 (30%)	12 (27%)	
Slight improvement	8 (17%)	17 (38%)	
No change	5 (11%)	9 (20%)	
Exacerbation	1 (2%)	2 (4%)	

Global Clinical Response Week 6			
	Lamisil (n=46)	Vehicle (n=44)	p value
Cleared	8 (17%)	0	< 0.001
Marked improvement	13 (28%)	6 (14%)	
Moderate improvement	18 (39%)	8 (18%)	
Slight improvement	5 (11%)	16 (36%)	
No change	1 (2%)	11 (25%)	
Exacerbation	1 (2%)	3 (7%)	

Global Clinical Response Week 8			
	Lamisil (n=46)	Vehicle (n=42)	p value
Cleared	11 (24%)	0	< 0.001
Marked improvement	18 (39%)	5 (12%)	
Moderate improvement	11 (24%)	9 (21%)	
Slight improvement	4 (9%)	13 (31%)	
No change	2 (4%)	11 (26%)	
Exacerbation	0	4 (10%)	

Global Clinical Response Endpoint			
	Lamisil (n=49)	Vehicle (n=47)	p value
Cleared	11 (22%)	0	< 0.001
Marked improvement	18 (37%)	5 (11%)	
Moderate improvement	13 (27%)	9 (19%)	
Slight improvement	5 (10%)	16 (34%)	
No change	2 (4%)	12 (26%)	
Exacerbation	0	5 (11%)	

e. Patient assessment: The patient's assessment of the response to treatment at week 2 and at endpoint was as follows.

Patient assessment Week 2			
	Lamisil (n=47)	Vehicle (n=45)	p value
Excellent	4 (9%)	3 (7%)	0.33
Very good	13 (28%)	10 (22%)	
Good	14 (30%)	13 (29%)	
Fair	9 (19%)	10 (22%)	
Poor	7 (15%)	9 (20%)	

Patient assessment Endpoint			
	Lamisil (n=49)	Vehicle (n=47)	p value
Excellent	13 (27%)	5 (11%)	< 0.001
Very good	13 (27%)	5 (11%)	
Good	14 (29%)	9 (19%)	
Fair	8 (16%)	6 (13%)	
Poor	1 (2%)	22 (47%)	

f. Cures of the target area: As described previously, the sponsor considered treatment to be effective if there were a 'complete cure' or a 'mycological cure'. A 'complete cure' was a negative KOH and culture with no residual signs and symptoms, while a 'mycological cure' was a negative KOH and culture with some residual signs and symptoms.

The number and percentage of patients with a 'complete cure', and with a 'complete cure' or 'mycological cure' at week 2 (the end of treatment), at followup weeks 4, 6, and 8, and at endpoint were as follows.

Patients with 'complete cure'			
	Lamisil (n=49)	Vehicle (n=47)	p value
Week 1	0	0	1.00
Week 2	1/47 (2%)	0	1.00
Week 4	4/46 (9%)	0	0.117
Week 6	7/46 (15%)	0	0.012
Week 8	11/46 (24%)	0	0.001
Endpoint	11/49 (22%)	0	0.001

Patients with 'complete cure' or 'mycological cure'			
	Lamisil (n=49)	Vehicle (n=47)	p value
Week 1	1/48 (2%)	0	1.00
Week 2	3/47 (6%)	3/45 (7%)	1.00
Week 4	9/46 (20%)	1/45 (2%)	0.015
Week 6	19/46 (41%)	1/44 (2%)	< 0.001
Week 8	22/46 (48%)	2/42 (5%)	< 0.001
Endpoint	22/49 (45%)	2/47 (4%)	< 0.001

There was no gender by treatment interaction with respect to negative mycology, effective treatment, or total signs and symptoms.

Adverse events were mild burning of the bottom of the feet in one vehicle patient.

The results for Study 2509-02 were as follows.

1) Patient enrollment and demographic characteristics: 122 patients were entered into the study, of which 97 patients were evaluable for efficacy. The demographic characteristics of all patients enrolled were as follows.

Demographic characteristics		
	Lamisil	Vehicle
# pts	61	61
Age (years) Mean Range	42	42
Sex Male Female	50 (82%) 11 (18%)	38 (62%) 23 (38%)
Race Caucasian Black Asian Hispanic	22 (36%) 16 (26%) 1 (2%) 22 (36%)	33 (54%) 11 (18%) 1 (2%) 16 (26%)

The baseline disease characteristics of the evaluable patients were as follows.

Baseline disease characteristics		
	Lamisil	Vehicle
# pts	48	49
Scaling/hyperkeratosis		
None	0	0
Mild	2 (4%)	3 (6%)
Moderate	31 (65%)	29 (59%)
Severe	15 (31%)	17 (35%)
Fissuring		
None	30 (63%)	30 (61%)
Mild	10 (21%)	8 (16%)
Moderate	8 (17%)	8 (16%)
Severe	0	3 (6%)
Erythema		
None	1 (2%)	0
Mild	27 (56%)	23 (47%)
Moderate	19 (40%)	23 (47%)
Severe	1 (2%)	3 (6%)
Pruritus		
None	7 (15%)	13 (27%)
Mild	14 (29%)	7 (14%)
Moderate	14 (29%)	17 (35%)
Severe	13 (27%)	12 (24%)
Overall severity		
Mild	6 (13%)	5 (10%)
Moderate	30 (63%)	26 (53%)
Severe	12 (25%)	18 (37%)
Organism		
T.rubrum	39 (81%)	39 (80%)
T. mentagrophytes	9 (19%)	9 (18%)
E. floccosum	0	1 (2%)

There were no statistically significant differences between the treatment groups in the severity of the signs and symptoms of the target lesions, the overall disease severity, or in the proportion of patients with T. rubrum infections. Of all patients enrolled, 45 (74%) of the Lamisil group and 42 (69%) of the vehicle group had onychomycosis of the toenails.

2) Patient discontinuations: The reasons for discontinuations were as follows.

Patient discontinuations		
	Lamisil	Vehicle
Negative culture	8	9
Non-compliance	0	1
Lost to followup	2	2
Treatment failure	1	1
Total	11	13

Only those patients who were lost to followup and those with a negative culture were excluded from the efficacy analysis.

3) Deviations from the protocol: There were a number of missed applications, which did not differ significantly between the treatment groups; no other protocol deviations were reported.

4) Effectiveness parameters.

a. Mycological examinations: The percentages of patients with negative KOH exams and cultures at each return visit and at endpoint were as follows.

Percentage of patients with negative mycology			
	Lamisil (n=48)	Vehicle (n=49)	p value
Week 1	14/48 (29%)	6/48 (13%)	0.077
Week 2	19/47 (40%)	11/49 (22%)	0.078
Week 4	18/46 (39%)	11/48 (23%)	0.119
Week 6	32/46 (70%)	12/48 (25%)	< 0.001
Week 8	33/46 (72%)	7/48 (15%)	< 0.001
Endpoint	34/48 (71%)	7/49 (14%)	< 0.001

b. Clinical signs and symptoms: The mean change and the percentage change in scores from baseline at endpoint for the clinical signs and symptoms of the target lesions were as follows.

Clinical signs and symptoms Mean change from baseline			
	Lamisil	Vehicle	p value
Scaling/hyperkeratosis Mean change Percent change	- 1.4 61%	- 0.3 13%	< 0.001
Fissuring Mean change Percent change	- 0.4 80%	- 0.3 43%	0.533
Erythema Mean change Percent change	- 0.9 64%	- 0.5 31%	0.038
Pruritus Mean change Percent change	- 1.5 88%	- 0.6 38%	0.001
Total signs/symptoms Mean change Percent change	- 4.1 68%	- 1.7 23%	< 0.001

c. Overall disease severity: The overall disease severity at week 2 (the end of treatment), at followup weeks 4, 6, and 8, and at endpoint was as follows.

Overall Disease Severity Week 2			
	Lamisil (n=47)	Vehicle (n=49)	p value
None	1 (2%)	0	0.001
Mild	28 (60%)	15 (31%)	
Moderate	17 (36%)	27 (55%)	
Severe	1 (2%)	7 (14%)	

Overall Disease Severity Week 4			
	Lamisil (n=46)	Vehicle (n=48)	p value
None	1 (2%)	0	0.003
Mild	25 (54%)	14 (29%)	
Moderate	19 (41%)	27 (56%)	
Severe	1 (2%)	7 (15%)	

Overall Disease Severity Week 6			
	Lamisil (n=46)	Vehicle (n=48)	p value
None	5 (11%)	0	< 0.001
Mild	29 (63%)	16 (33%)	
Moderate	11 (24%)	22 (46%)	
Severe	1 (2%)	10 (21%)	

Overall Disease Severity Week 8			
	Lamisil (n=46)	Vehicle (n=48)	p value
None	12 (26%)	0	< 0.001
Mild	21 (46%)	16 (33%)	
Moderate	13 (28%)	22 (46%)	
Severe	0	10 (21%)	

Overall Disease Severity Endpoint			
	Lamisil (n=48)	Vehicle (n=49)	p value
None	12 (25%)	0	< 0.001
Mild	21 (44%)	16 (33%)	
Moderate	15 (31%)	22 (45%)	
Severe	0	11 (22%)	

d. Global clinical response: The physician's assessment of the global clinical response at week 2 (the end of treatment), at followup weeks 4, 6, and 8, and at endpoint was as follows.

