

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-749

MICROBIOLOGY REVIEW(S)

REVIEW FOR HFD-540

OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805
Microbiologist's Review # 1 of NDA 20-749
January 3, 1997

- A. 1. APPLICATION NUMBER: NDA 20-749
- APPLICANT: Sandoz Pharmaceuticals Corp.
59 Route 10
East Hanover, NJ 07936-1080
2. PRODUCT NAME: Lamisil® Solution 1%
3. DOSAGE FORM: Terbinafine HCl Topical Solution 1%, and Spray 1%
4. METHOD OF STERILIZATION: none (non-sterile product)
5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
Terbinafine, a synthetic allylamine derivative, is an antifungal which inhibits sterol biosynthesis. The proposed indication is for topical treatment of pityriasis versicolor and tinea pedis/cruris/corporis.
6. DRUG PRIORITY CLASSIFICATION: 3S
- B. 1. DATE OF INITIAL SUBMISSION: October 17, 1996
2. DATE OF CONSULT: October 29, 1996
3. RELATED DOCUMENTS: (none)
4. ASSIGNED FOR REVIEW: November 1, 1996
- C. REMARKS: Lamisil® Solution is the second topical formulation of terbinafine HCl that has been developed by Sandoz. A 1% cream formulation (NDA 20-192) was approved on December 30, 1992 for the treatment of tinea pedis/corporis/cruris.

D. CONCLUSIONS:

The application was reviewed for issues concerning drug product microbial limits and preservative effectiveness. The application is approvable provided that the applicant supplies certain information.

Neal Sweeney, Ph.D.

1/13/97

1/13/97

cc:

Original NDA 20-749
HFD-540/ Division File
HFD-540/CSO/F. Cross
HFD-805/Consult File/N. Sweeney

Drafted by: Neal Sweeney, January 3, 1997
R/D initialed by P. Cooney January 3, 1997

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**Consultative Review for HFD-540
Division of Topical Drug Products
Division of Anti-Infective Drug Products (HFD-520)
Clinical Microbiology Review #1**

Requestor: Frank Cross, CSO HFD-540

Date of Request: 10-22-96

Reason for Request: Clinical Microbiology Review of antifungal activity

IND/NDA Number: NDA # 20-749

Review Date: 12-19-96

Submission/Type: Original NDA

Document Date: 10-17-96

CDER Date: 10-18-96

Assigned Date: 11-6-96

Applicant: Sandoz Pharmaceuticals Corp.
59 Route 10
East Hanover, NJ 07936

Contact Person: Stephenie Barba, Director
Drug Registration and Regulatory Affairs
59 Route 10
East Hanover, NJ 07936
Phone: (201) 503-7548

Drug Product Name:

Proprietary:	Lamisil
Nonproprietary/USAN:	Terbinafine hydrochloride
Code Names/#s:	None
Chemical Type:	Allylamine derivative
Therapeutic Class:	1S

ANDA Suitability Petition/DESI/Patent Status:
Not Applicable

NDA 20-749
Sandoz Pharmaceuticals corp.
1% terbinafine hydrochloride solution

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Pharmacological Category/Indication:

Antifungal—Allylamine/Tinea pedis, tinea cruris, tinea corporis, and pityriasis versicolor

Dosage Form: Solution
Strength(s): 1%
Route of Administration: Topical
Dispensed: X Rx OTC

Chemical Name, Structural Formula, Molecular Formula & Weight:

Chemical Name: (E)-N-(6,6-dimethyl-2-hepten-4-ynyl-N-methyl-1-naphthalenemethanamine hydrochloride
Structural Formula: See USP Dictionary, 1996, page 685.
Molecular Formula: C₂₁H₂₆ClN
Molecular Weight: 327.90

Supporting Documents:

DMF DMF DMF
NDA 20192, NDA 20539
IND IND IND IND IND

Related Documents (if applicable):

None

REMARKS/COMMENTS:

This microbiological review is concerned with only the clinical aspects of this applications [mechanism of action, *in-vitro* activity, *in-vivo* animal models]. The microbiological aspects of the manufacturing controls for this product are reviewed by a different consulting division.

