CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-749

MEDICAL REVIEW(S)

SEP 5 1997

Medical Officer's Review of Original NDA 20-749

Submission Date: October 17, 1996
Receipt Date: October 23, 1996
First Draft: April 18, 1997

Sponsor: Sandoz Pharmaceuticals
59 Route 10
East Hanover, New Jersey 07936-1080

Product Name (trade): Lamisil Solution, 1%
(generic): Terbanifine hydrochloride

Pharmacologic Class: Antifungal

Chemical Class: Allylamine

Therapeutic Class: 1S

Proposed Indications: Tinea versicolor, tinea pedis, tinea cruris and tinea corporis

Route of Administration: Topical

Proposed Dosage: Twice daily - Tinea versicolor
Once daily - Tinea corporis/cruris/pedis

Related NDA's: 20-192 (Lamisil 1% cream)
20-539 (Lamisil 250mg tablets)

Related IND's:

Foreign Marketing History: Lamisil 1% solution is not marketed in any country as of the date of this review. Applications for marketing have been submitted in Japan and in the United Kingdom. Lamisil 1% Cream was approved by the US Food and Drug Administration in December of 1992 for the treatment of dermatophyte infections affecting the skin. Lamisil 250 mg tablets were FDA approved in December of 1996 for the treatment of onychomycosis of the toenails or fingernails.

Manufacturing and Controls: (See Chemist's Review for Detailed Report) The drug substance and final product, (E)n(6,6-dimethyl2hepten-4-ynyl-N-methyl-1-naphthalenemethanamine hydrochloride, with a molecular weight of 291.44 will be synthesized by

Ingredients:	Terbanifine hydrochloride	0.010g	Active ingredient
	Cetomacrogol 1000	g	
	Propylene glycol	g	
	Ethanol 96%	g	
	Water purified	g	

Pharmacology and Toxicology: (See Pharmacologist's Review for Detailed Report)
A complete toxicology report was submitted in support of NDA's 20,192 and 20,539 (Lamisil cream and tablets, respectively). The sponsor requests that previously submitted data be incorporated into this NDA by cross reference. Toxicology studies evaluating the solution and submitted directly to NDA 20,749 include: acute toxicology (oral gavage), multidose toxicity and dermal and ocular irritation/sensitization studies.

Acute Toxicology: mice and WIST rats received either 1% Lamisil solution or placebo by oral gavage. Prior to necropsy, both groups were noted to have a decrease in body weight, altered equilibrium, flaccid muscle tone and drowsiness.

Multidose Toxicity: Lamisil 15% solution at dosages of 0.5, 1.5 and 3.0 mL/kg/day was applied to rabbit skin for 28 days. No macroscopic or microscopic organ changes were noted. There were no alterations in laboratory results.

Dermal Irritation/Sensitization: In a placebo controlled animal toxicity study, 0.5cc of Lamisil solution or vehicle was applied under occlusion to abraded and unabraded skin of male rabbits for 6 or 24 hours. Mild erythema was observed in both (Lamisil and vehicle) groups with an irritation index 0.2 and 0.3 for Lamisil and vehicle, respectively.

In an irritancy assessment, Lamisil solution (.1cc) or placebo was applied to occluded and non-occluded skin of rabbits for 28 days (placebo control was included). Erythema and edema were noted at both treatment sites. Irritation scores were 1.5 (Lamisil) and 2 for placebo. Reversible, histologic changes included hyperkeratosis, parakeratosis and mild dermal infiltration in both groups.

In a second dermal irritation study conducted in male rabbits: 0.1 cc of Lamisil 1% solution or deteriorated Lamisil solution applied daily for 28 days revealed erythema and edema in both groups. Histopathology and irritation scores were similar to the previous study (1.5 for Lamisil versus 1.67 for the deteriorated solution).

The results of dermal sensitization studies in guinea pigs using concentrations of Lamisil solution from % with as a positive control did not suggest that Lamisil was a sensitizer, in animals.

Clinical Pharmacokinetic Studies: Four cutaneous pharmacokinetic studies were submitted in support of this application; SFF 101,103, 307 and 205. Note: Study 205-E-00 did not include the study drug, Lamisil Gel (an unapproved agent) and Lamisil Cream formulation were evaluated., the results will not be reviewed here.

Study SFF 101 E-00: Determination of Plasma Concentration of Terbinafine and it's Metabolite in 11 Healthy Volunteers

Design: Eleven volunteers with normal skin were enrolled in this United States trial and instructed to apply Lamisil 1% solution to a 150cm2 area of inner thigh skin once daily for 7 days. Plasma samples for terbinafine and it's metabolite were measured before treatment, pre and post the final application.

Results: Both terbinafine and it's metabolite were below the quantifying level; 8ng/cc.

Comment: Percutaneous absorption of Lamisil appears to be negligible in patients with healthy skin.

Study SFF 103-E-00: Determination of Plasma Concentration of SF 86-327 Applied Once Daily as a Topical 1% Solution for 7 Days to Patients with Tinea Cruris

Design: Ten patients with tinea cruris were enrolled in this 7 day United States study which was designed to measure the systemic absorption of Lamisil 1% Solution from intertriginous skin. Patients were instructed to apply the study drug to affected areas (24 - 85 cm) once daily for 7 days; the average amount applied for the study duration was 0.8 grams. Measurement of plasma terbinafine levels was completed prior to treatment and 2 hours before and after the last dose on day 7.

Results: Plasma levels of Lamisil ranged from ng/ml at the 2 hour time point; levels of the metabolite were from ng/ml.

Comment: Percutaneous absorption of Lamisil solution does not significantly differ between normal and diseased intertriginous skin; remaining less than 2% of that seen with a single 250mg dose of the oral formulation.

Study SF 307-E-00: A Study to Investigate the Skin Pharmacokinetics of Two Delivery Devices of Lamisil 1% Solution Compared to Lamisil 1% Cream in Healthy Subjects, Following a Single Application on One, Five or Seven Consecutive Days

Design: Thirty-six healthy subjects were enrolled in this European clinical trial in order to compare the epidermal drug levels of Lamisil 1% solution (delivered by dropper or spray) and Lamisil 1% cream. In a open label, parallel design, patients were instructed to apply 5mg of terbanifine to a 190cm2 area of skin on the back once daily for 7 days.
Results: Terbinafine was detectable in the stratum corneum of all subjects with no clinically significant differences noted between formulations or dispenser type.
Comment: Lamisil 1% Solution is at least as bioavailable as the approved product, Lamisil 1% Cream.

Clinical Dermatotoxicity Studies

Principal Investigator: Lynne Harrison, PhD
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Co-Investigator: Lewis Stolman, MD

Study SF 102-E00/001: Study of the Cumulative Irritation Potential of SF 86-327 1-3% Solution Applied Topically to Volunteers

Design: Thirty healthy, adult males and females were enrolled in this 21 day safety study in order to assess the cumulative irritation potential of Lamisil Solution in 1, 2 and 3% concentrations as compared to vehicle and water. Test materials were applied to the skin of the backs of the study participants under occlusive or semi-occlusive every 48-72 hours for the study duration. Scoring of test sites was completed with each patch change. The scores were aggregated, summed and averaged for the 21 day trial.