Global Clinical Response Week 2			
	Lamisil (n=47)	Vehicle (n=49)	p value
Cleared	0	0	0.089
Marked improvement	9 (19%)	8 (16%)	
Moderate improvement	14 (30%)	7 (14%)	
Slight improvement	16 (34%)	20 (41%)	
No change	7 (15%)	9 (18%)	
Exacerbation	1 (2%)	5 (10%)	

Global Clinical Response Week 4			
	Lamisil (n=46)	Vehicle (n=48)	p value
Cleared	1 (2%)	0	0.010
Marked improvement	11 (24%)	10 (21%)	
Moderate improvement	9 (20%)	5 (10%)	
Slight improvement	16 (35%)	13 (27%)	
No change	9 (20%)	15 (31%)	
Exacerbation	0	5 (10%)	

Global Clinical Response Week 6			
	Lamisil (n=46)	Vehicle (n=48)	p value
Cleared	5 (11%)	0	< 0.001
Marked improvement	14 (30%)	9 (19%)	
Moderate improvement	11 (24%)	9 (19%)	
Slight improvement	9 (20%)	11 (23%)	
No change	6 (13%)	18 (38%)	
Exacerbation	1 (2%)	1 (2%)	

Global Clinical Response Week 8			
	Lamisil (n=46)	Vehicle (n=48)	p value
Cleared	11 (24%)	0	< 0.001
Marked improvement	17 (37%)	8 (17%)	
Moderate improvement	6 (13%)	4 (8%)	
Slight improvement	8 (17%)	16 (33%)	
No change	4 (9%)	16 (33%)	
Exacerbation	0	4 (8%)	

Global Clinical Response Endpoint			
	Lamisil (n=48)	Vehicle (n=49)	p value
Cleared	11 (23%)	0	< 0.001
Marked improvement	17 (35%)	8 (16%)	
Moderate improvement	6 (13%)	4 (8%)	
Slight improvement	9 (19%)	16 (33%)	
No change	5 (10%)	16 (33%)	
Exacerbation	0	5 (10%)	

e. Patient assessment: The patient's assessment of the response to treatment at week 2 and at endpoint was as follows.

Patient assessment Week 2			
	Lamisil (n=47)	Vehicle (n=49)	p value
Excellent	1 (2%)	3 (6%)	0.007
Very good	17 (36%)	11 (22%)	
Good	20 (43%)	11 (22%)	
Fair	7 (15%)	12 (24%)	
Poor	2 (4%)	12 (24%)	

Patient assessment Endpoint			
	Lamisil (n=48)	Vehicle (n=49)	p value
Excellent	14 (29%)	4 (8%)	< 0.001
Very good	13 (27%)	11 (22%)	
Good	11 (23%)	5 (10%)	
Fair	6 (13%)	12 (24%)	
Poor	4 (8%)	17 (35%)	

f. Cures of the target area: As described previously, the sponsor considered treatment to be effective if there were a 'complete cure' or a 'mycological cure'. A 'complete cure' was a negative KOH and culture with no residual signs and symptoms, while a 'mycological cure' was a negative KOH and culture with some residual signs and symptoms.

The number and percentage of patients with a 'complete cure', and with a 'complete cure' or 'mycological cure' at week 2 (the end of treatment), at followup weeks 4, 6, and 8, and at endpoint were as follows.

Patients with 'complete cure'			
	Lamisil (n=48)	Vehicle (n=49)	p value
Week 1	0/48	0/48	-
Week 2	1/47 (2%)	0/49	0.49
Week 4	0/46	0/48	-
Week 6	4/46 (9%)	0/48	0.054
Week 8	15/46 (33%)	0/48	<0.001
Endpoint	15/48 (31%)	0/49	<0.001

Patients with 'complete cure' or 'mycological cure'			
	Lamisil (n=48)	Vehicle (n=49)	p value
Week 1	2/48 (4%)	0/48	0.495
Week 2	6/47 (13%)	1/49 (2%)	0.057
Week 4	11/46 (24%)	4/48 (8%)	0.050
Week 6	22/46 (48%)	5/48 (10%)	< 0.001
Week 8	30/46 (65%)	3/48 (6%)	< 0.001
Endpoint	30/48 (63%)	3/49 (6%)	< 0.001

In an analysis of the results by gender, there was found to be a gender by treatment effect with respect to negative mycology results at week 2 and at endpoint, and treatment effectiveness at endpoint. Effectiveness was greater in the male patients than in the females; it was felt that this was probably due to the gender

imbalance of the study population. There was no gender by treatment interaction with respect to total signs and symptoms.

Adverse events were reported in six patients, of which four were in the Lamisil group and two were in the vehicle group. These included one case each of the following in the Lamisil group: mild increased pigmentation of the bottom of the feet, mild irritation, mild pruritus and burning, and mild tingling. In the vehicle group there was mild to moderate extension of the fungal infection in one, and mild itching in one.

Labeling review

The labeling indication has been revised as follows, with the underlined portion added:

Other revisions have been made in the ADVERSE REACTIONS section, and in the CLINICAL STUDIES section in the description of mean clinical scores at entry, and in the tabulation of results for tinea pedis of the interdigital type and for tinea corporis/cruris.

Reviewer's evaluation: The heading of the second paragraph under CLINICAL STUDIES, entitled should be changed to to distinguish the data in this section from those in the section on tinea pedis of the mocassin type.

The tabulation of clinical results for each of the three indications should include only the cure rate (clinical and mycological). Neither the negative mycology alone nor the rate of should be displayed.

The tabulation of the results for tinea pedis of the interdigital type after 4 weeks of therapy should have a positive control rather than the vehicle stated.

Under the results of the clinical studies on tinea pedis of the mocassin type, it would be desirable to include a statement that improvement is gradual, and that maximum improvement has been shown to occur during the six weeks after discontinuation of treatment. This is apparent on examination of the tabulation under CLINICAL STUDIES, but it is recommended that this also be included in the narrative portion of the description of clinical results.

It is felt that the proposed labeling revisions are otherwise acceptable.

Summary and evaluation

The sponsor has submitted two clinical studies in support of the effectiveness of Lamisil cream when applied BID for two weeks in the treatment of plantar tinea pedis (mocassin type). Both studies were multicenter, double blind, parallel group comparisons of Lamisil cream with the cream vehicle, conducted under an identical protocol. After the two week treatment period, the patients were followed for an additional six weeks.

The effectiveness parameters were mycological examinations (KOH and culture), grading of clinical signs and symptoms, physician's rating of the overall disease severity and clinical response, and the patient's evaluation of the response to treatment.

With the exception of the effect on fissuring, there was found in both studies a highly significant superiority of Lamisil cream over the vehicle at endpoint and at week six of the followup period in all of the other effectiveness parameters. The differences between Lamisil and the vehicle were generally not significant or were marginally significant at week 2 (the end of treatment), but became increasingly more significant throughout the six week followup period. There was also a significant superiority of Lamisil over the vehicle in the percentage of patients with a complete cure, i.e., a negative KOH and culture with no residual signs and symptoms, and in the percentage of patients with a 'mycological cure', defined as a negative KOH and culture with mild residual signs and symptoms.

It is felt that these studies provide an adequate demonstration of the effectiveness of Lamisil cream in the treatment of plantar tinea pedis of the mocassin type. Certain labeling revisions are recommended, as stated under the labeling review.

Recommendations: With the specified labeling revisions, it is recommended that this supplement for the treatment of plantar tinea pedis (mocassin type) with BID applications of Lamisil cream for two weeks be approved.

Phyllis A. Huene, M.D.

Phyllis A. Huene, M.D.

cc: Orig NDA
HFD-340
HFD-520
HFD-520/MO/PHuene
HFD-520/Pharm/
HFD-520/Chem/
HFD-520/CSO/RCook

WAC 1/27/94
JAO 3/22/94

12

Medical Officer's Review of NDA 20-192/S-003
Amendment to Supplement 3

NDA #20-192

Submission: 8/ 2/95
Review completed: 10/ 9/95

Generic name: Terbinafine hydrochloride cream
Proposed trade name: Lamisil Cream 1%

Sponsor:
Sandoz Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080
201-503-7500

Pharmacologic Category: Anti-fungal

Proposed Indication(s): Treatment of plantar tinea pedis (moccasin type)

Dosage Form(s) and Route(s) of Administration: Topical cream

Related Reviews:
MOR (Huene) dated: 12/13/93
MOR (Huene) dated: 4/26/95

Background: Supplement 3 (to add the indication for treatment of plantar tinea pedis, moccasin type) was submitted on 9/28/93. An approvable letter was issued on 9/27/94. Additional correspondence was submitted on 11/29/94, 2/24/95, 3/8/95, 7/10/95 and 8/2/95 (current submission).