This NDA is for a product which includes an active ingredient previously approved by FDA for drug use. The ingredient is an allylamine derivative, terbinafine hydrochloride, with antifungal activity. Its antifungal activity is derived from inhibition of squalene epoxidase, a key enzyme in ergosterol biosynthesis. The antifungal activity of terbinafine is related to the corresponding accumulation of squalene within the fungal cell wall.

The applicant is seeking approval for a new formulation, Lamisil 1% Solution(1% terbinafine hydrochloride solution), to be used in topical treatment of pityriasis versicolor due to *Malassezia furfur*, and tinea pedis, tinea cruris, or tinea corporis, due to *Trichophyton rubrum*, *Trichophyton mentagrophytes*, or *Epidermophyton floccosum*.

1. CLINICAL STUDIES

The efficacy and safety of Lamisil 1% solution is being supported by nine clinical trials in three indications. Of these studies, eight were placebo controlled and one was active controlled (clotrimazole solution). Table 1 lists these nine studies. Eight are considered pivotal and placebo controlled study SFF 104 is considered supporting.

TABLE 1. List of pivotal and supporting studies

Indication	Location	Pivotal		Supporting
		Placebo controlled	Active* controlled	Placebo controlled
Pityriasis Versicolor	US None US	SFF 353 SFF 305		
Tinea Pedis	US None US	SFF 351 SFF 301	SFF 309	SFF 104
Tinea Cruris/Corporis	US None US	SFF 105 SFF 303, 108		

* Clotrimazole control group.

All nine studies follow similar study designs and subject inclusion criteria. The protocols required that each subject had a clinical diagnosis of the study indication. In all indications this was to be confirmed by positive mycology (positive microscopy, confirmed by positive culture in all indications except pityriasis versicolor). On the basis of positive microscopy results, treatment could be initiated. The mycological examinations were performed on a target lesion which was identified at the screening visit and consistently evaluated, both mycologically and clinically, throughout the study. All visible lesions were treated. The study design for each of these studies are summarized in Table 2. A total of 1666 patients were enrolled. Of these, 962 were randomized to Lamisil. 351 to clotrimazole, and 353 to placebo.

In the pityriasis versicolor studies, the criteria for Effective Treatment were met if, at the same evaluation, a subject had both negative microscopy and a Total Signs and Symptoms Score (TSSS=sum of scores for individual signs and symptoms) of 0 or 1. Each sign or symptom was graded on a scale of 0-3 (absent, mild, moderate or severe). For TSSS, three symptoms were assessed in the pityriasis versicolor studies: erythema, desquamation and pruritus. The criteria for Complete Cure were met if a subject had negative microscopy results and a TSSS of 0, making it more stringent than Effective Treatment.

For the indication of pityriasis versicolor which will be a new indication for topical Lamisil in the USA, two key randomized, placebo-controlled studies (SFF 353 and SFF 305) examined the efficacy and safety of Lamisil 1% solution used twice daily for one week with seven weeks of blinded follow-up.

TABLE 2. Designs of clinical studies in claimed indications

Indication	Study ^{a,b}	Country	Duration of treatment (clotrimazole)	Follow-up period (clotrimazole)	No. Of Subjects Enrolled			Enrolled Subjects	
					Enrolled	Lamisil	Control	Age Range (mean)	Sex ^c %M %F
Pityriasis versicolor	SFF 305	Netherlands/ Belgium	1 week BID	7 weeks	115	79	36	(33.7)	51.3 48.7
	SFF 353	USA	1 week BID	7 weeks	152	103	49	(33.5)	51.3 48.7
Tinea pedis	SFF 301	Denmark/France/ Iceland/Britain	1 week OD	7 weeks	172	115	57	(42)	75.6 24.4
	SFF 351	USA	1 week BID	7 weeks	153	104	49	(42.7)	71.9 28.1
	SFF 309 ^d	Germany/ Czech. Rep.	1 week BID (4 weeks BID)	7 weeks (4 weeks)	699	348	351	(46.0)	68.4 31.6
	SFF 104 ^c	USA	2 weeks OD	4 weeks	86	43	43	(39.6)	72.1 27.9
Tinea corporis/ cruris	SFF 303	France/ Norway/ Switzerland	1 week OD	7 weeks	151	102	49	(44)	79.5 20.5
	SFF 105	USA	1 week OD	3 weeks	66	32	34	(42.7)	74.2 25.8
	SFF 108	Brazil	1 week OD	3 weeks	72	36	36	(34.4)	69.4 30.6