Results: Twenty-five subjects completed the study. There were no scores above 1 (erythema) recorded during the study for any of the test products, scores of 0.5 and 1 were recorded intermittently.

Conclusion: The results of this study suggest that Lamisil 1% Solution is not a cumulative irritatant.

Study SFF 107: Phototoxicity Test

Design: Patch tests containing: Lamisil 2% Solution, vehicle solution, Lotrimin Solution and vehicle N solution were applied to the arm skin of eleven adult male and female subjects for 24 hours. Following removal of the test products, the treated sites were graded for irritation. UVA irradiation was then applied to one treated arm of each subject; evaluation of these sites for irritation was completed 24 and 48 hours later.

Results: Three subjects exhibited +/- or 1 reaction in both photo-exposed and non-photo exposed vehicle treated sites. One subject exhibited a +/- reaction on the Lamisil irradiated site.

Conclusion: These results suggest that Lamisil 1% topical solution is not a cutaneous photosensitizer.

Study SFF 107: Photoallergy Test

Design: Thirty-seven subjects entered this 5 week trial designed to assess the photoallergic potential of topically applied Lamisil 2% Solution compared to vehicle and clotrimazole solution. Patch tests containing: Lamisil 2% Solution, vehicle solution, Lotrimin Solution and vehicle N solution were applied to each arm for 3 weeks. Patches were removed and administration of UVA irradiation to one arm was completed; areas were prior to and subsequent to. After a 2 week rest period, challenge irradiation was completed in a similar manner followed by scoring: immediately, 24 and 48 hours post-irradiation.

Results: Thirty-one subjects completed the trial, there were 6 non-drug related study discontinuances, ie., personal or failure to return. One third of all the irradiated sites exhibited low level reactions (+/-) following the induction phase. There were no reactions following the challenge except at the vehicle "N" solution sites (irradiated and non-irradiated).

Comments: Lamisil nor it's vehicle appear to be photoallergens based on the results of this study.

Clinical Dermatoxicity Cont'd

Study 107 SFF: Repeated Insult Patch Test

Design: Two-hundred forty-two healthy adult volunteers were enrolled in this dermatotoxicity trial in order to assess the allergic sensitization potential of Lamisil 1% solution. Subjects were patched with 4 test preparations: Lamisil solution, Lamisil vehicle solution, Lotrimin solution and vehicle "N" solution, each of which was applied to the skin of their backs 3 times weekly for 3 weeks. Reactions were quantified after patch removal and following the challenge phase.

Results: During the induction phase: 11 of the Lamisil solution group, 1 of the Lamisil vehicle group and 12 of the vehicle "N" were described as having low level (+/-) reactions. There were only 2 low level reactions reported in the Lamisil group during the challenge phase.

Conclusion: The results of this study suggests that Lamisil 1% solution is not a contact allergen.

The sponsor submitted the results of 9 clinical studies in support of the safety and efficacy of Lamisil 1% solution in the treatment of dermatophyte infections (see table 1). A total of 1666 patients were enrolled in the clinical trials: 962 were randomized to Lamisil, 351 to clotrimazole, 353 were randomized to placebo.

Design: Exclusive of Study 309 (actively controlled with clotrimazole therefore not reviewed here), all of the clinical trials were randomized, multi centered, double-blind and placebo controlled. Four of the trials were completed in the United States, the remaining 5 (including Study 309) were completed in Europe. All groups were treated for 8 days with the exception of Study 104 where the duration of therapy was three weeks.

Clinical Studies:	Pages 10 thru 16	Tinea Versicolor	SFF 353-E-00 SFF 305-E-00
	Pages 17 thru 25	Tinea Pedis	SFF 301-E-100 SFF 351-E-100
	Pages 26 thru 34	Tinea Corporis/Cruris	SFF 303-E-100 SFF 108-E-100 SFF 105-E-100

Methods: The duration of therapy, clinical assessments (1 ,2,4,6,8 weeks and end of study), exclusion and inclusion criteria were similar across studies. (see next page)

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Safety and Efficacy Studies - Tinea Versicolor

Introduction: Tinea versicolor. "fungus various colors", is a very common superficial fungal infection, the etiologic agent of which is *Malassezia furfur.* Malasezzia furfur, a dimorphic , lipophilic organism considered part of the normal cutaneous flora, becomes infectious when conditions (humidity, immunosupression, Cushings disease) allow for transformation of the fungus into the mycelial phase. The classic clinical presentation consists of scaling, fawn colored/hypo or hyperpigmented patches involving the primarily, but not exclusively, the thoracic skin. Tinea versicolor is generally diagnosed clinically, confirmation is made by microspic examination of associated cutaneous scales using KOH - potassium hydroxide. Effective topical treatments include: selenium sulfide, imidazoles and other antifungals, and keratolytic agents. More aggressive or recurrent cases respond to oral imidazoles.

Study SFF 353-E-00: A Randomized, Double-Blind, Placebo Controlled, Multi center Study of the Efficacy and Safety of Lamisil (terbinafine) 1% Solution -Topical Compared to Vehicle BID for One Week in Subjects with Pityriasis Versicolor

Design: This double-blind, vehicle controlled, 1 week trial enrolled 150 patients with tinea versicolor in 10 different centers within the United States. At the screening visit, subjects who were eligible for enrollment underwent skin scraping of a target lesion for direct microscopy in addition to an assessment of clinical signs and symptoms associated with tinea versicolor. Subsequently, patients were randomized in a 2 - 1 fashion to receive either Lamisil 1% Solution or vehicle with instructions for twice daily application of the study product to affected areas for 7 days. At days 8, 14, 28 and 56 (the end of study) patients were re-evaluated for mycology, clinical assessments and adverse events.

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Study SFF 353-00/Tinea Versicolor Cont'd

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Table 1) Disposition and Demographics

	Treatment Group			
	Lamisil		Placebo	
	N	(%)	N	(%)
Subjects entered	103	(100)	49	(100)
No. subjects with no post-baseline safety assessment	5	(5)	2	(4)
Safety population	98	(95)	47	(96)
Safety subjects excluded from the ITT population	1	(1)	0	(0)
ITT population	97	(94)	47	(96)
ITT subjects with protocol violations	15	(15)	8	(16)
Valid population	82	(80)	39	(80)
Number of males/females	47/50		26/21	
Mean age (yrs)	34		34	
Age range				

Reviewer's comments: Seven patients were excluded from the safety evaluation, these patients withdrew from the trial prior to the receipt of study drug. An additional patient in the Lamisil group received the study drug but was unavailable for post-baseline efficacy evaluations. The treatment groups appear to be demographically balanced.

Table 2) Discontinuances

	Treatment Group			
	Lamisil		Placebo	
	N	(%)	N	(%)
Withdrawal of Consent	2	(2)	0	(0)
Teatment Failure	2	(2)	2	(4)
Failure to Return for Scheduled Visits	10	(10)	4	(8)
Other	1	(1)	0	(0)
Total Discontinued	15	(15)	6	(21)

Reviewer's comments: Fifteen and 6 patients from the Lamisil and vehicle treament groups respectively, discontinued study participation early. There were no significant differences between the groups with respect to numbers or reasons for discontinuances. There were no discontinuances related to adverse events in either group.