Submitted: Revised labeling

Labeling:

Description unchanged

Reviewer's Comments: *No objection.*

Clinical Pharmacology
- Pharmacokinetics — unchanged
- Microbiology — unchanged

Reviewer's Comments: *No objection.*

Indications and Usage — The following has been added to the end of the current section:

Reviewer's Comments: *No objection.*

Contraindications — unchanged

Reviewer's Comments: *No objection.*

Warnings — unchanged

Reviewer's Comments: *No objection.*

Precautions
- General — unchanged
- Information for patients — unchanged
- Drug interactions — unchanged
- Carcinogenesis, mutagenesis, impairment of fertility — unchanged
- Pregnancy — unchanged
- Nursing mothers — unchanged

Reviewer's Comments: *No objection.*

Precautions

Pediatric use — unchanged

Reviewer's Comments: *The section should be revised to reflect changes published in the Federal Register in December 1994. The section should now read:*

> *"Safety and efficacy in pediatric patients below the age of 12 years have not been established."*

Adverse Reactions — This section has been revised to read:

Reviewer's Comments: *The section contains errors in the calculated percentages. Six of 2379 is 0.3%, not 0.2%. Fifty-six of 2379 is 2.4%, not 2.3%. A list of the verbatim terms should be provided so that the percentages of the other reactions can be verified.*

Overdosage — unchanged

Reviewer's Comments: *No objection*

Dosage and Administration — The following paragraph has been added to the section:

Reviewer's Comments: *The term "Type" should not be capitalized.*

Dosage and Administration (continued)

The "Note" in this section has been revised to read:

Reviewer's Comments: *No objection.*

How Supplied

The section has been revised to read:

Reviewer's Comments: *The degree symbol (°) has been left out following 5, 30, 41 and 86.*

Clinical Studies

This section has been revised to read:

Clinical Studies (continued)

Reviewer's Comments:

The text and/or table contains multiple of factual and typographical errors including:

1. *The numbers and percentages reflect patients with total clinical score of The table should be revised to reflect the text.*
2. *The division (/) symbols are missing.*
3. *The number should be*
4. *The term should be*
5. *A closed parentheses is missing following*
6. *The table is referred to as both and in the text.*

B. Tinea Corporis/Cruris

Reviewer's Comments: *Same issues as Table A.*

C. Plantar Tinea Pedis (Moccasin Type)

Two studies of Lamisil Cream, 1% (terbinafine hydrochloride cream) used in the treatment of plantar tinea pedis (moccasin type), were vehicle-controlled (placebo) evaluations of 2 weeks treatment duration (B.I.D.).

In the following table, patients are categorized according to whether or not they had associated toenail onychomycosis.

Associated Disease	Therapy	SUCCESSFUL OUTCOMES	
		At 2 wks (end of Rx)	**At 8 wks (6 wk f/up)**
Without Onychomycosis	Lamisil	23% (3%)* 7/30	65% (29%) 20/31
	Vehicle	12% (4%) 3/25	15% (0%) 4/26
With Onychomycosis	Lamisil	3% (2%) 2/64	48% (21%) 32/66
	Vehicle	1% (0%) 1/69	1% (0%) 1/70

Due to the severity of plantar tinea pedis, the thickness of the plantar skin, and/or differences in the rate of healing, some patients may still have mild residual signs and symptoms at week 8 in spite of negative mycology (KOH and culture). *The % of patients with complete eradication of signs and symptoms is given in parentheses.

Reviewer's Comments: *The numbers and percentages appear to reflect patients with total clinical score of The table should be revised to reflect the text.*

Conclusions: The labeling is not acceptable as submitted because it contains typographical and factual errors.

Recommendations: It is recommended that the labeling be revised as identified in this review.

MD
Wiley A. Chambers, M.D.
Supervisory Medical Officer

cc: NDA 20-192
HFD-540
HFD-340
HFD-540/CSO/Cross
HFD-540/CHEM/Higgins
HFD-540/PHARM/Mainigi
HFD-540/MO/Huene
HFD-540/SMO/Chambers

10/12/95

MEDICAL OFFICER'S REVIEW OF SUPPLEMENT AMENDMENT TO NDA 20-192
S-003

September 13, 1996

SPONSOR: Sandoz Pharmaceuticals
East Hanover, New Jersey

DRUG: Lamisil (terbinafine HCl) Cream, 1%

PROPOSED CLINICAL INDICATION: Plantar tinea pedis (moccasin type)

DATE OF SUPPLEMENT AMENDMENT: July 31, 1996

The submission of July 31, 1996 is in response to the approvable letter of July 25, 1996, which requested that certain revisions in the labeling be made. Revised draft labeling in accordance with these requests has been provided.

In the following review of each request and the response provided, the item numbers listed are those in the approvable letter.

1. The requested statement has been added to the Pediatric Use subsection of the PRECAUTIONS SECTION.

2.A. The first sentence of the ADVERSE REACTIONS section has been revised as requested.

2.B. A list of the verbatim terms for the adverse reactions has been provided. These are the same terms as are listed in the ADVERSE REACTIONS section. This request has thus been satisfied.

3. The typographical error in the DOSAGE AND ADMINISTRATION section has been corrected.

4. The approvable letter requested that the product name in the HOW SUPPLIED section should read "Lamisil Cream (terbinafine hydrochloride) 1%". The sponsor states in their facsimile of August 6, 1996, that in the original approvable letter of 12/30/92, they were specifically advised that the product name should appear as Lamisil Cream 1% (terbinafine hydrochloride), and so they continue to represent it in this way in the currently revised labeling.

According to our current policy the product name should either read "Lamisil Cream (terbinafine hydrochloride) 1%," or "Lamisil ~~Cream~~ (terbinafine hydrochloride cream) 1%". The sponsor therefore needs to revise this in the labeling.

5. Items 5.a. through 5.f. concern a number of typographical and factual errors in the text and tables in the CLINICAL STUDIES section; these have been corrected in accordance with our requests. However, as the sponsor points out in the facsimile of 8/6/96, our request to modify the tables to reflect the text is inconsistent with another statement made in the letter. In fact, this appears to be our error, and the statement in the approvable letter should have actually requested that the text be revised to reflect the table.

   The tabulations have been revised as requested.

   There are two additional minor typographical errors which were not noted in the approvable letter. These are a misspelling of the word 'onychomycosis' in the table on plantar tinea pedis, mocassin type, and the phrase 'at 1 wks' in the tabulation on tinea corporis/cruris.

The submission also provides a final safety update. There have been no additional clinical safety data either with the marketed product or from ongoing clinical trials which alter the safety profile of the drug from that at the time of the initial approval for other indications.

Evaluation: Except for the presentation of the product name, the labeling has been adequately revised in accordance with the requests in the approvable letter of July 25, 1996. The product name needs to be revised as stated under item 4. above. Two minor typographical errors can be corrected in the final printed labeling. The safety update has been provided; there are no new data which would change the safety profile of the drug.

Recommendations: With the labeling revisions described above, it is recommended that this supplemental application for the use of Lamisil Cream, 1% be approved for the indication plantar tinea pedis, mocassin type.

Phyllis A. Huene, M.D.

Phyllis A. Huene, M.D.

cc: Orig NDA
HFD-540
HFD-540/Huene
HFD-540/Cross
HFD-540/Jacobs
HFD-540/DeCamp

9/25/96

As above. Corrections with regard to the placement of "cream" has been hand-written into this review. The sponsor will need to notify the Agency of their preference with regard to item #4 above.

HFD-540
Ms. Cook

Statistical Review and Evaluation
Supplement

NDA:	20-192/1S
Applicant:	Sandoz Pharmaceuticals Corporation
Name of Drug:	Lamisil® (terbinafine hydrochloride) Cream, 0.1%
Documents Reviewed:	Volumes 1, 7-9, 12, 19 and 20 dated September, 1993
Indication:	Plantar Tinea Pedis (moccasin type)
Clinical Reviewer:	Dr. Huene, HFD-540

A. Introduction The sponsor has submitted results of two placebo-controlled studies, Study 2509-01 and Study 2509-02, evaluating the efficacy and safety of Lamisil 1% applied twice daily for two weeks in the treatment of tinea pedis, plantar lesions (moccasin type). In the following sections, I will present a synopsis of sponsor's results and conclusions followed by my review and conclusions.

B. Review of Studies

1. Study 2509-01

a. Study Design

This was a five center, double-blind, randomized, parallel-group study of the use of 1% Lamisil cream twice daily compared to its vehicle cream twice daily. The course of treatment was for two weeks with evaluation at the end of one week and two weeks. Follow-up evaluations occurred at Weeks 4, 6, and 8. The purpose of the follow-up period was to estimate the duration of clearing of the target lesions.

Patients were included in the study if:

a. they were patients with tinea pedis, plantar lesions (moccasin type) defined as lesions on the plantar surface of the foot, which includes at lease a score of 2 for scaling/hyperkeratosis, and one or more of the following to make a total score of 4;fissuring, erythema and pruritus. At least one third of the plantar surface of the foot should be involved.

b. they were patients with a clinical diagnosis of tinea pedis, plantar lesions (moccasin type) which has been provisionally confirmed by a KOH wet mount positive for dermatophyte and diagnosis confirmed by a culture positive for dermatophyte at the baseline visit. (A negative result was to exclude the patient from the study).