- ^a All studies are placebo-controlled, except for SFF 309 which was clotrimazole-controlled.
- ^b All studies are randomized, double-blind, controlled, parallel group, multicenter in design.
- ^c Study SFF 104 is considered a supporting study in tinea pedis because of its 2-week treatment period; all other studies are treatment pivotal studies since they support the proposed label of a one-week treatment duration.
- ^d Subject in the Lamisil arm of SFF 309 received three weeks placebo, BID following the one week treatment with Lamisil, to maintain the blind within the study.
- ^e Percentage may not equal 100 due to rounding.

In tinea pedis and tinea corporis/cruris, the criteria for Effective Treatment were met, if, at the same evaluation, a subject had negative microscopy, negative culture, sum of severity scores of erythema,

desquamation and pruritus ≤ 2 , individual severity scores for erythema, desquamation and pruritus ≤ 1 and individual severity scores for vesiculation, incrustation and pustules = 0. Complete Cure, with more stringent criteria than Effective Treatment, was defined as negative microscopy, negative culture, and TSSS for erythema, desquamation, pruritus, vesiculation, incrustation and pustule = 0.

Table 3 presents the end of study Effective Treatment, Complete Cure and Negative Microscopy rates for the individual studies and the pooled intent-to-treat (ITT) population in the pityriasis versicolor studies. A total of 173 Lamisil and 81 placebo treated subjects were included in the pooled ITT population for this indication. Nine Lamisil-treated subjects and 4 placebo-treated subjects were excluded from the pooled ITT population, the most common reason for exclusion being “no study medication” and no efficacy follow-up.”

TABLE 3. Rates for Effective Treatment, Complete Cure and Negative Microscopy at end of study SFF 353 and SFF 305 (pityriasis versicolor)(ITT population)

Study	Effective Treatment			Complete Cure			Negative Microscopy		
	Lamisil % (n/N)	Placebo % (n/N)	P-Value CMH Test	Lamisil % (n/N)	Placebo % (n/N)	P-Value CMH Test	Lamisil % (n/N)	Placebo % (n/N)	P-Value CMH Test
SFF 353 BID (US)	77% (75/97)	28% (13/47)	<0.001	66% (64/97)	26% (12/47)	<0.001	78% (76/97)	30% (14/47)	<0.001
SFF 305 BID (non-US)	70% (52/74)	32% (11/34)	<0.001	47% (35/75)	29% (10/34)	0.031	79% (58/73)	44% (15/34)	<0.001
Pooled	74% (127/171)	30% (24/81)	N/D	58% (99/172)	27% (22/81)	N/D	79% (134/170)	36% (29/81)	N/D

Note: End of study is the last non-missing post-baseline observation.
CMH indicates the Cochran-Mantel-Haenszel test for treatment comparisons (per Final Study Reports).
(n/N) = number of responders for variable/number of subjects evaluated for variable.

At End of Study, Lamisil was shown to be statistically significantly ($p \leq 0.031$) superior to placebo for all three of these measures of efficacy in both studies.

According to the sponsor, in the two studies, the mean TSSS at baseline ranged from 3.6 to 4.3 across studies and treatment groups, thus substantially exceeding the TSSS criterion for Effective Treatment (TSSS=0 or 1), which renders Effective Treatment clinically meaningful as the primary efficacy variable. At the End of Study, in the two studies, Lamisil had reduced the baseline mean TSSS by 3.1-3.5, compared to placebo, which reduced the mean baseline by 2.4-2.6. Clinically, this reduction was barely

statistically significant ($P \leq 0.045$) in both studies. However, the microscopy evaluation showed that Lamisil was significantly superior to placebo ($p < 0.001$) at weeks 4 and 8 and at End of Study for both studies.

The recurrence rate at the End of Study was 3%(4/125) for pityriasis versicolor in patients with both clinical and mycological evidence of recurrence. This is in contrast to 17%(7/41) recurrence rate for placebo-treated subjects.