Table 3) Number and Percent of Patients with Effective Treatment

Treatment	Week 1	Week 2	Week 4	Week 8	End of Study
Lamisil	46/96 (48%)	60/91 (66%)	68/86 (79%)	69/85 (81%)	75/97 (77%)
Placebo	14/46 (30%)	23/45 (51%)	20/44 (45%)	13/43 (30%)	13/47 (28%)
p-value	0.041	0.164	<0.001	<0.001	<0.001

Comments: At the end of weeks I, 4, 8 and end of study; the response to Lamisil solution was statistically better than the response to placebo as evidenced by the number and percent of patients with "effective treatment" -negative KOH and total signs/symptoms less than 1. At the end of week two, Lamisil did not demonstrate an advantage, this was probably due to a lowering of the difference in mean reduction from baseline between the 2 study products (Lamisil 3.2. vehicle 3.0).

Table 4) Number and Percent of Patients with Negative Microscopy

Treatment	ITT				
	Week 1	Week 2	Week 4	Week 8	End of Study
Lamisil	57/96 (59%)	69/91 (76%)	73/86 (85%)	69/85 (81%)	76/97 (78%)
Placebo	26/46 (57%)	27/45 (60%)	23/44 (52%)	14/43 (33%)	14/47 (30%)
p-value	0.642	0.074	<0.001	<0.001	<0.001

Comment: Minor differences between the 2 study products noted at the end of 2 weeks became statistically significant favoring Lamisil by the end of the 4th week through the end of the study.

Table 5) Total Signs and Symptoms Score - Reduction from Baseline

Treatment	Baseline		Week 1		Week 2		Week 4		Week 8		End of Study	
	(N)	Mean	(N)	Mean Reduction	(N)	Mean Reduction	(N)	Mean Reduction	(N)	Mean Reduction	(N)	Mean Reduction
Lamisil	97	4.1	96	2.7	92	3.2	88	3.5	85	3.6	97	3.5
Placebo	47	4.3	46	2.2	45	3.0	44	2.7	43	2.4	47	2.4
p-value	0.829		0.132		0.251		0.003		0.002		0.002	

Comments: Clinical improvement was noted in both groups at the end of treatment .Lamisil was not significantly better than placebo until week 4; where the mean reduction of 3.5 from baseline resulted in a disease activity score of .6; this advantage continued until the end of the study.

Table 6) Summary of Secondary Efficacy Variables at End of Study

	ITT (n/N)		Valid (n/N)		
	Lamisil	Placebo	Lamisil	Placebo	p-value for ITT
Complete Cure	64/97 (66%)	12/47 (26%)	56/82 (68%)	11/39 (28%)	<0.001
Clinical Cure	70/97 (72%)	17/47 (36%)	61/82 (74%)	15/39 (38%)	<0.001
Investigator Assessment Very Good or Good	74/91 (81%)	13/45 (29%)	66/82 (81%)	12/39 (31%)	<0.001
Patient Assessment Very Good or Good	71/91 (78%)	23/45 (51%)	64/82 (78%)	20/39 (51%)	<0.001

Comments: The end of study comparisons of Lamisil and placebo for both the intent to treat and valid patient populations including all the parameters measured (patient and physician assessments) supports the superiority of Lamisil over placebo in the treatment of tinea versicolor.

Table 7) Summary of Adverse Events by Body System

Body System	Preferred Term	Treatment Group			
		Lamisil (N=98)		Placebo (N=47)	
Skin And Appendages Disorders	Eczema	0	(0.0%)	1	(2.1%)
	Pruritus	1	(1.0%)	0	(0.0%)
	Rash	1	(1.0%)	0	(0.0%)
	Rash Maculo-Papular	1	(1.0%)	0	(0.0%)
	Skin Disorder	0	(0.0%)	1	(2.1%)
	Skin Dry	0	(0.0%)	1	(2.1%)
	Skin Exfoliation	1	(1.0%)	0	(0.0%)
Respiratory System Disorders	Pharyngitis	1	(1.0%)	0	(0.0%)
	Upper Resp Tract Infection	2	(2.0%)	0	(0.0%)
Urinary System Disorders	Urethral Disorder	1	(1.0%)	0	(0.0%)
	Urinary Tract Infection	1	(1.0%)	0	(0.0%)
Body As A Whole - General Disorders	Infection Bacterial	1	(1.0%)	0	(0.0%)
	Influenza-Like Symptoms	0	(0.0%)	1	(2.1%)
Application Site Disorders	Application Site Reaction	1	(1.0%)	1	(2.1%)
Nervous Sustem	Headache	2	(2.0%)	1	(2.1%
Cardiovascular Disorders, General	Hypertension	1	(1.0%)	0	(0.0%)
Vision Disorders	Photophobia	1	(1.0%)	0	(0.0%)
Metabolic And Nutritional Disorders	Hyperglycaemia	1	(1.0%)	0	(0.0%)
Musculo-Skeletal System Disorders	Back Pain	1	(1.0%)	0	(0.0%)

Comments: Approximately 10% of patients from each group (10/98 - Lamisil , 5/47 - vehicle) experienced an adverse event. These events were primarily of a non-serious nature and unrelated to study drug. The safety of Lamisil topical is supported by the low adverse event profile of the cream formulation and from the table above.

Study SFF 305-E00 A Randomized, Double-blind, Vehicle Controlled, Multicenter Study of the Efficacy and Safety of Lamisil 1% Solution Compared to Vehicle BID for One Week In Subjects with Pityriasis Versicolor

The design and methods of the European study were identical to those of Study SFF 353. One hundred-fifteen patients entered the trial; 79 were randomized to receive lamisil twice daily, the remaining 36 served as the vehicle control.

Table 8) Disposition and Demographics

	Treatment Group			
	Lamisil		Placebo	
	N	(%)	N	(%)
Subjects entered	79	(100)	36	(100)
No. subjects with no post-baseline safety assessment	2	(5)	1	(4)
Safety population	77	(95)	35	(96)
Safety subjects excluded from the ITT population	1	(1)	1	(0)
ITT population	76	(94)	34	(96)
ITT subjects with protocol violations	17	(15)	8	(16)
Valid population	59	(80)	26	(80)
Number of males/females	39/37		20/14	
Mean age (yrs)	34		32	
Age range				

Comment: The treatment arms were balanced. Two patients in each group withdrew consent, 2 of the Lamisil group failed to return for scheduled visits, therefore, 76 or 96% of the Lamisil treated patients and 35 or 97% of the vehicle treated patients completed the study.

Table 9) Number and Percent of Patients with Effective Treatment

Treatment group	Week 1	Week 2	Week 4	Week 8	End of Study
Lamisil solution	20/72 (28%)	37/65 (57%)	42/59 (71%)	42/58 (72%)	52/74 (70%)
Placebo	5/33 (15%)	10/31 (32%)	10/31 (32%)	7/27 (26%)	11/34 (32%)
p-value	0.106	0.006	<0.001	<0.001	<0.001

Comment: At the end of treatment (week 1); there were no significant differences between the two groups. By the end of week 2 and continuing through the end of the study, Lamisil provided a statistically significant ($p<0.001$) response in this group of patients.