Patients were excluded from the study if:

a. they had received topical antibiotic, anthelmintic, anti-fungal or antiflammatory therapy within two weeks prior to entry into the study.

b. they had concomitant yeast infections or bacterial infections which are systemic or localized to the foot.

d. "Delayed Exclusion": If the culture taken at baseline proves to be negative (no later than 3 weeks) for dermatophyte or shows evidence of a significant concomitant yeast or bacterial infection, the patient will be withdrawn from the study.

b. Criteria for efficacy and safety:

Negative Mycology: both KOH and culture negative for target area.

Clinical Signs and Symptoms of Target Area

Signs: erythema, scaling/hyperkeratosis, fissuring
Symptoms: pruritus

The scoring system ranged from 0-3, where 0 = none, 1 = mild, 2 = moderate, and 3 = severe. The total score of the clinical signs and symptoms of the target area had to be "4" in order for the patient to enter the study.

Overall Disease Severity

The overall severity of all affected areas on both feet was assessed according to a scoring system ranging from 0-3, where 0 = none, 1 = mild, 2 = moderate,a nd 3 = severe.

Patient's Assessment of Responsiveness

The patient was asked to rate the overall response to treatment on a scale of 0-4, where 0 = poor, 1 = fair, 2 = good, 3 = very good, and 4 = excellent.

Physician's Assessment of Global Clinical Response

The investigator rated the global clinical response to treatment of all affected areas on both feet using a scale of 1-6, where: 1 = cleared, 2 = marked improvement, 3 = moderate improvement, 3 = moderate improvement, 4 = slight improvement, 5 = no change, and 6 = exacerbation.

Effective treatment

Effective treatment was defined as either a complete cure or the mycological cure of the target area.

Complete Cure:
KOH and Culture were negative with no residual signs and symptoms.

Mycological Cure:
Both KOH and culture negative, with some residual signs and/or symptoms (total score of ≤ 2 based on all four observed: erythema, scaling/hyperkeratosis, pruritus and fissuring, but with individual scores for erythema and/or scaling and/or pruritus ≤ 1).

Criteria for Safety

Patients were asked to rate the tolerability of the treatment on a scale of 0-4, where 0=poor, 1=fair, 2=good, 3=very good, 4=excellent. In addition, all adverse events were documented.

The efficacy analysis was based on all efficacy evaluable patients admitted to the study. A patient was considered evaluable if they had a positive KOH and culture at baseline and returned for at least one visit. The primary efficacy variables are, **negative mycology and reduction in signs and symptoms.**

c. Study population and demographics

One hundred nine patients were admitted to the study, 54 (49.5%) to Lamisil and 55 (50.5%) to the vehicle group. There were 96 efficacy evaluable patients in total, 49 in the Lamisil group and 47 in the vehicle group. Three were lost to follow-up cases and of those three, one had no visit after enrollment. Twelve others did not meet the entry criteria, and of those twelve, one had no follow-up after baseline as well. Three of the five centers fell slightly short of the minimum goal of 20 patients enrolled per center (Centers 10, 20 and 25)

There are statistically no significant differences in age, sex, race, height or weight between the treatment groups ($p>0.05$). There were statistically no significant differences in history of tinea pedis, plantar lesions (moccasin type) between the groups ($p>0.05$). There were no significant differences in medical history ($p>0.05$). Treatment groups were balanced at baseline with respect to signs and symptoms, overall disease severity, and distribution of overall disease severity scores ($p>0.05$). 65% of Lamisil-treated patients and 78% of vehicle-treated patients had associated toenail onychomycosis; the average

percent of the nail surface area affected was 19% ± 2.8 and 21% ± 2.5, respectively, for the two groups. No significant differences among the groups were noted with respect to the number of missed applications ($p>0.05$) nor changes in concomitant medications ($p>0.05$).

d. Efficacy evaluation (by the sponsor and checked by the reviewer)

1. Negative mycology of the target area

Relative to negative mycology, the differences between Lamisil and Vehicle are statistically significant at Weeks 2 (18/47=38% vs. 4/45=9% $p=0.001$) 4 (25/46=54% vs. 2/45=4%; $p<0.001$), 6 (30/46=65% vs 2/44=5%;$p<0.001$)and 8 (32/46=70% vs, 6/42=14%; $p<0.001$), and at End Point (33/49=67% vs. 6/47=13%; $p<0.001$).

2. Evaluation of Clinical Signs and Symptoms of the Target Area

Four different clinical signs and symptoms were evaluated at each visit: scaling/hyperkeratosis, fissuring, erythema and pruritus. In tinea pedis, plantar lesions (moccasin type), these signs and symptoms usually take longer to disappear than int he interdigital (athlete's foot) type. The differences between Lamisil and vehicle in percent reduction from baseline in total score of signs and symptoms were statistically significant at Weeks 4 (54% vs. 37%; $p=0.002$), 6 (66% vs. 32%; $p<0.001$), 8 (72% vs. 34%; $p<0.001$), and at End Point (70% vs 32%; $p<0.001$).

Significant differences of the mean change from baseline between treatments in favor of Lamisil were noted for the individual symptoms of scaling/hyperkeratosis (-1.4 vs. -0.6; $p<0.001$), erythema (-1.3 vs. -0.5; $p<0.001$) and pruritus (-1.7 vs. -0.7; $p<0.001$) at Week 8. At End Point, significant differences favoring Lamisil over vehicle were noted for scaling/hyperkeratosis (-1.3 vs. -0.5; $p<0.001$), erythema (-1.2 vs. -0.4; $p<0.001$) and pruritus -1.7 vs. 0.7; $p<0.001$).

No treatment by center interaction was noted with respect to total signs and symptoms.

3. Overall Disease Severity of All Affected Areas on Both Feet

Lamisil patients had a significantly better response than vehicle patients with respect to overall disease severity at Weeks 6 and 8, and End Point ($p<0.001$). At End Point, the percentage of Lamisil-treated patients with moderate to severe disease had decreased from 100% to 26% compared to a reduction from 96% to 81% for vehicle.

4. Patient's Assessment of Responsiveness

The patient's assessments for response to treatment for the Lamisil group were significantly better t Weeks 4 ($p=0.005$), 6, and 8, and End Point ($p<0.001$ for all three time points). At Week 2, 37% of the Lamisil patients gave a very good or excellent assessment as compared to 29% of the vehicle patients. At Week 8 and End Point, the corresponding percents were 52 vs,. 22, and 54 vs. 22 respectively.

without onychomycosis compared to 67% of those with onychomycosis. It is noted that although the absolute response of the onychomycosis patients is lower, there is also a lower response to vehicle in this group and thus, the statistical comparisons between Lamisil and Vehicle for the patients with onychomycosis retain the same high degree of statistical significance ($p<0.001$) as seen in the total population. Possibly due to the smaller number of patients without onychomycosis, the difference between Lamisil and vehicle at Study End Point was not as highly statistically significant for treatment effectiveness ($p=0.016$) and negative mycology ($p=0.020$). At the Study End Point, the comparisons between Lamisil and vehicle for reduction of Total Score of Signs and Symptoms was highly significant ($p<0.001$) for patients with onychomycosis, patients without onychomycosis, and total patients.

9. Efficacy analysis by gender

In this study, 38 of the 49 efficacy evaluable Lamisil-treated patients (78%) and 38 of the 47 efficacy evaluable vehicle treated patients (81%) were male. No gender by treatment interaction was noted with respect to negative mycology, effective treatment or total signs and symptoms.

e. Safety analysis (by the sponsor and checked by the reviewer)

Four of the 107 safety evaluable patients (4%) reported adverse events, two in each group. However, only one of these patients reported an adverse event that was possibly related to the test medication. This was a vehicle treated patient who reported mild burning on the bottom of the feet.

No differences ($p=0.362$) in the two groups were noted with respect to tolerability (as rated by the patients) at the end of treatment (Week 2). Eighty-five percent of the Lamisil group indicated that tolerability was either excellent or very good as compared to 84% for the vehicle group.

f. Conclusions: This study shows that Lamisil 1% cream is statistically better than vehicle in treating tinea pedis, plantar lesions (moccasin type) when applied twice daily for two weeks. In this study, 70% of the Lamisil treated patients had a **negative mycology** at the end of the study compared to only 14% for vehicle ($p<0.001$).

The differences between Lamisil and vehicle in **percent reduction from baseline in total score of signs and symptoms** is statistically significant at Week 8 (end of study) (72% vs 34%; $p<0.001$).

The secondary variables, **Overall severity of all affected areas on both feet, Patient's assessment of responsiveness, Physician's assessment of clinical response** are supportive of the sponsor's claim.

Disease severity improved by End Point, with the percentage of Lamisil-treated patients with moderate-severe disease decreasing from 100% to 26% compared to a reduction from 96%to 81 %for vehicle ($p<0.001$).