For Effective Treatment and Complete Cure, statistically significant differences in favor of Lamisil were present by week 4 and continued through week 8 and were also present in the End of Study evaluation. The response rates were progressive and full therapeutic benefit were only seen several weeks after the end of treatment (twice daily x 7 days). Thus the sponsor proposes that the patients should be informed that full therapeutic benefit may only be seen several weeks after end of treatment.

A total of 346 Lamisil, 212 clotrimazole and 67 placebo-treated subjects were included in the pooled ITT population for the three key tinea pedis studies. The most common reason for exclusion from the ITT population was "delayed exclusion," this accounted for 215 (38%) subjects entered into the Lamisil group, 134 (38%) subjects entered into the clotrimazole group and 39 (37%) subjects entered into the placebo group. The remaining exclusions from the pooled ITT population were "no efficacy follow-up" in 22 (2%) subjects, and "no study medication" in 4 subjects.

A total of 133 Lamisil-treated subjects and 98 placebo-treated subjects were included in the pooled ITT population for three key tinea corporis/cruris studies. The most common reason for exclusion from the ITT population was "delayed exclusion," this accounted for 35 (21%) subjects entered into the Lamisil group and 21 (18%) subjects entered into the placebo group. The remaining exclusions from the ITT population were "no efficacy follow-up" and "no study medication" in 5 (2%) and 4 (1%) of subjects, respectively.

Table 4 presents the End of Study Effective Treatment, Complete Cure and Negative Mycology rates for the individual studies and the pooled ITT population in the indications of tinea pedis and tinea corporis/cruris.

In the three tinea pedis studies, at End of Study, one week of Lamisil was shown to be statistically significantly ($p \leq 0.007$) superior to placebo and not statistically different from 4 weeks of clotrimazole for all three of these measures of efficacy.

TABLE 4. End of Study rates Effective Treatment, Complete Cure and Negative Mycology in tinea pedis and tinea corporis/cruris (ITT population).

Study Dose Schedule	Effective Treatment				Complete Cure				Negative Mycology			
	LAM % (n/M)	CLO % (n/N)	PBO % (n/M)	p-Value CMH Test	LAM % (n/M)	CLO % (n/N)	PBO % (n/M)	p-Value CMH Test	LAM % (n/M)	CLO % (n/N)	PBO % (n/M)	p-Value CMH Test
Tinea pedis												
SFF 351 BID (US)	66% (38/58)	–	4% (1/28)	<0.001	21% (12/58)	–	0% (0/28)	0.007	88% (51/58)	–	14% (4/28)	<0.001
SFF 301 QD (non-US)	76% (54/71)	–	21% (8/39)	<0.001	51% (36/71)	–	5% (2/39)	<0.001	85% (60/71)	–	23% (9/39)	<0.001
SFF 309 BID (non-US)	83% (181/217)	82% (174/212)	–	0.649	54% (117/217)	57% (121/212)	–	0.536	92% (199/216)	91% (193/212)	–	0.411
Pooled	79% (273/346)	82% (174/212)	13% (9/67)	N/D	48% (165/346)	57% (121/212)	3% (2/67)	N/D	90% (310/345)	91% (193/212)	19% (13/67)	N/D
Tinea corporis/cruris												
SFF 105 QD (US)	71% (51/72)	–	11% (4/36)	<0.001	53% (38/72)	–	3% (1/36)	<0.001	85% (61/72)	–	28% (10/36)	<0.001
SFF 108 QD (non-US)	65% (22/34)	–	8% (2/26)	<0.001	38% (10/26)	–	8% (2/26)	N/D	69% (18/26)	–	23% (6/26)	<0.001
Pooled	68% (90/132)	–	13% (13/97)	N/D	47% (62/132)	–	5% (5/97)	N/D	79% (104/131)	–	27% (26/97)	N/D

Note: End of Study is last non-missing post-baseline observation.
CMH indicates the Cochran-Mantel-Haenszel test for treatment comparisons (per Final Study Reports)
LAM = Lamisil 1% solution
CLO = Clotrimazole 1% solution
PBO = placebo (vehicle)
N/D = not done
– = not applicable
(n/N) = number of responders for variable/number of subjects evaluated for variable