Table 10) Number and Percent of Patients with Negative Microscopy

Treatment group	Week 1	Week 2	Week 4	Week 8	End of Study
Lamisil solution	26/68 (38%)	47/65 (72%)	46/59 (78%)	47/58 (81%)	58/73 (79%)
Placebo	8/32 (25%)	14/30 (47%)	12/31 (39%)	11/27 (41%)	15/34 (44%)
p-value	0.141	0.012	<0.001	<0.001	<0.001

Comment: Supporting the primary efficacy variable (effective treatment), a greater percentage and relative of number Lamisil treated patients demonstrated mycological cure beginning at the end of 2 weeks and continuing through the end of the study.

Table 11) Total Signs and Symptoms Score - Reduction from Baseline

Treatment	Baseline	Reduction Week 1	Reduction Week 2	Reduction Week 4	Reduction Week 8	Reduction End of Study
Lamisil solution	3.6±1.2	2.0±1.5	2.7±1.6	2.9±1.5	3.1±1.4	3.1±1.4
Placebo	3.9±1.5	2.0±1.8	2.6±1.7	2.9±1.5	2.6±1.5	2.6±1.6
p-valuea	0.488	0.996	0.968	0.305	0.037	0.045

Comment: There were no significant differences between treatment groups until week 8 or end of study, at which time, a statistically significant number of Lamisil treated patients were clinically cured.

Table 12) Summary of Secondary Efficacy Variables at End of Study

Variable	Number and Percent of Patients		p-value
	Lamisil N=76	Placebo N=34	
Secondary efficacy			
Complete Cure	35/75 (47%)	10/34 (29%)	0.031
Clinical Cure	49/76 (64%)	14/34 (41%)	0.016
Negative Microscopy	58/73 (79%)	15/34 (44%)	<0.001
Mean Reduction in Total Signs/Sympt	3.1	2.6	0.045
Investigator Assessment >Good	53/76(70%)	13/34(38%)	0.001

Table 13) Summary of Adverse Events

Body System		Treatment Group			
		Lamisil (N=77)		Placebo (N=35)	
Skin And Appendages Disorders	Eczema	1	(1.3%)	1	(2.9%)
	Pruritus	2	(2.6%)	1	(2.9%)
	Rash	1	(2.6%)	0	(0.0%)
	Follicutitis	1	(1.3%)	0	(0.0%)
	Abscess	1	(1.3%)	0	(0.0%)
	Skin Dry	1	(1.3%)	0	(0.0%)
	Skin Exfoliation	0	(0.0%)	1	(2.9%)
Respiratory System Disorders	Lower Resp Tract Symptoms	4	(5.2%)	4	(11.5%)
	Upper Resp Tract Infection	1	(1.3%)	1	(2.9%)
Female Reproductive System Disorders	Tumor Benign	1	(1.3%)	0	(0.0%)
	Urinary Tract	1	(1.3%)	0	(0.0%)
Body As A Whole - General Disorders	Infection	3	(3.9%)	0	(0.0%)
	Pain	1	(1.3%)	1	(2.9%)
Body As A Whole	Fever	0	(0.0%)	1	(2.9%)
Central And Peripheral Nervous Syst. Disorders	Headache	2	(2.6%)	1	(2.9%)
Cardiovascular Disorders, General	Hypertension	1	(1.3%)	0	(0.0%)
Psychiatric Disorders	Depression	1	(1.3%)	0	(0.0%)
Gastro-Intestinal System Disorders	Abdominal pain	1	(1.3%)	0	(0.0%)
Musculo-Skeletal System Disorders	Myalgia	1	(1.3%)	0	(0.0%)

Comments: The safety of Lamisil solution is supported by the paucity of adverse events, which are comparable in number and severity to vehicle

Reviewer's Summary Comments: The sponsor has submitted the results of 2 well controlled clinical studies in which 127 of 171 patients with tinea versicolor were effectively treated by applying Lamisil solution to affected areas of skin twice daily for one week. Despite the relative ease with which tinea versicolor responds to most therapies; the comparative advantage demonstrated by Lamisil over vehicle was statistically significant throughout the study (p values at week two $=0.012$ and 0.006 for the respective studies 305 and 353 with end of study pvalues <0.001 for both) results. The mycological response was evident earlier than the clinical improvement which is consistent with the nature of tinea versicolor infections. The minimal adverse event profiles of the active and "inactive" preparations were equivalent. These studies support the efficacy and safety of topically applied Lamisil 1% solution in the treatment of Tinea versicolor.

Clinical Efficacy and Safety Studies - Tinea Pedis

Background: Tinea pedis is an exogenously transmitted dermatophyte infection, caused most frequently by Trichophyton rubrum or Trichophyton mentagrophytes or Epidermophyton floccosum. Epidemiologic studies suggest moisture, humidity and personal contact as risk factors. Clinically, the infection presents in one of four varieties: patchy, diffuse mocassin-like pattern with scaling, vesiduobullous papules on the plantar surface, an acute ulcerative variant or most commonly a scaling, macerated interdigital pattern. Culture and KOH microscopy help confirm the clinical diagnosis. Oral griseofulvin and or topical antifungals used for several weeks in conjunction with measures to keep the infected area dry are effective treatments.

Study 301-E-100 A randomized, double-blind, placebo-controlled, multi-centre study of the efficacy and safety of Lamisil (terbinafine 1 %) topical solution compared to placebo once daily for one week in subjects with interdigital type tinea pedis

Design: The design and methodology of this European (Denmark, Iceland, France and the United Kingdom) clinical trial were very similar to that of the studies completed in patients with tinea versicolor, with 2 important differences: 1) patients must have clinical and *mycologic diagnoses of tinea pedis* and 2) study products were to be applied once daily.

The primary efficacy variable 'effective treatment' was defined as: *negative microscopy (KOH) and culture* and a total signs and symptoms score of less than 2. 1, individual severity scores (erythema, pruritus and desquamation) less than 1.1 and individual severity scores for pustules, vesiculation and incrustation =0. Patients designated as effectively treated were classified as completely cured if their total signs and symptoms score was 0. Patients whose total signs and symptoms score was 2 or less were classified as 'cure'.

Clinical assessments for efficacy and safety were made at weeks 1,2,8 and the end of study.

Table 14) Disposition and Demographics

	Treatment Group			
	Lamisil		Placebo	
	N	(%)	N	(%)
Subjects entered	115	(100)	57	(100)
No. subjects with no post-baseline safety assessment	2	(2)	0	(0)
Safety population	113	(98)	57	(100)
Safety subjects excluded from the ITT population (delayed exclusions)	42	(37)	18	(32)
ITT population	71	0	39	0
ITT subjects with protocol violations	24	0	16	(
Valid population	47	0	23	0
Number of males/females	51/20		35/4	
Mean age (yrs)	41		42	
Age rangea				

Comment: One hundred sixty-nine patients entered the study. Forty-two of the Lamisil group and 18 of the placebo group had negative baseline mycology and were therefore delayed exclusions. The study groups were demographically similar.

Table 15) Patients Discontinued from Study

Primary Reason for Discontinuation From the Study	Lamisil (N = 115)		Placebo (N = 57)		Total (N = 172)	
Withdrawal of Consent	0	(0%)	1	(2%)	1	(1%)
Protocol Violation	2	(2%)	1	(2%)	3	(2%)
Treatment Failure	1	(1%)	2	(4%)	3	(2%)
Failure to Return for Scheduled Visits	5	(4%)	2	(4%)	7	(4%)
Other	2	(2%)	0	(0%)	2	(1%)
Total Discontinued	10	(9%)	6	(11%)	16	(9%)

Comment: One hundred - ten patients entered the treatment phase; 71 in the Lamisil group and 39 in the vehicle group. The number of discontinuances were approximately equal.