No differences ($p=0.362$) in the two groups were noted with respect to tolerability (as rated by the patients) at the end of treatment (Week 2). Eighty-five percent of the Lamisil group indicated that tolerability was either excellent or very good compared to 84%for the vehicle group. No patients discontinued because of an adverse event.

2. Study 2509-2

The study design, dosage regimen, inclusion and exclusion criteria, efficacy criteria, and the statistical methods are the same as in the Study 2509-2.

a. Study population and demographics

One hundred twenty two patients were admitted to the study, 61 (50%) to Lamisil and 61 (50%) to the vehicle group. Five patients were erroneously assigned the wrong drug. One (Pt. received tubes of vehicle instead of Lamisil. Four others (Pts. received tubes of both vehicle and Lamisil. The latter four were deleted from the efficacy analysis, but assumed to have used only active for the safety analysis. The other patient was analyzed as a vehicle patient. There were 97 efficacy evaluable patients in total, 48 in the Lamisil group and 49 in the vehicle group. Four were lost to follow-up cases and of those four, three had no visit after enrollment. One non-compliant patient had no follow-up and 17 other did not meet the entry criteria.

There were not significant differences in age, sex, race, height or weight between the groups ($p>0.05$). There were no significant differences in history of tinea pedis, planter lesions (moccasin type) ($p>0.05$). There were no significant differences in medical history between the two groups ($p>0.05$). The treatment groups were balanced with respect to signs and symptoms, overall disease severity and distribution of overall disease severity scores ($p>0.05$). Disease was categorized as moderate or severe in all but six of the 48 Lamisil-treated patients and 69% of vehicle-treated patients had associated toenail onychomycosis; the average percent of the nail surface area affected was $29\% \pm 3.1$ and $24\% \pm 2.4$, respectively, for the two groups. Baseline mycological findings were statistically similar ($p>0.05$).

b. Efficacy evaluation (by the sponsor and checked by the reviewer)

1. Negative mycology of the target area

The differences between Lamisil and Vehicle are statistically significant at Weeks 6 (32/46 =70% vs 12/48=25%;$p<0.001$), 8 30/46=72% vs 7/48=15%; $p<0.001$), and at End Point (34/48=71% vs 7/49=14%; $p<0.001$).

2. Evaluation of clinical signs and symptoms of the target area

Four different clinical signs and symptoms were evaluated at each visit: scaling/hyperkeratosis, fissuring, erythema and pruritus. In tinea pedis, plantar lesions (moccasin type), these signs and symptoms usually take longer to disappear than in the interdigital (athlete's foot). The differences between Lamisil and vehicle in percent

reduction from baseline in total score of signs and symptoms were statistically significant at Weeks 2 (48% vs 29%; $p=0.002$), 4 (47% vs 28%; $p=0.010$), 6 (59% vs 32%; $p<0.001$) 8, (71% vs 24%; $p<0.001$), and at End Point (68% vs 23%; $p<0.001$).

Significant differences of the mean change from baseline between treatments in favor of Lamisil were noted for the individual symptoms of scaling/hyperkeratosis (-0.9 vs -0.6; $p=0.047$) and pruritus (-1.3 vs -0.8; $p=0.026$) at the end of treatment (Week 2). At End Point, significant differences favoring Lamisil over vehicle were noted for scaling/hyperkeratosis (-1.4 vs -0.3; $p<0.001$), erythema (-0.9 vs -0.5; $p=0.038$) and pruritus (-1.5 va -0.6; $p<0.001$).

No treatment by center interaction was noted with respect to total signs and symptoms.

3. Overall disease severity of all affected areas on feet

Lamisil patients had a significantly better response than vehicle patients with respect to overall disease severity at Weeks 2, 4, 6 and 8, and End Point ($p<0.001$). At End Point, the percentage of Lamisil-treated patients with moderate to severe disease had decreased from 88% to 31% compared to a reduction from 90% to 67% vehicle.

4. Patient's assessment of responsiveness

The patient's assessments for response to treatment for the Lamisil group were significantly better at Weeks 2,4,6, and 8, End Point ($p<0.001$). At Week 2, 38% of the Lamisil patients gave a very good or excellent assessment as compared to 28% of the vehicle patients. At Week 8 and End Point, the corresponding percents were 58 vs 31, and 56 vs 30, respectively ($p<0.001$).

5. Physician's assessment of global clinical response

Significant differences favoring Lamisil over vehicle were noted at Weeks 4, 6, 8 and End Point. At Week 8, 61% of the Lamisil patients were evaluated as either cleared or marked improvement as compared to 17% of the vehicle patients, and at End Point, the percents were 58 and 16, respectively.

6. Effective treatment of target area

Effective treatment is defined as in the Study 1509-01. Significant differences in effectiveness were noted between the treatments at Weeks 4, 6 and 8 and at End Point. At the Week 8 visit, 65% of the Lamisil group were effectively treated as compared to six percent for vehicle $p<0.001$). In the Lamisil-treated group, the percentage of patients effectively treated increased steadily over time (4% at 1 week, 13% at 2 weeks, 24%4 weeks, 48% at 6 weeks, and 65% at 8 weeks). The differences between Lamisil and vehicle were statistically significant at Weeks 4 ($p=0.05$), 6 ($p<0.001$) and 8 ($p<0.001$), and at End Point ($p<0.001$).

No treatment by center interaction was noted with respect to negative mycology and effective treatment.

7. Efficacy analysis by presence or absence of Onychomycosis

In this study, 33 of the 48 efficacy evaluable Lamisil-treated patients (69%) and 35 of the 49 efficacy evaluable vehicle treated patients (71%) were diagnosed as having onychomycosis of the toenails concurrently with the tinea pedis, plantar lesions (moccasin type). This was a subjective diagnosis by the investigator and was not confirmed by either KOH or culture of the toenail(s). At the study End Point, 73% of the Lamisil-treated patients without onychomycosis were effectively treated compared to only 58% of the Lamisil-treated patients with onychomycosis. The percentage of Lamisil-treated patients with negative mycology at study End Point was 87% of those without onychomycosis compared to 64% of those with onychomycosis compared to 67% of those with onychomycosis. At the Study End Point, the comparisons between Lamisil and vehicle for treatment effectiveness and negative mycology were highly significant for patients with onychomycosis ($p<0.001$ for both), patients without onychomycosis ($p=0.009$ and $p=0.008$, respectively), and total patients ($p<0.001$ for both).

8. Efficacy analysis by gender:

In this study, 39 of the 48 efficacy evaluable Lamisil-treated patients (81%) and 30 of the 49 efficacy evaluable vehicle treated patients (61%) were male. Gender by treatment effect was noted with respect to negative mycology results (at Week 2, and End Point) and treatment effectiveness (at End Point). Male patients had higher efficacy for Lamisil 1% cream than female patients. This is likely due to the gender imbalance of the study population. No gender by treatment interaction was noted with respect to total signs and symptoms.

c. Safety analysis (by the sponsor and checked by the reviewer)

A total of 35 of the 118 safety evaluable patients admitted to this study (30%) reported adverse event, 15 in Lamisil-treated group (25%) and 20 in the vehicle group (34%). However, only 6 of these 35 patients (17%) reported adverse events that were possibly or probably related to the test medication. Of these 6 patients, 4 were in Lamisil treated group (67%) and 2 were in the vehicle group (33%).

No differences ($p=0.652$) in the two treatment groups were noted with respect to tolerability (as rated by the patients) at the end of treatment (Week 2). 85% of the Lamisil group indicated that tolerability was either excellent or very good as compared to 81% for the vehicle group. No patients discontinued because of an adverse event.

d. Conclusions

This study shows that Lamisil 1% cream is statistically better than vehicle in treating tinea pedis, plantar lesions (moccasin type) when applied twice daily for two weeks. In this study, 72% of the Lamisil treated patients had a **negative mycology** at the end of the study compared to only 15% for vehicle ($p<0.001$).

The differences between Lamisil and vehicle in **percent reduction from baseline in total score of signs and symptoms** is statistically significant at Week 8 (end of study) (71% vs 24%; $p<0.001$).

Disease severity improved by End Point, with the percentage of Lamisil-treated patients with moderate-severe disease decreasing from 88% to 31% compared to a reduction from 90% to 67% for vehicle ($p<0.001$).

The secondary variables, **Overall severity of all affected areas on both feet, Patient's assessment of responsiveness, Physician's assessment of clinical response** are supportive of the sponsor's claim.

No differences ($p=0.652$) in the two groups were noted with respect to tolerability (as rated by the patients) at the end of treatment (Week 2). Eighty-five percent of the Lamisil group indicated that tolerability was either excellent or very good compared to 81% for the vehicle group. No patients discontinued because of an adverse event.

C. Overall conclusions (which may be conveyed to the sponsor)

Study 2509-1 provides statistical support to the sponsor's claim that Lamisil 1% cream is effective in the treatment of tinea pedis, plantar lesions (moccasin type) when applied twice daily for two weeks. In this study, 70% of the Lamisil treated patients had a **negative mycology** at the end of the study compared to only 14% for vehicle ($p<0.001$).