In the studies, all visible lesions were treated with study medication. In tinea pedis study SFF 351, and to a lesser extent in Study SFF 301, the efficacy results were affected by the proportion of subjects with extended (plantar) involvement, which is recognized as being less responsive to treatment than pure interdigital infections. When the Effective Treatment rates for each subgroups were calculated in table 5 it became evident that the Effective Treatment rates for Lamisil-treated subjects with pure interdigital tinea pedis in Studies SFF 351(US) and SFF 301 (non-US) were similar to the rates of Effective Treatment for Lamisil-treated subjects in Study SFF 309 (non-US), in which all ITT subjects, except one, had pure interdigital disease. The table further shows that interdigital disease in subjects with extended

involvement also responded well, as compared to placebo, in studies SFF 351 and SFF 301, despite the presence of the more recalcitrant plantar disease.

TABLE 5. Effective Treatment at End of Study by type of infection in tinea pedis (ITT population).

Study Dose Schedule	Pure Interdigital				Extended Involvement			
	LAM % (n/M)	CLO % (n/N)	PBO % (n/M)	p-Value CMH Test	LAM % (n/M)	CLO % (n/N)	PBO % (n/M)	p-Value CMH Test
SFF 351 BID	71% (27/38)	--	6% (1/17)	<0.001	55% (11/20)	--	0% (0/11)	0.010
SFF 301 QD	78% (45/58)	--	18% (5/28)	<0.001	69% (9/13)	--	27% (3/11)	0.026
SFF 309 BID	83% (180/216)	82% (174/212)	--	0.649	100% (1/1)	--	--	--
Pooled	81% (252/312)	82% (174/212)	13% (6/45)	N/D	62% (21/34)	--	14% (3/22)	N/D

Note: End of Study is last non-missing post-baseline observation.

CMH indicates the Cochran-Mantel-Haenszel test for treatment comparisons (per Final Study Reports)

LAM = Lamisil 1% solution

CLO = Clotrimazole 1% solution

PBO = placebo (vehicle)

N/D = not done

-- = not applicable

(n/N) = number of responders for variable/number of subjects evaluated for variable

According to the sponsor the majority of subjects in the tinea pedis studies had robust TSSS at baseline, ranging from across studies and treatment groups, which is sufficiently high to make Effective Treatment clinically relevant as the primary variable of efficacy. At End of Study, in the three key studies, Lamisil had reduced the baseline mean TSSS by 4.7-5.5 and clotrimazole reduced the baseline mean TSSS by 5.4. This is in contrast to placebo, which reduced the baseline mean TSSS by 1.3-2.9; Lamisil applied for 1 week was statistically significantly ($p < 0.001$) superior to placebo in both studies SFF 301 and SFF 351 and not statistically different ($p = 0.603$) from clotrimazole applied for 4 weeks in study SFF 309.

The majority of subjects in the tinea corporis/cruris studies had robust TSSS at baseline, ranging from across studies and treatment groups, which according to the sponsor is sufficiently high to make

Effective Treatment clinically relevant as the primary variable of efficacy. In study SFF 303, at End of Study, Lamisil had reduced the baseline mean TSSS by 5.2, whereas placebo had reduced the baseline mean TSSS by only 1.8. This was statistically significant ($p < 0.001$, Van Elteren test using center as stratification factor). In studies SFF 105 and SFF 108, at End of Study, Lamisil had reduced the baseline mean TSSS by 5.1 and 5.6, whereas placebo had reduced the baseline mean TSSS by 2.0 and 1.7, respectively. The superiority of Lamisil compared to placebo for mean reduction in TSSS from baseline to End of Study was statistically significant ($p < 0.0001$, Van Elteren test using center as stratification factor) in each of the studies.

Table 6 presents the response rates at End of Study by organism at baseline for the key tinea pedis studies.

TABLE 6. Response rates (% , n/N) at End of Study^a by organism at baseline (key tinea pedis studies pooled)

Organism	Effective Treatment			Negative Mycology		
	LAM % (n/M)	CLO % (n/N)	PBO % (n/M)	LAM % (n/M)	CLO % (n/N)	PBO % (n/M)
Pooled: SFF 351, 301, and 309						
<i>T. rubrum</i>	80% (221/276)	82% (149/182)	13% (6/48)	91% (250/276)	91% (166/182)	19% (9/48)
<i>T. mentagrophytes</i>	78% (43/55)	84% (27/32)	19% (3/16)	91% (49/55)	91% (29/32)	25% (4/16)
<i>E. floccosum</i>	50% (8/16)	100% (2/2)	0% (0/3)	69% (11/16)	100% (2/2)	0% (0/3)

^a End of Study is last non-missing post-baseline observation.