Table 16) Number and Percent of Patients with Effective Treatment

Treatment group	Week 1	Week 2	Week 8	End of Study
Lamisil	14/69 (20%)	18/67 (27%)	44/53 (83%)	54/71 (76%)
Placebo	2/37 (5%)	2/33 (6%)	7/32 (22%)	8/39 (21%)
p-value	0.049	0.014	<0.001	<0.001

Comment: At the end of treatment, 20% of Lamisil patients were "effectively treated" as compared ot 5% of the vehicle group. A statistical advantage was maintained by Lamisil through the study end.

Table 17) Number and Percent of Patients with Negative Mycology

Treatment group	Week 1	Week 2	Week 8	End of Study
Lamisil	34/69 (49%)	36/66 (55%)	50/53 (94%)	60/71 (85%)
Placebo	5/37 (14%)	6/32 (19%)	8/32 (25%)	9/39 (23%)
p-value	0.002	<0.001	<0.001	<0.001

Table 18) Total Signs and Symptoms Score - Reduction from Baseline

Treatment	Baseline		Week 1		Week 2		Week 8		End of Study	
	N	Mean	N	Mean reduction	N	Mean reduction	N	Mean reduction	N	Mean reduction
Lamisil	71	6.1	69	3.0	67	4.1	56	5.6	71	5.5
Placebo	39	6.5	38	2.5	34	3.2	32	3.1	39	2.9
p-value	0.220		0.572		0.113		<0.001		<0.001	

Table 19) Summary of Secondary Variables at End of Study

Efficacy Variable	Treatment Group		p-value
	Lamisil (n/N)	Placebo (n/N)	
Negative Microscopy	62/71 (87%)	13/39(33%	<0.001
Negative Culture	65/71(92%)	13/39(33%	<0.001
Complete Cure	36/71(51%)	2/39 (5%)	<0.001
Clinical Cure	43/71(61%)	3/39 (8%)	<0.001
Overall Assessment of Efficacy by Investigator (Very Good or Good)	61/71 (87%)	10/39 (26%)	<0.001

Comments: A statistically significant number (34/69) of Lamisil treated patients were mycologically negative at the end of the first week of therapy. By the end of the study, 85% of the Lamisil patients were mycologically negative. The reduction in signs and symptoms although better than vehicle throughout the study did not reach statistical significance until week 8.

Summary of Adverse Events by Body System

Body System	Preferred Term	Treatment Group			
		Lamisil (N=113)		Placebo (N=57)	
Body As A Whole - General Disorders	Accidental Trauma	1	(0.9%)	0	(0.0%)
	Allergic Reaction	0	(0.0%)	1	(1.8%)
	Back Pain	1	(0.9%)	0	(0.0%)
	Infection	1	(0.9%)	0	(0.0%)
	Infection Viral	1	(0.9%)	0	(0.0%)
Respiratory System Disorders	Sinusitis	1	(0.9%)	0	(0.0%)
Skin And Appendages Disorders	Pruritus	2	(1.8%)	1	(1.8%)
	Rash Erythematous	1	(0.9%)	0	(0.0%)
	Rash Maculo-Papular	0	(0.0%)	1	(1.8%)
	Rash Pustular	0	(0.0%)	1	(1.8%)
	Skin Disorder	3	(2.7%)	3	(5.3%)
	Skin Exfoliation	1	(0.9%)	5	(8.8%)
Vision Disorders	Miosis	1	(0.9%)	0	(0.0%)

Comment: The adverse event profile of Lamisil and vehicle were comparable and of minimal incidence.

Study SFF 351-E-100 Tinea Pedis A Randomized, Double blind, Placebo Controlled, Multicenter Study of the Efficacy and Safety of Lamisil 1% Solution-Topical Compared to Vehicle "BID" for One Week in subjects with Interdigital Type Tinea Pedis.

Design: The overall design of this clinical trial was similar to the previously reviewed Study SFF 301 with one insignificant (evaluations were made at weeks 4 and 6 in addition to weeks 1, 2 and 8) and one very significant difference (dosage). The study product was applied "twice daily" for one week as opposed to once daily as in Study SFF 301.

Comment: The planned labeling indication is for once daily dosing for a period of seven days. There were no other studies submitted in support of this dosage and formulation which assessed the efficacy and safety of the once daily dosage for 7 days. Study 104 was performed as a clinical assessment of the efficacy of once daily application of Lamisil solution, however, the treatment duration was for 2 weeks. Furthermore, two of the investigators (Drs. Boni Elewski and Ronald Savin participated in Study SFF 301. Regulatory comments will be made Following the abstraction of the review.

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Methods: One hundred fifty-four patients entered the trial, disposition, demographic and discontinuance data is provided below.

Table 21) Disposition and Demographics

	Treatment Group			
	Lamisil		Placebo	
	N	(%)	N	(%)
Subjects entered	104	(100)	49	(100)
No. subjects with no post-baseline safety assessment	0	(0)	0	(0)
Safety population	104	(100)	49	(100)
Safety subjects excluded from the ITT population (delayed exclusions)	46	(44)	21	(43)
ITT population	58	(56)	28	(57)
ITT subjects with protocol violations	24	(23)	13	(27)
Valid population	34	(32)	15	(33)
Number of males/females	47/11		18/10	
Mean age (yrs)	41		43	
Age range				

Table 22) Discontinuances

Primary Reason for Discontinuation From the Study	Lamisil (N = 104)		Placebo (N = 49)		Total (N = 153)	
Withdrawal of Consent	1	(1%)	0	(0%)	1	(1%)
Protocol Violation	1	(1%)	1	(2%)	2	(1%)
Treatment Failure	5	(5%)	4	(8%)	9	(6%)
Failure to Return for Scheduled Visits	2	(2%)	2	(4%)	7	(3%)
Other	14	(13%)	4	(8%)	18	(12%)
Total Discontinued	23	(22%)	11	(22%)	34	(22%)
Total Completed	81	(78%)	38	(78%)	119	(78%)

Comment: One hundred nineteen patients completed the trial; discontinuances were equal across treatment arms. There were no discontinuances for adverse events.

Table 23) Number and Percent with Effective Treatment

Treatment	Week 1	Week 2	Week 4	Week 6	Week 8	End of Study
Lamisil	10/56 (18%)	9/57 (16%)	24/55 (44%)	32/53 (60%)	35/54 (65%)	38/58 (66%)
Placebo	1/28 (4%)	2/25 (8%)	3/24 (13%)	2/23 (9%)	1/23 (4%)	1/28 (4%)
p-value	0.085	0.324	0.008	<0.001	<0.001	<0.001

Comment: A statistically significant number (38/58) or 66% of Lamisil treated patients were effectively treated at the end of the study ($p<0.001$). Comparatively, only 1 of 28 vehicle treated patients achieved the same degree of success.

Table 24) Number and Percent of Patients with Negative Mycology

Treatment	Week 1	Week 2	Week 4	Week 6	Week 8	End of Study
Lamisil	24/56 (43%)	34/57 (60%)	43/55 (78%)	46/53 (87%)	47/54 (87%)	51/58 (88%)
Placebo	4/28 (14%)	3/25 (12%)	3/24 (13%)	2/23 (9%)	3/23 (13%)	4/28 (14%)
p-value	0.008	<0.001	<0.001	<0.001	<0.001	<0.001

Comment: A statistically significant mycological cure advantage was demonstrated at the week 1 evaluation in the Lamisil group, this advantage continued through the end of the study.

Table 25) Total Signs and Symptoms Score

Treatment	ITT											
	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8		End of Study	
	(N)	Mean	(N)	Mean Reduction	(N)	Mean Reduction	(N)	Mean Reduction	(N)	Mean Reduction	(N)	Mean Reduction	(N)	Mean Reduction
Lamisil	(58)	6.3	(56)	2.8	(57)	3.2	(56)	3.7	(54)	4.5	(56)	4.7	(58)	4.7
Placebo	(28)	6.4	(28)	1.9	(25)	2.9	(24)	2.4	(23)	1.9	(23)	1.6	(28)	1.3
p-value	0.627		0.135		0.450		0.017		<0.001		<0.001		<0.001	

Table 26) Summary of Secondary Efficacy Variables

	Lamisil	Placebo	p-values
Complete Cure	12/58 (21%)	0/28 (0%)	0.007
Clinical Cure	14/58 (24%)	1/28 (4%)	0.018
Assessment of Efficacy by Investigator, Good or >	45/56 (80%)	2/26 (8%)	<0.001
Assessment of Efficacy by Subject, Good or >	49/56 (88%)	6/26 (23%)	<0.001

Table 27) Summary of Adverse Events

Body System	Preferred Term	Treatment Group			
		Lamisil (N=104)		Placebo (N=49)	
Skin And Appendages Disorders	Eczema	1	(1.0%)	0	(0.0%)
	Seborrhoea	1	(1.0%)	0	(0.0%)
	Skin Disorder	0	(0.0%)	2	(4.1%)
	Dermatitis Contact	1	(1.0%)	0	(0.0%)
	Herpes Simplex	1	(1.0%)	0	(0.0%)
	Bullous Eruption	1	(1.0%)	0	(0.0%)
	Onychomycosis	0	(0.0%)	1	(2.0%)
Respiratory System Disorders	Coughing	2	(1.9%)	0	(0.0%)
	Pharyngitis	0	(0.0%)	1	(2.0%)
	Pneumonia	1	(1.0%)	0	(0.0%)
	Rhinitis	1	(1.0%)	0	(0.0%)
	Sinusitis	3	(2.9%)	1	(2.0%)
	Upper Resp Tract Infection	2	(1.9%)	0	(0.0%)
	Bronchitis	1	(1.0%)	0	(0.0%)
Body As A Whole - General Disorders	Infection Viral	1	(1.0%)	0	(0.0%)
	Accidental Trauma	1	(1.0%)	0	(0.0%)
Application Site Disorders	Application Site Reaction	3	(2.9%)	0	(0.0%)
Musculo-Skeletal System Disorders	Myopathy	1	(1.0%)	0	(0.0%)
Central And Peripheral Nervous Syst. Disorders	Headache	2	(1.9%)	0	(0.0%)
Hearing And Vestibular Disorders	Ear Disorder NOS	1	(1.0%)	0	(0.0%)

Comments: The adverse event profile of Lamisil was low and not significantly different from that seen with vehicle.

Overall Comments - Tinea Pedis Studies: 25

The sponsor submitted one efficacy study (SFF 301) in which Lamisil was used once daily for 7 days, conforming to the proposed label. This study supported the efficacy of once daily administration. A "supporting" study for twice daily dosing was submitted and although there were no head to head comparison trials; the results when compared to vehicle were superior with the once daily regimen, ie., effective treatment - once daily 76%, effective treatment - twice daily 66%. Additional studies included an active comparison with clotrimazole - both agents (Lamisil {1 weeks} and clotrimazole {4 weeks}) were used twice daily; efficacy results were similar. This study was not included in the review as it is the opinion of this author that those results do not address the issues. The sponsor asserts that since twice daily application of clotrimazole for 4 weeks is equivalent to twice daily application of Lamisil for 1 week; and once daily application of Lamisil for 1 weeks is superior to twice daily application - safety being assured; then the lowest dose (once daily) should be the label indication.

Note: Labeling for the cream formulation consists of BID dosing for 1 to 4 weeks.

The agency usually requires "2" double blind, vehicle controlled trials in order to support efficacy claims - same was not submitted for this review. Possible resolutions include: having the sponsor complete an additional efficacy trial at once daily dosing prior to approval, requiring a Phase 4 commitment to do same, (line extension from the cream is not an alternative), approving twice daily dosing as either a line extension or based on active control studies and 1 submitted efficacy study or approving the once daily dose.

The opinion of this author is that the indication for once daily- dosing in Tinea Pedis receive an "approvable" status and the sponsor be instructed that as a Phase 4 commitment an additional study should be submitted employing once daily dosing.

Note: After reviewing the first draft of this document, the Division Director - Dr. Jonathan Wilkin, commented that "Phase IV commitments are for approvals and cannot be contingent on outcome". As the sponsor submitted only one study demonstrating once daily dosing efficacy for one week of therapy in support of a tinea pedis indication, Lamisil solution can only be approved for twice daily dosing dosing according to the data available.

The primary reviewer supports this decision.

The sponsor submitted 3 double blind, vehicle controlled, multi center efficacy and safety studies in support of a labeling claim for once daily application of Lamisil solution to affected areas of Tinea corporis/cruris for 7 days.

Design: Two of the trials (SFF 303 - Europe and SFF 108 - Brazil) were completed outside of the United States. The design and methods were similar except study SFF 303 had a 7 week post treatment follow-up/studies 108 and 105 had 3 week follow-up periods.

Study SFF 303-E-00 A Randomized, Double-blind, Placebo-controlled, Multi center Study of the Efficacy and Safety of Lamisil 1% Solution Compared to Vehicle Once Daily for One Week in Subjects with Tinea Corporis/Cruris.

Table 28) Disposition and Demographics

	Treatment group	
	Lamisil Solution	Placebo
Subjects entered	102	49
No. subjects with no post-baseline assessment	3	1
Safety population	99	48
No. subjects with negative mycology at baseline	27	11
ITT population	72	37
No. subjects with protocol violations	15	6
Valid population	57	31
Male: female	56:16	28:9
Mean age (years)	42	45
Age range (years)		

Comment: Patients were demographically balanced between treatment arms.

Table 29 Discontinuances

Primary Reason for Discontinuation From the Study	Lamisil (N = 102)		Placebo (N = 49)		Total (N = 151)	
Adverse Events	2	(2%)	2	(4%)	4	(3%)
Protocol Violation	4	(4%)	1	(2%)	5	(3%)
Treatment Failure	10	(10%)	24	(49%)	34	(23%)
Failure to Return for Scheduled Visits	10	(10%)	2	(4%)	12	(8%)
Other	5	(5%)	0	(0%)	5	(3%)
Total Discontinued	31	(30%)	29	(59%)	60	(40%)
Total Completed	71	(70%)	20	(41%)	91	(60%)

Table 30) Number and Percent with Effective Treatment

	ITT (n/N)				
Treatment Group	Week 1	Week 2	Week 4	Week 8	End of Study
Lamisil (n=72)	26/69 (38%)	44/64 (69%)	36/51 (71%)	33/39(85%)	51/72 (71%)
Placebo (n=37)	0/36 (0%)	3/31 (10%)	3/16 (19%)	4/12(33%)	4/36 (11%)
p-value	<0.001	<0.001	0.007	0.013	<0.001

Comment: Beginning with the first evaluation, Lamisil treated patients demonstrated significant response rates compared to the vehicle group; the response continued through the end of study where 71% of the Lamisil group were "effectively treated" for a pvalue of <0.001.

Table 31) Number and Percent with Negative Mycology

Treatment Group	Week 1	Week 2	Week 4	Week 8	End of Study
Lamisil (n=72)	54/69 (78%)	53/63 (84%)	41/51 (80%)	35/38 (92%)	61/72 (85%)
Placebo (n=37)	4/36 (11%)	9/30 (30%)	5/16 (31%)	5/12 (42%)	10/36 (28%)
p-value	<0.001	<0.001	0.010	0.006	<0.001

Table 32) Total Signs and Symptoms Score from Baseline

Treatment	ITT Population					
	Baseline	Week 1	Week 1	Week 1	Week 1	End of Study
	(N) Mean	Mean (N)Reduction	Mean (N)Reduction	Mean (N)Reduction	Mean (N)Reduction	Mean (N)Reductionc
Lamisil	(72) 6.4	(71) 3.0	(67) 4.6	(58) 5.8	(47) 6.0	(72) 5.2
Placebo	(37) 6.7	(36) 1.5	(31) 2.2	(17) 2.9	(13) 4.3	(37) 1.8
p-value	0.095	0.004	0.001	0.010	0.399	<0.001

Table 33) Secondary Efficacy Variables at End of Study

	Treatment Group		
EFFICACY VARIABLE	Lamisil (n=72)	Placebo (n=37)	p-value
Complete Cure	38/72 (53%)	1/36 (3%)	<0.001
Clinical Cure	44/72 (61%)	4/37 (11%)	<0.001
Overall Assessment of Efficacy by Investigator (Very Good/Good)	59/72 (82%)	5/37 (13%)	<0.001

Table 34) Summary of Adverse Events

Body System	Preferred Term	Treatment Group			
		Lamisil (N=99)		Placebo (N=48)	
Application Site Disorders	Application Site Reaction	1	(1.0%)	2	(4.2%)
Body As A Whole - General Disorders	Condition Aggravated	3	(3.0%)	2	(4.2%)
	Infection Bacterial	0	(0.0%)	1	(2.1%)
	Infection Fungal	1	(1.0%)	1	(2.1%)
Liver And Biliary System Disorders	Hepatitis Cholestatic	0	(0.0%)	1	(2.1%)
Reproductive Disorders, Male	Balanoposthitis	1	(1.0%)	0	(0.0%)
Respiratory System Disorders	Bronchitis	1	(1.0%)	0	(0.0%)
Skin And Appendages Disorders	Folliculitis	1	(1.0%)	3	(6.3%)
	Pigmentation Abnormal	2	(2.0%)	0	(0.0%)
	Pruritus	6	(6.1%)	3	(6.3%)
	Rash	1	(1.0%)	0	(0.0%)
	Rash Erythematous	5	(5.1%)	5	(10.4%)
	Rash, Maculo-Papular	2	(2.0%)	1	(2.1%)
	Rash Papular	0	(0.0%)	1	(2.1%)
	Rash Pustular	1	(1.0%)	2	(4.2%)
	Skin Depigmentation	1	(1.0%)	0	(0.0%)
	Skin Disorder	3	(3.0%)	0	(0.0%)
	Skin Exfoliation	3	(3.0%)	2	(4.2%)
	Urticaria	1	(1.0%)	0	(0.0%)
Urinary System Disorders	Pyelonephritis	1	(1.0%)	0	(0.0%)

Comments: The incidence of adverse events (all of which were minor) was not significantly different between the treatment groups.

Study SFF 105-E-00 Tinea Corporis/Cruris Double blind Clinical Therapeutic Trial of the Efficacy and Safety of 1% Topical SF86-327 Applied Once Daily, Compared to Placebo (vehicle) During 1 Week in Subjects with Tinea Corporis/Cruris

This US, multi center, randomized trial following the basic scheme of Study SFF303 enrolled 66 patients who were instructed to apply the study product to affected areas once daily for 7 days. Follow-up assessments for efficacy and safety were completed at weeks 1, 2 and 4.

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Table 35) Disposition and Demographics

Patient Group	Lamisil	Placebo	Total
Subjects entered/ completing	32/29	34/22	66/51
No. Subjects with no Post-Baseline assessment Complete ITT population (= Safety Population)	0 32	0 34	0 66
No. Subjects with Negative Baseline Cultures Reduced ITT population (=Valid Subjects Population)	6 26	8 26	14 52
Male/ female	17/9	18/8	35/17
Mean age	41	44	-
Age range			-

Table 36) Discontinuances

Treatment group	No. entered and exposed	No. (%) completed	Treatment failure	Negative initial culture	Other reason
1% Lamisil Solution	32	29 (91%)	3	0	0
Placebo	34	22 (65%)	9	2	1*
TOTAL	66	51 (77%)	12	2	1

Table 37) Number and Percent with Effective Treatment

Treatment	Reduced ITT (=valid)			Complete ITT		
	Week 1	Week 4	Endpoint	Week 1	Week 4	Endpoint
Lamisil	5/26(19%)	17/23 (74%)	17/26(65%)	8/32(25%)	22/29(76%)	22/32(69%)
Placebo	2/26 (8%)	2/16(13%)	2/26 (8%)	3/34 (9%)	5/21 (24%)	5/34(15%)
p-value	0.419	<0.001	<0.001	0.104	<0.001	<0.001

Comment: The week 4 results in both the valid and intent-to-treat subgroups demonstarted a statistically significant advantage favoring Lamisil.

Table 38) Number and Percent with Negative Mycology

Treatment	Reduced ITT (=valid)			Complete ITT		
	Week 1	Week 4	Endpoint	Week 1	Week 4	Endpoint
Lamisil	10/26 (38%)	18/23 (78.%)	18/26 (69%)	13/34 (41%)	23/29 (79%)	23/32 (72%)
Placebo	6/26 (23%)	5/16 (31%)	6/26 (23%)	7/34 (21%)	10/21 (48%)	12/34 (35%)
p-value	0.368	0.007	0.002	0.109	0.033	0.004

Comment: Supportive of the effective treatment designation, 69 and 72% of the valid and intent-to-treat subgroups who received Lamisil acheived a statistically significant (p 0.002 and p 0.004) mycologial cure at the end of study.

Table 39) Sum of Clinical Score (Mean)

Treatment	Reduced ITT(=valid)			Complete ITT		
	Week 0	Week 1	Week 4	Week 0	Week 1	Week 4
Lamisil	(26) 6.65	(26) 3.65	(23) 0.96	(32) 6.66	(32) 3.53	(29) 1.14
Placebo	(26) 6.42	(26) 4.42	(16) 3.06	(34) 6.41	(34) 4.35	(22) 2.73

Comment: The mean clinical score for the Lamisil treated patients reached statistical significance for an absolute decrease by week 2 (p 0.001) continuing through week 4.

Table 40) Summary Including Secondary Parameters

	Reduced ITT (=valid)		Complete ITT		p-value for reduced ITT
	Lamisil	Placebo	Lamisil	Placebo	
Effective Treatment	17/26 (65%)	2/26 (8%)	22/32(69%)	5/34(15%)	<0.001
Complete Cure	10/26 (38%)	2/26(8%)	13/32(41%)	3/34(9%)	-
Cure	7/26 (27%)	0/26 (0.%)	9/32 (28%)	2/34 (6%)	-

Table 41) Summary of Adverse Events

Body System	Preferred Term	Treatment Group	
		1% Lamisil solution	Placebo
Skin and appendages disorders	No. subjects	-	1 (3%)
	Surgery	-	1 (3%)
Central and peripheral nervous sys. disorders	No. subjects	1 (3%)	1 (3%)
	Headache	1 (3%)	1 (3%)
Gastro-intestinal sys. disorders	No. subjects	1 (3%)	1 (3%)
	Diarrhoea	1 (3%)	1 (3%)
Respiratory sys. disorders	No. subjects	1 (3%)	-
	Pharyngitis	1 (3%)	-
Body as a whole - general disorders	No. subjects	1 (3%)	1 (3%)
	Influenza-like symps.	1 (3%)	-
	Back pain	-	1 (3%)
Application site disorders	No. subjects	2 (6%)	1 (3%)
	Application site reaction	2 (6%)	1 (3%)

Comments: There were no severe adverse events; the possibly related reactions that did occur (2 with Lamisil and 1 with vehicle) affected the application site and were mild.

Study SFF 108-E-00 Double-blind Clinical Therapeutic Trial of the Efficacy and Safety of 1% Solution Topical SF86-327 Applied Once Daily, Compared to Vehicle During One Week in Subjects with Tinea Corporis/Cruris.

This three-center, Brazilian trial, following the design of Study SFF 105 enrolled 72 patients. Noteworthy is the inclusion of subjects down to age 5 years.

Table 42) Disposition and Demographics

Subject Group	Lamisil	Placebo	Total
Subjects entered/ completing	36/34	36/35	72/69
Subjects with no post-baseline assessment Complete ITT population/safety population	1 35	0 36	1 71
Subjects with negative baseline culture Reduced ITT population	0 35	1 35	1 70
Subjects excluded from the valid population Valid subjects population	1 34	1 34	2 68
Male/ female	26/9	23/12	49/21
Mean age (yr)	32	37	34.5
Age range			

Table 43) Discontinuances

Primary reason for discontinuation	Lamisil 1% solution (N=36)	Placebo (N=36)	Total (N=72)
Lost to follow-up	2	0	2
Treatment failure	0	1	1
Total	2 (6%)	1 (3%)	3 (4%)

Table 44) Number and Percent with Effective Treatment

Treatment	Reduced ITT (n/N)			Complete ITT (n/N)		
	Week 1	Week 4	Endpoint	Week 1	Week 4	Endpoint
Lamisil	9/33 (27%)	20/27 (74%)	22/34 (65%)	9/33 (27%)	20/27 (74%)	22/34 (65%)
Placebo	2/35 (6%)	7/33 (21%)	7/35 (20%)	2/36 (6%)	7/34 (21%)	7/36 (19%)
p-value	0.021	<0.001	<0.001	0.020	<0.001	<0.001

Comment: As in the previously reviewed studies, Lamisil demonstrated a statistically significant advantage over vehicle.

Table 45) Number and Percent with Negative Mycology

Treatment	Reduced ITT (n/N)			Complete ITT (n/N)		
	Week 1	Week 4	Endpoint	Week 1	Week 4	Endpoint
Lamisil	15/32 (47%)	21/27 (78%)	25/33 (76%)	15/32 (47%)	21/27 (78%)	25/33 (76%)
Placebo	5/34 (15%)	9/32 (28%)	10/35 (29%)	6/35 (17%)	9/32 (28%)	11/36 (31%)
p-value*	<0.01	<0.001	<0.001	0.017	<0.001	<0.001

Table 46) Summary of Clinical Scores

Treatment	Reduced ITT			Complete ITT		
	Week 1	Week 2	Week 4	Week 1	Week 2	Week 4
Lamisil	3.21 ± 1.70	1.62±1.35	1.24 ± 2.55	3.21 ± 1.70	1.62±1.35	1.24 ± 2.55
Placebo	4.89 ± 2.58	5.43±3.17	5.32 ± 3.32	5.00 ± 2.63	5.50±3.16	5.26 ± 3.29
p-value	0.003	<0.001	<0.001	0.002	<0.001	<0.001

Table 47) Summary of Efficacy at Endpoint

	Reduced ITT		Complete ITT		Valid		p-value for reduced ITT
	Lamisil	Placebo	Lamisil	Placebo	Lamisil	Placebo	
Effective Treatment	22 (65%)	7 (20%)	22 (65%)	7 (19%)	20 (74%)	7 (21%)	<0.001
Complete Cure	14 (41%)	2 (6%)	14 (41%)	2 (5%)	14 (52%)	2 (6%)	
Cure	8 (24%)	5 (14%)	8 (24%)	5 (14%)	6 (22%)	5 (15%)	
Ineffective	12 (35%)	28 (80%)	12 (35%)	29 (81%)	7 (26%)	26 (79%)	

Comments: The superiority of Lamisil over vehicle is supported by the "Effective Treatment" results. This data, secondary is included in the review for ease of access relative to labeling and advertising.

Comments: There were very few adverse events in this Brazilian study, which is consistent with the safety data from previously reviewed studies. Please note: Lamisil cream have been marketed for tinea corporis for greater than two years with a very acceptable safety profile.

Overall Comments - Indication Tinea Corporis/Cruris The sponsor has provided appropriate data from adequate efficacy and safety studies which clearly support an indication for the once daily application of Lamisil solution for 7 days in the treatment of Tinea Corporis and Cruris.

Conclusion: According to the results of the studies submitted to this NDA Lamisil 1 % solution is a safe and effective drug for twice daily use in Tinea versicolor for 7 days. Similarly, Lamisil 1 % solution is safe and effective for once daily treatment of tinea corporis/cruris. In each of these indications, the sponsor submitted at least 2 adequate and well controlled trials. As previously discussed the same was not true for tinea pedis, and this author is not aware of the reasoning behind same. Had the sponsor reversed the position so that more studies were submitted in support of tinea pedis as opposed to tinea corporis; than one could make the argument that tinea pedis is more resistant to therapy and therefore, one trial might be adequate for tinea corporis. That is not the case.

On the other hand, Lamisil is available orally as well as in a cream formulation, so safety has been established.

Recommendation: Approval - twice daily use for 7 days in Tinea Versicolor
Approval - once daily use for 7 days in Tinea Corporis/Cruris
Approval - twice daily use for 7 days in Tinea Pedis (interdigital-type)

9/18/97

a L. Toombs, MD
dical Officer

HFD 540
HFD 540/Wilkin
HFD 540/Cross
HFD 540/Mainigi
HFD 540/Thompson
HFD 540/Chem

9/5/97