The differences between Lamisil and vehicle in **percent reduction from baseline in total score of signs and symptoms** is statistically significant at Week 8 (end of study) (72% vs 34%; $p<0.001$).

The secondary variables, **Overall severity of all affected areas on both feet, Patient's assessment of responsiveness, Physician's assessment of global clinical response,** are supportive of sponsor's claim.

No differences ($p=0.362$) in the two groups were noted with respect to tolerability (as rated by the patients) at the end of treatment (Week 2). Eighty-five percent of the Lamisil group indicated that tolerability was either excellent or very good as compared to 84% for the vehicle group.

Study 2509-2 provides statistical support to the sponsor's claim that Lamisil 1% cream is effective in the treatment of tinea pedis, plantar lesions (moccasin type) when applied twice daily for two weeks. In this study, 72% of the Lamisil treated patients had a **negative mycology** at the end of the study compared to only 15% for vehicle ($p<0.001$).

The secondary variables, **Overall severity of all affected areas on both feet, Patient's assessment of responsiveness, Physician's assessment of global clinical response,** are supportive of sponsor's claim.

No differences (p=0.652) in the two groups were noted with respect to tolerability (as rated by the patients) at the end of treatment (Week 2). Eighty-five percent of the Lamisil group indicated that tolerability was either excellent or very good as compared to 81% for the vehicle group.

Thus, these two placebo-controlled studies provide statistical support to the sponsor's claim that Lamisil 1% cream is effective and safe in the treatment of tinea pedis, plantar lesions (moccasin type).

R.Srinivasan, Ph.D
Mathematical Statistician, Group 7

Concur: Dr.Ralph Harkins Ralph Harkins, PhD 5/4/94

Dr.Satya Dubey 5-6-94

cc:
Orig. NDA 20-192

HFD-540
HFD-540/Ms. Cook
HFD-540/Dr. Wilkin
HFD-540/Dr. Chambers
HFD-540/Dr. Huene
HFD-713/Dr. Dubey [File: DRU 1.3.2]
HFD-713/Dr. Harkins
HFD-713/Dr. Srinivasan
HFD-344/Dr. Lisook

Chron.
This ***review contains 11 pages***
Srinivasan/05/03/94/X4710/WPTEXT/C:\reviews.nda\lamisil.sup

SANDOZ PHARMACEUTICALS CORPORATION
59 ROUTE 10, EAST HANOVER, NEW JERSEY 07936-1080

SANDOZ

DRUG REGISTRATION & REGULATORY AFFAIRS

TEL 201 503 7500
FAX 201 503 6325

October 10, 1996

Jonathan Wilkin, MD
Director
Division of Dermatologic and Dental
Drug Products/HFD-540
Office of Drug Evaluation V
Att: Document Control Room 12B-30
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20657

NDA 20-192/S-003

LAMISIL®
(terbinafine hydrochloride cream) Cream, 1%

REVISED FINAL DRAFT LABELING

FINAL SAFETY UPDATE

Dear Dr. Wilkin:

Reference is made to our Supplemental New Drug Application for Lamisil Cream , 1%, NDA 20-192/S003 which was submitted on September 28, 1993. This supplemental application provides for the addition of plantar tinea pedis (mocassin type) to the INDICATIONS AND USAGE section, as well as other associated changes, in the Lamisil Cream, 1% labeling. Reference is also made to my October 8, 1996 telephone discussion with Mr. Frank Cross of your division during which Mr. Cross requested that the following modifications be incorporated into the revised draft labeling for this supplemental application:

1. Revise the drug name as follows:

   FROM:

   TO: Lamisil (terbinafine hydrochloride cream) Cream, 1%

2. Under CLINICAL STUDIES, B. Tinea Corporis/Cruris, correct table as follows:

   FROM:

   TO: at 1 wk

3. Under CLINICAL STUDIES, C. Plantar Tinea Pedis (Mocassin type), correct spelling of onychomycosis in table.

A revised copy of this labeling incorporating these changes is appended to this letter. Additionally, copy of this labeling in WordPerfect 5.1 has been provided to Mr. Cross on disk.

Please note that this correspondence will also serve as our final safety update. There has been no additional clinical safety data derived from either the marketplace or ongoing clinical trials which alters the safety profile to this drug in any way from that which was available at the time of its initial approval for the other indications.

Should you have any questions or comments, please contact me directly at (201) 503-7548.

Sincerely,

Stephenie Barba
Director
Drug Registration and Regulatory Affairs

SB/dmh
Submitted in duplicate
cc: Mr. F. Cross with disk

SANDOZ PHARMACEUTICALS CORPORATION
59 ROUTE 10, EAST HANOVER, NEW JERSEY 07936-1080

SANDOZ

DRUG REGISTRATION & REGULATORY AFFAIRS

TEL. 201 503 7500
FAX 201 503 6325

February 24, 1995

Jonathan Wilkin, MD, Director
Division of Topical Drug Products, HFD-540
Office of Drug Evaluation II
Attention Document Control Room: 17B-30
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

AL
NDA ORIG AMENDMENT
S-003

NDA No. 20-192/S-003
LAMISIL (terbinafine hydrochloride) 1%, Cream
Revised Final Draft Labeling

SUPPLEMENTAL AMENDMENT

Dear Dr. Wilkin:

Reference is made to our approvable Supplemental New Drug Application for Lamisil 1% Cream, NDA 20-192/S-003 dated September 28, 1993. This supplemental application provides for the addition of plantar tinea pedis (moccasin type) to the INDICATIONS AND USAGE Section of the Lamisil 1% Cream labeling. We refer also to your correspondence dated September 27, 1994 in which you inform Sandoz that the above-referenced supplemental application is approvable pending our incorporation of several requested changes in the draft product labeling prior to its submission in final printed form. In addition, we refer to correspondence to the Division dated November 29, 1994 in which we outline our concerns relative to some of these requested changes to the labeling. Lastly, we refer to a discussion in HFD-540 on February 14, 1995 between Mr. S. Turtil, Consumer Safety Officer, and the undersigned during which Sandoz was requested to resubmit final draft labeling for review and evaluation.

In accordance with the above mentioned request, Sandoz is submitting herewith, revised final draft labeling related to the plantar tinea pedis (moccasin type) indication which incorporates the majority of the revisions requested in your September 27, 1994 correspondence. However, as noted in our earlier correspondence, the response factors described in the CLINICAL STUDIES Section of the labeling continue to present the study results in terms of "Successful Outcomes". This parameter is a composite of both mycological cure and clinical effectiveness and represents a meaningful presentation of study results and treatment expectations to the prescriber. With respect to the use of cure rates alone, as delineated under Point 2 of your September 27 correspondence, it is our belief that such is inappropriate for a number of reasons as follows:

1. It is inconsistent with our currently approved labeling for other indications.
2. It is inconsistent with the labeling for competitive products in the marketplace.
3. The use of "successful outcomes" is a clinically relevant and meaningful outcomes measure which is readily understood by both patient and prescriber.

Please note that only two (2) other products in the marketplace currently quote rates of effectiveness, and that in both cases, such rates are based on outcome measures which represent less than a complete cure. Both products (Oxistat and Exelderm) utilize endpoints related to improvement in clinical signs and symptoms. Oxistat presents data on greater than 90% improvement while Exelderm presents the data on the basis of negative KOH, culture and a clinical response graded as good or excellent. Neither product was required to label outcome measures on the basis of complete cure alone, nor were they required to identify a cohort or percentage of patients that were completely cured in the product labeling (copies of appropriate sections attached). By comparison, the "successful outcomes" measure employed by Sandoz similarly represents a composite of both mycology assessments and reduction in clinical signs and symptoms.

While Sandoz does not object to the establishment of Class Labeling for this group of drug products, we believe that a requirement to include only complete cure rates on the part of the Division would place us at a competitive disadvantage and represents a significant deviation from previously applied labeling practice for both Lamisil 1% Cream and its competitors. Moreover, it would inhibit the dissemination of important clinical information to the prescriber in this difficult to treat form of tinea pedis where there is typically some form of residual symptomatology (especially some desquamation) for a short duration and which varies from patient to patient.

Based upon the above arguments, the enclosed final draft labeling for Lamisil 1% Cream incorporates the comments put forth by the Division under points 1, 3 and 4 of your September 27, 1994 correspondence. In addition, we have deleted reference to the negative mycology as requested under point 2 of the above-referenced correspondence even though we believe that it is important information for the prescriber, and even though this information was permitted in the labeling for Oxistat. However, the outcomes measures retain the use of "successful outcomes", a clinically meaningful representation to the prescriber comprised of negative mycology (culture and KOH preparation) in conjunction with a reduction in clinical signs and symptoms. We believe that this presentation of study results is more informative, more clinically relevant, more consistent with previously approved labeling for both Lamisil and other similarly labeled products, and maintains competitive balance in the marketplace.

We believe that, with the submission of the attached draft labeling, all outstanding information related to the final approval of this application is complete and we look forward to final approval in the near future. In the event that the Division continues to disagree with our position, we respectfully request a labeling conference with the Division Director to resolve our disagreements regarding the appropriate outcome measures to be displayed in the labeling.