LAM = Lamisil 1% solution; CLO = Clotrimazole 1% solution; PBO = placebo (vehicle)

(n/N) = number of responders for variable/number of subjects evaluated for variable

Trichophyton rubrum, *Trichophyton mentagrophytes* and *Epidermophyton floccosum* accounted for virtually all of the infections observed at baseline in the tinea pedis studies, and were distributed comparably in the three studies irrespective of geographical location. The majority of isolates were *Trichophyton rubrum*. Lamisil eradicated *Trichophyton rubrum* and *Trichophyton mentagrophytes* in 91% of the cases. However, Lamisil eradicated *Epidermophyton floccosum* less effectively at a rate of 69%. This low eradication rate was supported by the low rate of Effective Treatment (50%) when the causative agent was *Epidermophyton floccosum*.

In the tinea corporis/cruris studies, according to the sponsor, the organisms were present in proportions

which were similar to the tinea pedis studies at baseline (with the addition of 20 *Microsporum canis* subjects). Lamisil Effective Treatment and mycologic eradication rates at End of Study by organism at baseline are presented in table 7.

TABLE 7. Response rates at End of Study by organism at baseline, tinea corporis/cruris, ITT population

Study	Organism at Baseline	Effective Treatment		Negative Mycology	
		Lamisil n/N (%)	Placebo n/N (%)	Lamisil n/N (%)	Placebo n/N (%)
SFF 303	<i>E. floccosum</i>	1/1 (100)	N/I	1/1 (100)	N/I
	<i>M. canis</i>	2/6 (33)	0/3 (0)	2/6 (33)	0/3 (0)
	<i>T. mentagrophytes</i>	3/7 (43)	0/6 (0)	6/7 (86)	3/6 (50)
	<i>T. rubrum</i>	42/54 (78)	4/23 (17)	48/54 (89)	7/23 (30)
	Other	3/4 (75)	0/4 (0)	4/4 (100)	0/4 (0)
SFF 105	<i>E. floccosum</i>	½ (500)	N/I	½ (50)	N/I
	<i>M. canis</i>	0/3 (0)	1/4 (25)	0/3 (0)	2/4 (50)
	<i>T. mentagrophytes</i>	3/3 (100)	0/1 (0)	3/3 (100)	1/1 (100)
	<i>T. rubrum</i>	13/18 (72)	1/21 (5)	14/18 (78)	3/21 (14)
	Other	N/I	N/I	N/I	N/I
SFF 108	<i>E. floccosum</i>	2/4 (50)	½ (50)	2/3 (67)	½ (50)
	<i>M. canis</i>	0/3 (0)	0/1 (0)	2/3 (67)	1/1 (100)
	<i>T. mentagrophytes</i>	N/I	N/I	N/I	N/I
	<i>T. rubrum</i>	20/27 (74)	6/31 (19)	21/27 (78)	7/31 (23)
	Other	N/I	0/1 (0)	N/I	1/1 (100)
Pooled**	<i>E. floccosum</i>	4/7 (57)	½ (50)	4/6 (67)	½ (50)
	<i>M. canis</i>	2/12 (17)	1/8 (13)	4/12 (33)	3/8 (38)
	<i>T. mentagrophytes</i>	6/10 (60)	0/7 (0)	9/10 (90)	4/7 (57)
	<i>T. rubrum</i>	74/99 (75)	11/75 (15)	83/99 (84)	17/75 (23)
	Other	3/4 (75)	0/5 (0)	4/4 (100)	1/5 (20)

* Note: End of study is the last non-missing post-baseline evaluation

n/N= number of responders for variable/number of subjects evaluated for variable

N/I= none isolated

ITT: Any patient who was randomized, received at least one of study medication, had at least one post-baseline efficacy evaluation and had positive mycology (for dermatophyte) at baseline

** It is statistically inappropriate to pool these data because duration of studies SFF 105 and 108 was 4 weeks (1 week treatment and 3 weeks follow-up) and for study SFF 303 was 8 weeks (1 week treatment and 7 weeks follow-up). The data however were pooled to simply give an idea of how effective Lamisil is in eradicating organisms causing tinea corporis/cruris.

Lamisil Effective Treatment rates at End of Study by organism at baseline were: *Trichophyton rubrum* 75% (74/99), *Trichophyton mentagrophytes* 60% (6/10) and *Epidermophyton floccosum* 57% (4/7). The eradication rates by organism for these studies were: *Trichophyton rubrum* 84% (83/99), *Trichophyton mentagrophytes* 90% (9/10) and *Epidermophyton floccosum* 67% (4/6).

The sponsor states that the clinical response rates for Lamisil-treated subjects with tinea corporis/cruris was progressive during post-treatment follow-up, so subjects should be informed that full clinical benefit may only be achieved several weeks after completion of therapy.

2. IN VITRO STUDIES

The sponsor have not submitted any new *in vitro* data under this application. Reference is made to NDA 20-192, Lamisil 1% Cream, approved December 30, 1992, and NDA 20-539, Lamisil Tablets, approved May 10, 1996. The microbiology portion of NDA 20-192 was reviewed by Dr. Soprey on December 31, 1991, April 27, and November 13, 1992. The microbiology portion of NDA 20-539 was reviewed by Dr. Creedon on July 21, 1995. Dr. Soprey's review resulted in the following list of organisms for the *in vivo* and *in vitro* lists in the approved Product Insert (PI) of Lamisil 1% cream for treatment of interdigital tinea pedis, tinea cruris and tinea corporis:

In vivo (clinical efficacy) list:

Epidermophyton floccosum
Trichophyton mentagrophytes
Trichophyton rubrum

In vitro inhibition list:

Microsporum canis
Microsporum gypseum
Microsporum nanum
Trichophyton verrucosum

Dr. Creedon's review resulted in the following list of organisms for the *in vivo* and *in vitro* lists in the approved Product Insert (PI) of Lamisil 250 mg tablets for treatment of onychomycosis:

In vivo(clinical efficacy) list:

Trichophyton mentagrophytes
Trichophyton rubrum

In vitro inhibition list:

Epidermophyton floccosum

Microsporum gypseum
Microsporum nanum
Trichophyton verrucosum
Candida albicans
Scopulariopsis brevicaulis

3. ORGANISMS ALLOWED IN THE LABEL

It is the policy of this Division to include in the *in vitro* section of a drug product's label, only those organisms which are pathogens in the clinical indications being approved. In addition there must be *in vitro* data available on at least 100 recent clinical isolates. Consequently, only those organisms involved in tinea pedis, tinea cruris, tinea corporis may potentially be placed in the *in vitro* microbiology section of the package insert for the 1% solution formulation. Table 8 summarizes the causative agents of tinea pedis, corporis and cruris.

TABLE 8. Causative agents of tinea pedis, corporis, cruris, barbae, capitis, faciei, manum, and unguium in humans.

Organism	Tinea Barbae	Tinea Capitis	Tinea Corporis	Tinea Cruris	Tinea Faciei	Tinea Manum	Tinea Pedis	Tinea unguium
Dermatophytid molds								
<i>Trichophyton rubrum</i>	X	X*	X	X	X	X	X	X
<i>Trichophyton tonsurans</i>		X	X			X	X	X
<i>Trichophyton mentagrophytes</i>	X	X	X	X		X	X	X
<i>Trichophyton violaceum</i>	X	X	X			X		X
<i>Trichophyton verrucosum</i>	X	X	X	X	X		X	X
<i>Trichophyton schoenleinii</i>		X	X					X
<i>Trichophyton concentricum</i>			X		X			
<i>Epidermophyton floccosum</i>			X	X			X	X
<i>Microsporum canis</i>	X	X	X		X			X
<i>Microsporum audouinii</i>		X	X					
<i>Microsporum gypseum</i>	X	X	X		X			
<i>Microsporum nanum</i>		X*	X*					

Organism	Tinea Barbae	Tinea Capitis	Tinea Corporis	Tinea Cruris	Tinea Faciei	Tinea Manum	Tinea Pedis	Tinea unguium
<i>Microsporum distortum</i>		X						
<i>Microsporum ferrugineum</i>		X						
Nondermatophytid molds								
<i>Scopulariopsis brevicaulis</i>								X
<i>Scytalidium spp.</i>								X
<i>Acremonium spp.</i>								X
<i>Fusarium spp.</i>								X
<i>Hendersonula spp.</i>								X
Yeasts								
<i>Candida albicans</i>				X			X	X
<i>Candida parapsilosis</i>								X ^a
<i>Candida krusei</i>								X ^a
<i>Candida tropicalis</i>								X ^a

^a It is rarely the causative agent of the indicated dermatophytosis.

It is evident from table 8 and the pivotal studies summarized above, that dermatophytes are the most common cause of the tineas for which the sponsor is seeking approval..

Table 9 summarizes the *in vitro* activity of terbinafine hydrochloride and was constructed by Dr. Creedon from the data submitted by the sponsor under NDAs 20-192 and 20-539. These data shows that terbinafine hydrochloride has good activity against the dermatophytes but a limited activity against *Fusarium* and *Candida* spp. In fact the sponsor states in NDA 20-192, page 07-00011 of Vol. 47, that "Against *C. albicans* the MIC of SF 82-327 (terbinafine hydrochloride) was fungistatic; fungicidal effects were observed only at concentrations 5 times the MIC."

TABLE 9. *In vitro* susceptibility profile of terbinafine hydrochloride.

Microorganism	No. of Isolates	MIC range (µg/mL)	MIC ₉₀ range (µg/mL)
<i>Trichophyton rubrum</i>	66		
<i>Trichophyton mentagrophytes</i>	86		
<i>Trichophyton tonsurans</i>	11		
<i>Epidermophyton floccosum</i>	26		
<i>Microsporum canis</i>	54		
<i>Microsporum gypseum</i>	13		
<i>Microsporum nanum</i>	8		
<i>Aspergillus flavus</i>	32		
<i>Aspergillus fumigatus</i>	102		
<i>Aspergillus nidulans</i>	3		
<i>Aspergillus niger</i>	56		
<i>Aspergillus terreus</i>	17		
<i>Scopulariopsis brevicaulis</i>	101		
<i>Fusarium</i> spp.	27		
<i>Candida albicans</i>	268		
<i>Candida glabrata</i>	45		
<i>Candida krusei</i>	18		
<i>Candida parapsilosis</i>	73		
<i>Candida pseudotropicalis</i>	7		
<i>Candida tropicalis</i>	36		

The sponsor have requested that the following organisms be placed in the *in vitro* section of the package insert:

Microbiologist's comments: must be omitted from the *in vitro* list for two reasons:

The applicant is requesting the following microorganisms to be placed in the *in vivo* section of the package insert:

Microbiologist's comments:

1. The list must be written in an alphabetical order.
2. In the pivotal studies for pityriasis versicolor, according to the sponsor's analysis, the TSSS reduction by Lamisil was statistically borderline ($P \leq 0.045$) compared to placebo. When the medical officer reviews the data there is the possibility that this indication will not get approved. In such a case should be omitted from the list of the organisms for which clinical efficacy has been shown in clinical trials.

4. PACKAGE INSERT

The Microbiology subsection of the package insert should be rewritten as follows. The changes are highlighted:

NDA 20-749
Sandoz Pharmaceuticals corp.
1% terbinafine hydrochloride solution

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CONCLUSION & RECOMMENDATIONS:

The application is approvable from the clinical microbiology viewpoint under section 505 of the Act. The sponsor should be notified to revise the Microbiology subsection of the package insert as indicated on pages 15-16 of this review.

Sousan S. Altaie, Ph. D.
Clinical Microbiology Review Officer
3-18-97

cc: Orig. NDA 20-749
HFD-540/Division File
HFD-520/Micro/S Altaie
HFD-540/MO/E Toombs
HFD-540/Pharm/K Mainigi
HFD-540/Chem/J Vidra
HFD-540/Stat/S Thomson
HFD-160/Micro/N Sweeney
HFD-540/ Biopharm/D Bashaw
HFD-540/CSO/F Cross

Concurrence Only:
HFD-540/Dir/J Wilkin
HFD-520/SMicro/A Sheldon

Final Init 3/18/97 ASDP
JD 3/18/97

10 3/20/97