Should there be any questions or comments concerning this correspondence or the attached, please contact the undersigned at (201) 503-8290.

Sincerely,

Roy W. Dodsworth
Senior Associate Director
Drug Registration and Regulatory Affairs

Attachments -
Form FDA 356h
Submitted in duplicate (draft labeling in quadruplicate)

Desk Copy: Mr. S. Turtil, Consumer Safety Officer, HFD-540

SANDOZ PHARMACEUTICALS CORPORATION
59 ROUTE 10, EAST HANOVER, NEW JERSEY 07936-1080

SANDOZ

DRUG REGISTRATION & REGULATORY AFFAIRS

TEL. 201 503 7500
FAX 201 503 6325

March 8, 1995

Jonathan Wilkin, MD, Director
Division of Topical Drug Products, HFD-540
Office of Drug Evaluation II
Attention Document Control Room: 17B-30
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

NDA No. 20-192/S-003
LAMISIL (terbinafine hydrochloride) 1%, Cream
Revised Final Draft Labeling

Dear Dr. Wilkin:

Reference is made to our approvable Supplemental New Drug Application for Lamisil 1% Cream, NDA 20-192/S-003 dated September 28, 1993. This supplemental application provides for the addition of plantar tinea pedis (moccasin type) to the INDICATIONS AND USAGE Section of the Lamisil 1% Cream labeling, as well as other associated labeling changes. We refer also to our correspondence dated February 24, 1995 under cover of which we submitted revised final draft labeling incorporating many of the comments raised in the September 27, 1994 approvable letter for this application. We further refer to telephone conversations on March 6, 1995 and March 8, 1995 between the undersigned and Dr. Phyllis Huene, MD, Medical Officer in HFD-540, regarding several additional minor changes requested by Dr. Huene.

In accordance with Dr. Huene's above mentioned request, Sandoz is submitting herewith, further revised final draft labeling (last three pages only) related to the plantar tinea pedis (moccasin type) indication which incorporates the language changes discussed with and agreed upon by Dr. Huene. Language revised in accordance with these agreements are highlighted in the attached pages for ease of review, but will be reduced to regular type when incorporated into final printed labeling. It is our intent that these changes, as well as those other changes previously agreed upon with the Division with respect to this supplemental application and described in our February 24, 1995 submission, will be incorporated into the next printing of final printed labeling and submitted to the file subsequent to approval thereof but prior to launch of this new indication for Lamisil Cream, 1%.

We believe that, with the submission of the attached final draft labeling which incorporates agreed upon changes, all outstanding information related to the final approval of this application is complete and we look forward to final approval in the very near future.

Should there be any questions or comments concerning this correspondence or the attached, please contact the undersigned at (201) 503-8290.

Sincerely,

Roy W. Dodsworth
Senior Associate Director
Drug Registration and Regulatory Affairs

Attachments
Submitted in duplicate (draft labeling in quadruplicate)

Desk Copy: Mr. S. Turtil, Consumer Safety Officer, HFD-540
Dr. P. Huene, MD, Medical Officer, HFD-540

SANDOZ PHARMACEUTICALS CORPORATION
59 ROUTE 10, EAST HANOVER, NEW JERSEY 07936-1080

SANDOZ

TEL. 201 503 7500
FAX 201 503 8265
Personal Fax Number 201.503.6461

May 11, 1995

Steven Turtil
Project Manager
Division of Topical Drug Products
Room 17B45 (HFD-540)
5600 Fishers Lane
Rockville, MD 20857

Dear Steve:

As a follow up to our conversation today, here is the statement which Sandoz proposes to address the fact that some successful outcome patients still had residual signs and symptoms: "Due to the severity of plantar tinea pedis and/or differences in the rate of healing, some patients may still have mild residual signs and symptoms at week 8 in spite of negative KOH and culture".

This statement would be added to the most recent version of the clinical studies section (subsection C) of the Package Insert along with data on successful outcomes. We believe that differentiating the successful outcome patients into two categories, i.e. those with and without residual signs and symptoms, becomes quite confusing since we have already distinguished between the patients with and without onychomycosis.

Please consider this to be an informal communication of a draft proposal to be used for further discussion with you and Dr. Wilkin. I can be reached tomorrow in The Netherlands, c/o Dorint Hotel, phone: 011-31-40-326-111, fax: 011-31-40-40-440-148 and next week in Austria c/o Grand Hotel Sauerhof, phone: 011-43-2252-412510, fax: 011-43-2252-48047.

Best regards,

Jay E. Birnbaum (kh)

Jay E. Birnbaum, Ph.D.
Vice President
Corporate Project Management

JEB:kah

SANDOZ PHARMACEUTICALS CORPORATION
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SANDOZ

DRUG REGISTRATION & REGULATORY AFFAIRS

TEL. 201 503 7500
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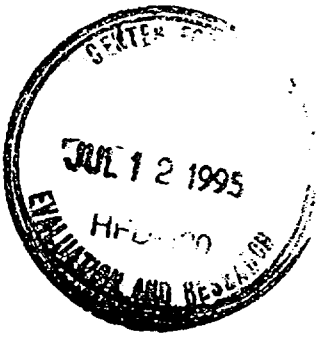
H.P

SF/003 (RL)

July 10, 1995



Jonathan Wilkin, MD, Director
Division of Topical Drug Products, HFD-540
Office of Drug Evaluation II
Attention Document Control Room: 17B-30
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

NDA No. 20-192/S-003
LAMISIL (terbinafine hydrochloride) 1%, Cream
Revised Final Draft Labeling

SUPPLEMENTAL AMENDMENT

Dear Dr. Wilkin:

Reference is made to our approvable Supplemental New Drug Application for Lamisil 1% Cream, NDA 20-192/S-003 dated September 28, 1993. This supplemental application provides for the addition of plantar tinea pedis (moccasin type) to the INDICATIONS AND USAGE Section of the Lamisil 1% Cream labeling as well as other associated labeling changes. We refer also to your correspondence dated September 27, 1994 in which you inform Sandoz that the above-referenced supplemental application is approvable pending our incorporation of several requested changes in the draft product labeling prior to its submission in final printed form. Reference is also made to our submission of revised draft labeling dated March 8, 1995, to subsequent telephone discussions with Dr. P. Huene of your office, to our meeting with HFD-540 on May 1, 1995 and to our many telephone conferences during May and June wherein further revisions to the draft labeling as last submitted were discussed. Lastly, we refer to our latest discussion related to final revisions to the Clinical Trials Subsection of the labeling dealing with the presentation of tabular data on "successful outcomes", and cure rates (both mycological and complete cure rates).

In accordance with the above mentioned discussions, Sandoz is submitting herewith, revised final draft labeling [Clinical Trials Subsection for T. pedis (moccasin type) only] related to the plantar tinea pedis (moccasin type) indication which incorporates the revisions discussed during our most recent teleconferences related to complete cure rates and mycological cure rates.

We believe that, with the submission of the attached draft labeling, all outstanding information related to the final approval of this application is complete and we look forward

to final approval in the near future. Please note that it is our intent to incorporate the attached (and previously agreed upon) changes at the time of introduction of this new indication to the marketplace. Consequently, we respectfully request that final approval be granted on the basis of the agreed upon final draft labeling with the understanding that revised final printed labeling will be submitted to the file at the time of revision and introduction as provided for under 21 CFR 314.105(b).

Should there be any questions or comments concerning this correspondence or the attached, please contact the undersigned at (201) 503-8290.

Sincerely,

Roy W. Dodsworth
Senior Associate Director
Drug Registration and Regulatory Affairs

Attachments
Form FDA 356h
Submitted in duplicate (draft labeling in quadruplicate)

Desk Copy: Mr. S. Turtil, Consumer Safety Officer, HFD-540

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

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

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001. Expiration Date: April 30, 1994. See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT
Sandoz Pharmaceuticals Corporation

ADDRESS *(Number, Street, City, State and Zip Code)*
59 Route 10
East Hanover, New Jersey 07936-1080

DATE OF SUBMISSION
July 11, 1995

TELEPHONE NO. *(Include Area Code)*
(201) 503-8290

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
20-192/S-003

DRUG PRODUCT

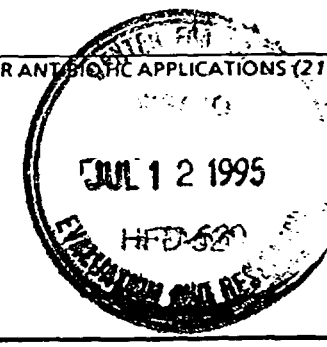
ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
terbinafine hydrochloride	LAMISIL 1% Cream

CODE NAME *(If any)*	CHEMICAL NAME

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Cream	Topical	

PROPOSED INDICATIONS FOR USE

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314.420)* REFERRED TO IN THIS APPLICATION:



INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☒ SUPPLEMENTAL APPLICATION
☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., *Part 314.70(b)(2)(iv)*) _____

PROPOSED MARKETING STATUS *(Check one)*

☐ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*

CONTENTS OF APPLICATION

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

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

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

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

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Roy W. Dodsworth, Senior Associate Director, Drug Registration and Regulatory Affairs	Elsie Bradley for R. Dodsworth	7/10/95

ADDRESS *(Street, City, State, Zip Code)*	TELEPHONE NO. *(Include Area Code)*
59 Route 10 East Hanover, New Jersey 07936-1080	(201) 503-8290

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

SANDOZ PHARMACEUTICALS CORPORATION
59 ROUTE 10, EAST HANOVER, NEW JERSEY 07936-1080

SANDOZ

DRUG REGISTRATION & REGULATORY AFFAIRS

TEL 201 503 7500
FAX 201 503 8325

August 2, 1995

Jonathan Wilkin, MD, Director
Division of Topical Drug Products, HFD-540
Office of Drug Evaluation II
Attention Document Control Room: 12B-30
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

NDA No. 20-192/S-003
LAMISIL (terbinafine hydrochloride) 1%, Cream
Revised Final Draft Labeling

SUPPLEMENTAL AMENDMENT

Dear Dr. Wilkin:

Reference is made to our approvable Supplemental New Drug Application for Lamisil 1% Cream, NDA 20-192/S-003 dated September 28, 1993. This supplemental application provides for the addition of plantar tinea pedis (moccasin type) to the INDICATIONS AND USAGE Section as well as other associated changes in the Lamisil 1% Cream labeling. We refer also to your correspondence dated September 27, 1994 in which you inform Sandoz that the above-referenced supplemental application is approvable pending our incorporation of several requested changes in the draft product labeling prior to its submission in final printed form. In addition, we refer to several subsequent submissions and teleconferences with the Division with respect to this matter. Lastly, we refer to a meeting held in your offices on July 31, 1995 during which agreements were reached between HFD-540 and Sandoz with respect to the final language to appear in the labeling for Lamisil Cream as it relates to this pending, approvable supplemental application.

In follow-up to those discussions, attached herewith, is final draft labeling which incorporates the changes which were the subject of the July 31 meeting and the agreements which came therefrom. Accordingly, we look forward to final approval of this application at your earliest convenience. Pursuant to 21 CFR 314.105(b), we request final approval on the basis of the attached, agreed upon draft labeling. Sandoz agrees to submit labeling in final printed form which is identical to the attached prior to the introduction of this new indication and associated labeling in the marketplace.

Please note that this correspondence will also serve as our final safety update for this pending file. There has been no additional clinical safety data derived from either the marketplace or ongoing clinical trials which alters the safety profile of this drug in any way from that which was available at the time of its initial approval for other indications.

Should there be any questions or comments concerning this correspondence or the attached, please contact the undersigned at (201) 503-8290.

Sincerely,

Roy W. Dodsworth
Senior Associate Director
Drug Registration and Regulatory Affairs

Attachments
Form FDA 356h
Submitted in duplicate (draft labeling in quadruplicate)

Desk Copy: Ms. R. Cook, Supervisory Consumer Safety Officer, HFD-540

ORIGINAL

NDA SUPPL AMEND
SE1-003(AF)
SE1-003(SU)

SANDOZ PHARMACEUTICALS CORPORATION
59 ROUTE 10, EAST HANOVER, NEW JERSEY 07936-1080

SANDOZ

DRUG REGISTRATION & REGULATORY AFFAIRS

TEL. 201 503 7500
FAX 201 503 6325

July 31, 1996

Jonathan Wilkin, MD
Director
Division of Dermatologic and Dental
Drug Products/HFD-540
Office of Drug Evaluation V
Att: Document Control Room 12B-30
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-192/S-003

LAMISIL CREAM 1%
(terbinafine hydrochloride cream)

REVISED FINAL DRAFT LABELING

FINAL SAFETY UPDATE

Dear Dr. Wilkin:

Reference is made to our Supplemental New Drug Application for Lamisil Cream, 1%, NDA 20-192/S-003 which was submitted on September 28, 1993. This supplemental application provides for the addition of plantar tinea pedis (moccasin type) to the INDICATIONS AND USAGE section , as well as other associated changes, in the Lamisil Cream. 1% labeling. We also refer to your correspondence dated September 27, 1994 in which you informed Sandoz that the above-referenced supplemental application is approvable pending our incorporation of several requested changes in the draft product labeling and to our August 2, 1995 submission of revised labeling which reflected agreements reached between the Division and Sandoz at a July 31, 1995 meeting. Lastly we refer to your letter dated July 25, 1996 where you once again inform us that this application is approvable and request the submission of revised draft labeling incorporating the minor modifications specified in your letter.

In response to your request, attached herewith, is final draft labeling which incorporates the changes outlined in your letter. As these changes are primarily typographical, we look forward to your rapid approval of this supplement.

Additionally, we have provided the list of verbatim terms requested in Item 2B of your letter (page 08-01376 of our original submission).

Please note that this correspondence will also serve as our final safety update. There has been no additional clinical safety data derived from either the marketplace or ongoing clinical trials which alters the safety profile of this drug in any way from that which was available at the time of its initial approval for other indications.

Jonathan Wilkin, MD Con't
Director

Should you have any questions or comments, please contact me directly at (201) 503-7548.

Sincerely,

Stephenie Barba
Director
Drug Registration and Regulatory Affairs

SB/dmh
Submitted in duplicate
cc: Ms. R. Cook Desk Copy
Mr. F. Cross Desk Copy

SANDOZ PHARMACEUTICALS CORPORATION
59 ROUTE 10, EAST HANOVER, NEW JERSEY 07936-1080

DUPLICATE

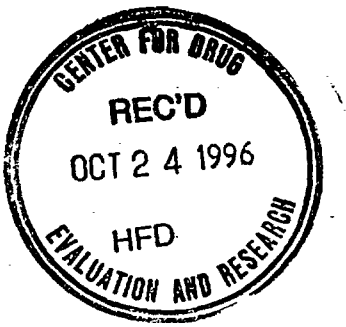
SANDOZ

DRUG REGISTRATION & REGULATORY AFFAIRS

TEL. 201 503 7500
FAX 201 503 6325

SU
PRINCIPAL AMENDMENT
S-003

October 22, 1996



Jonathan Wilkin, MD
Director
Division of Dermatologic and Dental
Drug Products/HFD-540
Office of Drug Evaluation V
Att: Document Control Room 12B-30
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20657

NDA NO. 20-192/S-003
LAMISIL®
(terbinafine hydrochloride cream) Cream, 1%

REVISED FINAL DRAFT LABELING

FINAL SAFETY UPDATE

Dear Dr. Wilkin:

Reference is made to our Supplemental New Drug Application for Lamisil Cream, 1%, NDA 20-192/S-003 which was submitted on September 28, 1993. This supplemental application provides for the addition of plantar tinea pedis (mocassin type) to the INDICATIONS AND USAGE section, as well as other associated changes, in the Lamisil Cream, 1% labeling. Reference is also made to my October 17, 1996 telephone discussion with Mr. Frank Cross, of your division, during which Mr. Cross requested that additional minor formatting changes be made to our proposed draft labeling for this supplemental application and that a disk containing this labeling in WordPerfect format be provided.

A copy of this revised labeling is attached. Additionally, a copy on disk has been provided directly to Mr. Cross.

Should you have any questions, please contact me at (201) 503-7548.

Sincerely,

Stephenie Barba
Director
Drug Registration and Regulatory Affairs

SB/dmh
Submitted in duplicate
cc: Mr. Frank Cross with disk

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

DUPLICATE

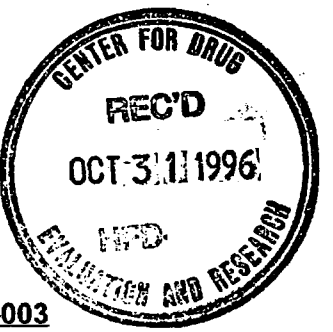
SANDOZ PHARMACEUTICALS CORPORATION
59 ROUTE 10, EAST HANOVER, NEW JERSEY 07936-1080

SANDOZ

DRUG REGISTRATION & REGULATORY AFFAIRS

TEL 201 503 7500
FAX 201 503 6325

S-003
SUPPL NEW CORRESP



October 30, 1996

Jonathan Wilkin, MD
Director
Division of Dermatologic and Dental
Drug Products/HFD-540
Office of Drug Evaluation V
Att: Document control Room
Center for Drug Evaluation and Research
Corporate Building, 9201 Corporate Boulevard
Rockville, Maryland 20850

NDA NO. 20-192/S-003

LAMISIL® (terbinafine hydrochloride cream) Cream, 1%

GENERAL CORRESPONDENCE

Dear Dr. Wilkin:

As requested today by Mr. Frank Cross of your division, I am officially submitting a copy of a fax dated August 6, 1996 to NDA 20-192. Should you have any comments or questions, please contact me directly at (201) 503-7548.

Sincerely,

Stephenie Barba
Director
Drug Registration and Regulatory Affairs

SB/dmh
Attachment
Submitted in duplicate
cc: Mr. Frank Cross - Desk Copy

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE