CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 20-846

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20-846

Trade Name: LAMISIL DERMGEL, 1%

Generic Name:(terbinafine)

Sponsor:Novartis Pharmaceuticals Corporation

Approval Date:April 29, 1998

Indication: Provides for the topical treatment of the following dermatologic infections: tinea (pityriasis) versicolor due to Malassezia furfur (formerlyPityrosporum ovale), tinea pedis (athlete's foot) or tinea corporis (ringworm), due to Trichophyton rubrum, Trichophyton mentagrophytes, or Epidermophyton floccosum.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20-846

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-846

APR 29 1998

Novartis Pharmaceuticals Corporation
Attention: James L. DeMartino, Ph.D.
Associate Director, Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Dr. DeMartino:

Please refer to your new drug application dated April 29, 1997, received April 29, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamisil (terbinafine) Dermgel, 1%.

We acknowledge receipt of your submissions dated May 30, June 20, August 28, Sept 3, 5, and undated (26 receipt date), October 23 and 28, and November 18, 1997, and January 23, February 25, and April 3, 28 and 29, 1998. The User Fee goal date for this application is April 29, 1998.

This new drug application provides for the topical treatment of the following dermatologic infections: tinea (pityriasis) versicolor due to *Malassezia furfur* (formerly *Pityrosporum ovale*), tinea pedis (athlete's foot) or tinea corporis (ringworm), due to *Trichophyton rubrum, Trichophyton mentagrophytes*, or *Epidermophyton floccosum.*

We have completed the review of this application, 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 approved labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed approved labeling text. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 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 20-846. 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 this Division 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

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product 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 Susan Kummerer, M.S., Project Manager at (301) 827-2020.

Sincerely yours,

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-846

MEDICAL REVIEW(S)

Medical Officer's Review of Original NDA 20-846

Submission Date:	April 29, 1997	**First Draft:**	February 27, 1998
Received Back:	March 6, 1998	**Second Draft:**	March 9, 1998
Received Back:	April 10, 1998	**Third Draft:**	April 14, 1998
Received Back:	April 22, 1998	**Fourth Draft:**	April 23, 1998
Received Back:	April 28, 1998	**Fifth Draft:**	April 28, 1998 29 (PJ)

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

Drug Name: Generic-Terbinafine emulsion gel
Trade - Lamisil Derm Gel 1%

Pharmacologic Class: Allylamine antifungual

Chemical Name: (E)-N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-1-napthalenemethanamine hydrochloride

Proposed Indication: Tinea pedis, tinea corporis and tinea versicolor

Route of Administration: Topical

Proposed Dosage: Once daily for seven days - tinea versicolor
Once daily for seven days - tinea pedis

Related NDA's: 20-192 (Lamisil Cream 1%)
20-539 (Lamisil Tablets 250 mg)
20-749 (Lamisil Solution 1%)

Related IND's:

Marketing History: Lamisil (terbinafine hydrochloride) 250 mg tablets were approved for the treatment of onychomycosis affecting the fingernails and/or toenails by the U.S. Food and Drug Administration in December of 1995. In December 1992 and April of 1997, respectively, Lamisil Cream 1% and Lamisil Solution 1% were approved for the treatment of dermatophyte infections (excluding tinea capitis) and tinea versicolor (Lamisil Solution, only).

The sponsor states that, "To further the treatment options for the physician, a third terbinafine topical formulation has recently been developed: 1% Emulsion Gel". This submission, NDA 20-846, contains data accumulated by the sponsor in support of the efficacy and safety of the new derm-gel formulation.

Foreign Marketing History: Lamisil Derm Gel 1% is not marketed in any other country. An application for approval has been submitted to the United Kingdom.

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Manufacturing and Controls (See Review Chemistry) The drug substance manufactured in Basle, Switzerland, is a water insoluble whitish crystalline powder with a molecular weight of 291.44 and a solvent dependent Ph of 6.9 to 8.9. Novartis Pharma in Nuremberg, Germany is responsible for manufacturing, packaging and release of the oil in water emulsion (final drug product), Lamisil Derm Gel 1%. Note: The drug substance terbinafine *hydrochloride* is the "active" moiety in Lamisil Cream and Solution (1%); terbinafine *base* is the active ingredient in Lamisil Derm Gel 1%. The weight of the salt in the former results in a lowered drug concentration (11.1%) as compared to the base. The sponsor has agreed to address these differences and is in the process of clarifying the actual drug concentration on all product labels.

Active Ingredients	Terbinafine base	1.0 g
Inactive Ingredients	Butylated hydroxytoluene, NF	
	Sodium hydroxide, Ph, Eur.	
	Benzyl alcohol, NF	
	Sorbitan monolaurate, NF	
	Carbomer 934P (benzene free)*, NF	
	Polysorbate 20, NF	
	Isopropyl myristate	
	Ethanol (V/V)	
	Water purified, USP	

Pharmacology-Toxicology (See Pharmacology Review) The sponsor wishes to incorporate by cross reference extensive toxicology results: mutagenicity, carcinogenicity, reproductive, acute and chronic animal toxicity information from approved NDA's for Lamisil cream, solution and tablets Pharmacologic toxicity data submitted specific to the gel formulation are summarized below.

Acute Toxicity - (203-116/7/8): A single dose of Lamisil Derm Gel 1% was administered orally to male and female OF 1 mice as well to Sprague dawley rats followed by 14 days of observation. According to the sponsor; there no deaths, clinical or gross signs of toxicity at necroscopy.

Multidose Dermal Toxicity - (203-119): Following topical administration of Lamisil Derm Gel at concentrations of 1%, 2%, or 3% compared to vehicle for 4 weeks in rabbits, no systemic treatment related effects were detected. Reversible, dermal irritation (clinically described as erythema, edema and scabbing, histologically described as vascular ectasia, acanthosis, and hyperkeratosis) was noted in both groups. Pharmacokinetic results revealed dose related higher concentrations of the parent drug in male rabbits and higher metabolite concentrations (N-methylated Lamisil) in female rabbits.

Single Dose Dermal Toxicity - (203-115): Dermal irritation, described as erythema and edema lasting approximately 72 hours was noted in rabbits following a single, 4 hour application of .5cc Lamisil 1% Gel.

Single Dose Ocular Toxicity - (203-114): Conjunctival erythema and edema resolving within 24 hours were detected 1 hour following instillation of .1cc Lamisil 1% Gel into the ocular apparatus of rabbits.

Human Bioavailability and Pharmacokinetics: (See Biopharmaceutics Review)

Study SF 409-E-00 "Determination of Plasma Concentrations of Terbinafine After Repeated Applications as a 1% Lamisil Emulsion Gel to the Normal Skin in Healthy Volunteers."

Primary Investigator:

Design: This uncontrolled, open-labeled, single center study enrolled 6 male and 6 female healthy, adult subjects in order to assess the plasma concentration of terbinafine following once daily application for 7 days.

Methods: Following a baseline medical examination and laboratory evaluation including: complete blood count, serum chemistry, urinalysis, ECG, pregnancy test and drug screen approved subjects admitted to the hospital. On Day 1 terbinafine gel (2 mg/cm2 = .02 mg/cm2 terbinafine) was *applied to an area skin of the back skin representing 20% of body surface.* Levels of terbinafine and its metabolite were measured: 1) prior to the application of study drug on days 1, 4 and 7, 2) 2, 4, 10 and 24 hours after application on days 1 and 7 and 3) at the completion visit between day 12 and 17. Plasma concentration of terbinafine and its metabolite were assessed using Maximum concentration, peak concentration times and area under the curve were measured on days 1 and 7. Note: Level of quantification = 1 ng/ml.

Adverse events including application site reactions were recorded daily throughout the study.

Disposition: All subjects completed the trial.

Results:	Mean	Standard Deviation	Range
tmax	7.33	3.45	
cmax	3.82	2.05	
AUC	62.55	46.54	

Safety: No serious adverse events were associated with the administration of study drug. One subject reported a headache.

Reviewer's Comments: In summary this data suggests that the plasma concentration of terbinafine applied topically is about 45 times lower than repeated once daily oral administration. The AUC is <1% of that following oral administration for 28 days.

Human Bioavailability and Pharmacokinetics

Study SFW 410-E-00 "Determination of Plasma Concentrations of Terbinafine After Repeated Applications as a 1% Lamisil Emulsion Gel to the Diseased Skin in Patients with Tinea Cruris/Corporis."

Primary Investigator:

Design: This uncontrolled, open-labeled, single centered study enrolled 6 male and 6 female adult patients with a diagnosis of tinea corporis or tinea cruris. Enrolled patients had Lamisil Emulsion Gel 1% applied to the infected areas and an additional 2.5 cm margin of normal skin once daily for 7 days.

Methods: Prior to study entry a baseline medical examination and laboratory evaluation including: complete blood count, serum chemistry, urinalysis, ECG, pregnancy test and drug screen were completed. Levels of terbinafine and its metabolite were measured: 1) prior to the first application of study drug on days 1, 4 and 7, 2) 2, 4, 10 and 24 hours after application on days 1 and 7, 3) 48 hours after the final application on day 9 and 4) at the post study assessment. Plasma concentration of terbinafine and its metabolite were assessed using Maximum concentration, peak concentration times and area under the curve were measured on days 1 and 7. Note: Level of quantification = 1 ng/ml.

Between day 12 and 20, i.e. a post study assessment: physical examination including clinical response, ECG and laboratory evaluation were completed. Patients were referred to their private dermatologists for continued follow-up. Adverse events were recorded daily throughout the study.

Disposition: All subjects completed the trial. The mean daily amount of Lamisil Derm Gel 1% applied ranged from mg.

Results	Means	Standard Deviation	Range
tmax	.83	7.11	
cmax	.48	1.85	
AUC	0.54	36.30	

Safety: No adverse events were associated with the administration of study drug. One subject reported a toothache. Minor laboratory abnormalities were noted at screening and end of study. The latter did not appear to be related to study drug.

Reviewer's Comments: In summary, the plasma concentrations of terbinafine applied topically were approximately 37 times lower than those observed after repeated dose oral administration

Human Bioavailability and Pharmacokinetics

Study SFG-205-E-00 "A Study to Investigate the Skin Pharmacokinetics of Lamisil Derm Gel 1% Compared to Lamisil 1% Cream in Healthy Subjects Following a Single Application for One, Five or Seven Consecutive Days."

Primary Investigator:

Objective: This randomized, parallel, open labeled trial was designed to determine :1) whether the application of Lamisil Derm Gel 1% or Lamisil Cream 1% formulation resulted in different cutaneous pharmacokinetics and 2) whether stratum corneum concentrations persisted in correlation with increased number of days of application.

Methods: Thirty-six healthy, caucasian subjects (equal numbers of males and females) were enrolled and divided into one of three groups: 1 day regimen, 5 day regimen or a 7 day regimen. Six subjects were enrolled in each arm of the study. Back skin tape striping were completed prior to and at 4, 8, 12, 24 hours and 2,3,4 and 7 days following application of 0.5 gm of the test products. Stratum corneum terbinafine levels were measured for derivation of: the maximum concentration over 7 days, the area of concentration versus time, time to reach maximum concentration and the half life.

Adverse events were recorded at each visit throughout the study.

Disposition: All subjects completed the trial.

Results: See biopharmaceutics review for details. In summary, increasing the number of applications increases the amount of drug present in the stratum corneum as well as the length of time the drug is detectable, with a slight tendency toward greater concentrations with the gel as opposed to the cream, early on. By the 7th day, the concentrations were equal.

Safety: No serious adverse events were associated with the administration of study drug. One subject developed a treatment site (cream) acneiform eruption which responded to Bactroban within 48 hours.

Human Bioavailability and Pharmacokinetics

Study SFG 101-E-00 "Randomized, Double-Blind, Parallel Group Study of Healthy Male Subjects, with Emulsion Gel Topically Applied for 1 Week in Combination with Either Orally Administered Lamisil or Placebo."

Primary Investigator:

Objective: This randomized, single center, double-blind parallel group study was designed to determine whether co-administration of Lamisil tablets with Lamisil Derm Gel 1% resulted in higher tissue levels than Lamisil Derm Gel 1% used as a single agent.

Methods: Twenty-four healthy adult male subjects were randomized into 2 groups, receiving either Lamisil Derm Gel 1% and an oral placebo or Lamisil Derm Gel 1% with Lamisil 250 mg tablets once daily - for 7 days. Skin biopsies/tape stripping (plantar surface of foot and back) and plasma samples were obtained for pharmacokinetic assessment prior to receipt of medication and on days 1, 2, 6, 12, 24, 36, 48 and 54 after treatment.

Laboratory parameters were assessed and adverse events were recorded.

Disposition: All subjects completed the trial.

Results: See biopharmaceutics review for details. No terbinafine was measurable in plasma samples from subjects administered the oral placebo combination. The highest mean concentration from the stratum (back) skin was on day 8 for the combination treatment and day 9 for the topical treatment .Terbinafine stratum corneum foot levels were approximately 2 times those of stratum corneum from the back.

Safety: No serious adverse events were associated with the administration of study drug.

Reviewer's Comments: Neither the data obtained from nor the objective of this study add any pertinent information to the proposed labeling. There was no statistical analysis of the data. Intersubject variability was high. Future studies may provide informative data which may affect the label and ultimate use.

Dermatotoxicity Studies Contact Sensitivity

SFW 406-E-00 "Repeat Insult Patch-Test Study of Lamisil Gels According to the Modified Procedure of Draize-Shelanski-Jordan in 100 Healthy Volunteers."

Primary Investigator:

Test Products:	Lamisil Derm Gel 1%	Vehicle
	Lamisil Derm Gel 2%	Canestene Cream (clotrimazole)
	Lamisil Derm Gel 3%	Blank Patch

Note: investigator for all submitted Dermatotoxicity studies. Identical test products were used in all dermatotoxicity studies.

Methods: One hundred healthy adult subjects (50 male, 50 female) underwent induction (patches applied-every other day), rest (16 days) and challenge phases with the test products.

Disposition: All subjects completed the trial.

Results: Three subjects exhibited (+1) reactions at the Lamisil Derm Gel 1% site during the induction period, only. Similarly, low grade responses occurred in 5 of the placebo application sites subjects.

Reviewer Comments: According to the results of this study Lamisil Derm Gel 1% does not appear to be a contact sensitizer.

Dermatotoxicity Studies Phototesting

SFW 408-E-00 "Comparative Study of the Photosensitizing Potential of Three Lamisil Derm Gel Formulations Versus Placebo in Thirty Healthy Adult Volunteers."

Investigator:

Design/Objectives: Thirty adult caucasian subjects (15 male, 15 female) with skin types 2, 3a or 3b were randomized in this open labeled trial in order to assess the phototoxicity/allergenicity of Lamisil gel compared to vehicle and clotrimazole.

Disposition: All subjects completed the trial.

Methods/Phototoxicity: Finn chamber patch tests containing each of test products and a blank were applied in triplicate to the skin of the subjects' back. After 6 hours the patches were removed; one of the three areas was irradiated with 0.75 MED UVB, a second with 0.75 MED UVA and the third was not irradiated. (light source - Osram xenon 2500 Watt lamp with a Schott WG optical filter limiting the wavelength to 290 nanometers through the infrared spectrum) Cutaneous reactions were recorded immediately after removal and at 10 minutes, 24 hours and 48 hours after patch removal (tables 1 and 2). Photoallergy testing was also completed using the modified Kaidbey/Kligman method: 3 week induction, 2 week rest, followed by a single 24 hour challenge application; results are in table 3 followed by a comment.

Table 1) Lamisil Derm Gel 1% Irradiated with 0.75 MED UVB Versus: Blank, Vehicle or Clotrimazole

Score	Patch Removal				Immed post irradiation				24 hours post irradiation				48 hours post irradiation.			
	L	V	B	C	L	V	B	C	L	V	B	C	L	V	B	C
0	30	30	30	30	25	25	26	26	10	9	10	11	22	17	20	20
0.5	0	0	0	0	4	4	4	4	13	13	12	10	6	12	9	8
1	0	0	0	0	1	1	0	0	7	8	8	8	2	1	1	1
2	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1

Table 2) Lamisil Derm Gel 1% Irradiated with 0.75 MED UVA Versus: Blank, Vehicle or Clotrimazole

Score	Patch Removal				Immed post irradiation				24 hours post irradiation				48 hours post irradiation			
	L	V	B	C	L	V	B	C	L	V	B	C	L	V	B	C
0	30	30	30	30	10	11	11	11	20	20	20	20	26	28	28	28
0.5	0	0	0	0	17	16	16	16	8	9	9	9	3	2	2	2
1	0	0	0	0	2	2	2	2	2	1	1	1	1	0	0	0
2	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0

Table 3) Lamisil Derm Gel 1% Irradiated with 0.10 MED UVA Versus: Blank, Vehicle or Clotrimazole

Score	Patch Removal				Immed post irradiation				24 hours post irradiation				48 hours post irradiation			
	L	V	B	C	L	V	B	C	L	V	B	C	L	V	B	C
0	30	30	30	30	30	30	30	28	24	24	29	30	28	28	30	30
0.5	0	0	0	0	0	0	0	2	2	2	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	4	4	1	0	1	2	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0

L= Lamisil V= Vehicle B= Blank C= clotrimazole

Reviewer's Comments: The highest 72 hour photoallergenicity grades were (1) +1 (weak response) in the Lamisil 1% group and (1) 0.5 (very weak) in the vehicle group. The results of this well conducted trial suggest that Lamisil Derm Gel 1% is not a phototoxic nor a photosensitizing drug.

Clinical Efficacy and Safety Studies

The sponsor submitted the results of 5 multi-center, double blind, vehicle controlled clinical studies to support the efficacy and safety of Lamisil Derm Gel 1% in the treatment of: tinea versicolor (2) once daily for 7 days, tinea corporis/cruris once daily for 7 days (1) and tinea pedis once daily for 5 and 7 days (2). All studies were performed outside of the United States (table 4).

The methods, inclusion, exclusion, efficacy criteria (listed below) and safety evaluation were very similar in all studies with the appropriate exception that KOH microscopy confirmed the mycologic diagnosis of tinea versicolor vs KOH microscopy and culture for tinea corporis/cruris and pedis. Clinical and mycological assessment of a *target lesion* was evaluated at weeks 1,2,4,6 and or 8 (primary endpoint=end of study = last non-missing post-baseline observation). Safety was monitored through reporting of adverse events according to body system. The primary efficacy variable was "effective treatment" at end of study in the intent to treat patient population.

Inclusion Criteria

Patients clinically diagnosed with moderately severe tinea infection, confirmed by microscopy in the case of pityriasis versicolor or mycology(culture) and microscopy in the case of tinea pedis, corporis/cruris

Males and females at least 12 years of age who are willing and able to participate and complete the study.

Guardian consent required for ages less than 18 years of age, females of childbearing potential must use reliable contraception throughout the study

Exclusion Criteria

Drug abuse, pregnancy, lactation, immunodeficiency or other dermatophytic infections

Immunosuppressive therapy during or 2 weeks preceding study entry; topical antifungals within 4 weeks or oral antifungals within 6 weeks or other investigational therapy within 8 weeks of baseline assessment

History of drug hypersensitivity

Efficacy Assessment

Primary Efficacy Variable

Effective treatment - Negative target lesion mycolgy/microscopy and total signs/symptoms ≤ 1.

Secondary Efficacy Variable

Complete cure - negative mycology/microscopy plus signs and symptoms equal 0
Cure - negative mycology/microscopy plus signs and symptoms equal 1

Clinical signs and symptoms: erythema, desquamation and or pruritus
Scoring: 0 - absent 1 - mild 2 - moderate 3 - severe

Clinical Efficacy and Safety Studies

Table 4) List of Clinical Studies Described in Text

Indication	Study*	Country(ies)	Duration of Treatment	Follow-up Period	No. of Subjects Enrolled			Enrolled Subjects	
					Enrolled	Lamisil 1% (3%)	Placebo	Age Range (Mean)	Sex %M %F
Pityriasis versicolor	SFG 203	Sweden	1 week OD	7 weeks	61	31	30	(36.6)	50.8 49.2
	SFG 302	Norway/Sweden	1 week OD	7 weeks	129	87	42	(36.0)	51.9 48.1
Tinea pedis	SFG 102	United Kingdom	5 days OD	37 days	85	30 (28)	27	(39.8)	69.4 30.6
	SFG 202	Finland/Belgium	1 week OD	7 weeks	101	51	50	(43.3)	66.3 33.7
Tinea corporis/cruris	SFG 201	South Africa	1 week OD	7 weeks	83	40	43	(37.9)	78.3 21.7

Clinical Efficacy and Safety Studies Tinea (Pityriasis) Versicolor

Study SFG 203-E-00 "A randomized, double blind, placebo-controlled, multi-centre study of the efficacy and safety of Lamisil Derm Gel 1% compared to vehicle once daily for 1 week in patients with pityriasis versicolor."

Methods: Sixty-one patients were enrolled in 2 Swedish centers and randomly assigned in a 1:1 ratio to receive either Lamisil Derm Gel 1% or an identical appearing vehicle with instructions for once daily application of the test product to the affected areas for 7 days. Assessment of efficacy and safety were made on day 7 and at the end of weeks 2, 6 and 8: following receipt of a baseline positive skin scraping evaluated microscopically for pityrosporum orbicularis.

Note: Results recorded for all studies were based on the intent to treat (evaluable for safety) patient population. Values for the "valid " or reduced intent to treat populations were not significantly different.

First subject recruited; August 29, 1994 Last subject completed: February 7, 1995

Efficacy Results

Table 5) Disposition

	Lamisil Derm Gel 1%	Vehicle
Number of patients entered	31	30
Intent to treat (safety)	28	30
Male to female ratio	14:14	16:14
Age years (mean)	37	37
Age years (range)		
Race (caucasian/black/oriental)	26/0/2	26/1/3
Discontinuations (lost to follow-up)	5	1
Discontinuations (treatment failure)	5	24

Table 6) Number and Percent of Patients with Negative Microscopy

	7 Days	Week 2	Week 6	Week 8	End of Study
Lamisil Derm Gel 1%	17/28 (61%)	21/28 (75%)	19/21 (90%)	21/28 (75%)	21/28 (75%)
Vehicle	10/29 (34%)	7/26 (27%)	4/19 (21%)	4/5 (80%)	4/29 (14%)
p-value	0.011	<0.001	0.001	0.509	0.001

Table 7) Total Signs and Symptoms Score at Baseline and Reduction from Baseline at each Visit

	Baseline	Day 7	Week 2	Week 6	Week 8	End of Study
Lamisil Derm Gel 1%	5.1	3.2	4.2	4.6	4.3	4.5
Vehicle	5.0	2.0	2.8	2.5	3.4	2.2
p-value	0.569	0.023	0.001	<0.001	0.120	<0.001

Table 8) Effective Treatment End of Study (see definitions page 10)

	Complete Cure	Cure	* Effective Treatment
Lamisil Derm Gel 1%	20/28 (71%)	4/28 (14%)	24/28 (85%)
Vehicle	4/29 (14%)	0/29 (0%)	4/29 (14%)
p-value	0.001		0.001

Clinical Efficacy and Safety Studies Tinea (Pityriasis) Versicolor

Results Safety

Table 9) Adverse Events Number and Type

Treatment	N	N	Event
Lamisil Derm Gel 1%	(28)	2	Common cold, malaise
Vehicle	(30)	1	Common cold

Reviewer's comments: Eighty-five percent (24/28) percent of Lamisil Derm Gel 1% treated patients vs 14% or 4/29 vehicle treated patients were "effectively treated". The statistical advantage of Lamisil Derm Gel 1% was detectable mycologically as well as clinically after 7 days of therapy.

The large number of dropouts in the vehicle arm for the 8th week visit provide the explanation for the increased p-values. However, the superiority of the "active" drug is maintained through the end of study evaluation.

As would be expected, due to the minimal systemic absorption of Lamisil Derm Gel 1% and lack of topical irritancy the incidence of adverse events was very low and not treatment related.

Reviewer's conclusion: Study SFG 203-E-00 supports the efficacy and safety of Lamisil Derm Gel 1% in the treatment of patients with moderately severe tinea versicolor.

Clinical Efficacy and Safety Studies Tinea (Pityriasis) Versicolor

Study SFG 302-E-00 "A randomized, double blind, placebo-controlled, multi-centre study of the efficacy and safety of Lamisil Derm Gel 1% compared to vehicle once daily for 1 week in patients with Pityriasis Versicolor."

First patient entered: March 22, 1995 Last patient completed: November 14, 1995

Methods: Thirteen Norwegian and 3 Swedish centers participated in this randomized, vehicle controlled, double-blind study which enrolled 129 patients in order to assess the efficacy and safety of Lamisil Derm Gel 1% as compared to vehicle in the treatment of Tinea (Pityriasis) versicolor. Exclusion and inclusion criteria were identical to those used n Study SFG 203-E-00. Clinical assessments were made at Day 7, weeks 2, 4, 8 and end of study. Efficacy was determined using the same standards as in the aforementioned study.

Results Efficacy

Table 10) Disposition

	Lamisil Derm Gel 1%	Vehicle
Number of patients entered	87	42
Intent to treat (safety)	87	42
Male to female ratio	42:45	25:17
Age years (mean)	36	36
Age years (range)		
Race (caucasian/black/oriental)	80/3/4	40/0/2
Discontinuations (lost to follow-up)	3	1
Discontinuations (treatment failure)	5	16
Discontinuations (withdrawal of consent, etc.)	5	1

Table 11) Number and Percent of Patients with Negative Microscopy

	7 Days	Week 2	Week 4	Week 8	End of Study
Lamisil Derm Gel 1%	57/85 (67%)	56/76 (74%)	63/75 (84%)	42/57 (74%)	63/86 (74%)
Vehicle	9/39 (23%)	10/36 (28%)	5/29 (17%)	3/21(14%)	4/41 (10%)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001

Table 12) Total Signs and Symptoms Score at Baseline Compared to Reduction at Each Visit

	Baseline	Day 7	Week 2	Week 4	Week 8	End of Study
Lamisil Derm Gel 1%	3.9	2.4	3.1	3.4	3.3	3.3
Vehicle	3.7	1.8	1.9	1.6	1.3	1.0
p-value	0.681	0.048	0.003	<0.001	<0.001	<0.001

Table 13) Effective Treatment End of Study

	Complete Cure	Cure	* Effective Treatment
Lamisil Derm Gel 1%	58/86 (67%)	5/86 (6%)	63/86 (73%)
Vehicle	4/41 (10%)	0/41 (0%)	4/41 (10%)
p-value	0.001		0.001

Clinical Efficacy and Safety Studies Tinea (Pityriasis) Versicolor

Reviewer's comments: As in Study 203-E-00, Lamisil Derm Gel 1% reduced the signs and symptoms associated with tinea versicolor by end of the first week of therapy. This reduction continued throughout the follow-up phase and was supported objectively by negative microscopy. Lamisil Derm Gel 1% being statistically better at all post-treatment time points (<0.001). The effective treatment rates were Lamisil Derm Gel 1% 63 out of 86 patients versus vehicle 4 out of 41 resulting in a statistically significant advantage (p<0.001) of Lamisil Derm Gel 1%.
Results Safety

Table 14a) Adverse Events Number and Type

Treatment	N	N	Event
Lamisil Derm Gel 1%	(87)	8	4 skin, gastrointestinal, bronchitis, bursitis, headache, depression
Vehicle	(42)	6	4 skin, bronchitis, vaginal infection

Table 14b

Cutaneous Adverse Events	Lamisil Derm Gel 1% (N)	Vehicle (N)
Pruritus	3	2
Rash	0	1
Application site reaction	1	1
Total	4	4

Reviewer's Comments: There were no serious adverse events reported. The events that were recorded were of equal incidence between the two groups.

Reviewer's conclusion: Study SFG 302-E-00 supports the efficacy and safety of Lamisil Derm Gel 1% in the treatment of patients with moderately severe tinea versicolor.

The sponsor has submitted 2 adequate and well controlled clinical studies which contain data to support the safety and efficacy of Lamisil Derm Gel 1% when applied once daily for 7 days in the treatment of moderately severe tinea versicolor. The sponsor did not address the issue of pigmentary changes that can occur as part of the clinical presentation of tinea versicolor and may be very disconcerting. It is not known whether Lamisil Derm Gel 1% would have had a beneficial effect on the "various colors" aspect of tinea versicolor. There may be a time lag between normalization of pigment after successful treatment of the disease (mycologically and symptomatically), pigment generally normalizes assumed and no Phase IV studies are recommended by this author.

Clinical Efficacy and Safety Studies Tinea Pedis

Study SFG 102-E-00 "Double-blind, placebo controlled study with Lamisil Derm Gel 1% and 3%, each compared to placebo in tinea pedis (Athletes Foot)."

First patient enrolled: August, 1993 Last subject completed: March, 1994

Methods: Fourteen investigators participated in this multicenter, double blind, vehicle controlled study conducted in the United Kingdom which was designed to compare the effectiveness and safety of Lamisil Derm Gel in 1% and 3% concentrations versus vehicle in patients with tinea pedis. Eighty-five patients were randomized in a 1:1:1 fashion with instructions for once daily application of the study product. Clinical assessments including culture were completed at day 5 and weeks 2, 4 and 6. Study conduct was 'similar' to the tinea versicolor trial: incrustation, vesiculation and pustulation were included as clinical parameters - clinical scores of 2 or less were deemed 'cure". The efficacy portion of the trial did not suggest any benefit from use of the higher concentration, therefore those results/analysis are not included herein. This review is tailored to address the study product; data from the 28 patients in the Lamisil Derm Gel 3% treatment arm is not included as its pertinence is obscure.

Results Efficacy

Table 15) Disposition

	Lamisil Derm Gel 1%	Vehicle
Number of patients entered	30	27
Intent to treat (safety)	29	27
Male to female ratio	21:8	18:9
Age years (mean)	41	39
Age years (range)		
Race (caucasian/black/oriental)	29	22/5 other
Discontinuations (lost to follow-up)	3	1
Discontinuations (treatment failure)	0	2

Table 16) Number and Percent of Patients with Negative Mycology (culture and KOH)

	Day 5	Week 2	Week 4	Week 6	End of Study
Lamisil Derm Gel 1%	13/29 (45%)	18/27 (67%)	25/26 (96%)	26/27 (96%)	28/29 (97%)
Vehicle	7/26 (27%)	10/26 (38%)	5/23 (22%)	6/24 (25%)	6/27 (22%)
p-value	0.262	0.056	<0.001	<0.001	<0.001

Table 17) Mean Total Signs and Symptoms Score at Baseline Compared to Reduction at Each Visit

	Baseline	Day 5	Week 2	Week 4	Week 6	End of Study
Lamisil Derm Gel 1%	6.5	3.5	2.6	1.4	0.8	0.7
Vehicle	7.3	3.7	3.6	2.8	3.8	4.7
p-value	0.400	0.861	0.334	0.029	0.001	0.001

Table 18) Effective Treatment End of Study

	Complete Cure	Cure	* Effective Treatment
Lamisil Derm Gel 1%	12/29 (41%)	13/29 (44%)	25/29 (85%)
Vehicle	1/27 (4%)	2/27 (7%)	3/27 (11%)
p-value	0.004		0.001

Clinical Efficacy and Safety Studies Tinea Pedis

Reviewer's comments: By the end of study a statistically significant number of Lamisil Derm Gel 1% treated patients were effectively treated, p value 0.001. Approximately 25% of the vehicle treated patients were improved or had negative mycology at some point during the trial.
A significant advantage favoring Lamisil Derm Gel 1% was evident clinically and microscopically.

Results Safety

Table 19a) Adverse Events Number and Type

Treatment	N	N	Event
Lamisil Derm Gel 1%	(29)	10	1arthropathy, 2 otitis, 1purpura, 4 respiratory infection/tonsilitis, 1 site rxn
Vehicle	(27)	5	4 skin (3 non-related), 1 arthropathy

Table 19b

Cutaneous Adverse Events	Lamisil Derm Gel 1% (N)	Vehicle (N)
Eczema	0	1
Rash	0	1
Contact Dermatitis	0	1
Application site reaction	1	1
Total	1	4

No serious adverse events were reported. Except for possible application site reaction (burning and stinging on application) which has been associated with the vehicle and active agent, there were no other "active" treatment related events.

Clinical Efficacy and Safety Studies Tinea Pedis

Study SFG 202-E-00 " A randomized, double-blind, placebo controlled, multicenter study of the efficacy and safety of Lamisil Derm Gel 1% compared to vehicle once a day for seven days in subjects with Tinea Pedis (Athletes Foot, Interdigital type)."

First patient entered: September 15, 1994 Last patient completed: August 28, 1995

Methods: Three centers in Finland and 3 centers in Belgium participated in this controlled multicenter trial comparing the clinical response of once daily treatment with Lamisil Derm Gel 1% versus vehicle in 101 patients with tinea pedis. Unlike the previous trial; Study SFG 102-E-00, patients were treated for 7 days with a single "active agent"; assessments were made at weeks 1, 2, 6 and 8 (end of study). Other aspects of the 2 studies were identical.

Results Efficacy

Table 20) Disposition

	Lamisil Derm Gel 1%	Vehicle
Number of patients entered	51	50
Intent to treat (safety)	51	49
Male to female ratio	27:12	16:15
Age years (mean)	41	45
Age years (range)		
Race (caucasian/black/oriental)	39/0	30/1
Discontinuations (protocol violations/other)	1	4
Discontinuations (lost to follow-up)	2	3
Discontinuations (treatment failure)	0	5

Table 21) Number and Percent of Patients with Negative Mycology (culture and KOH)

	Day 7	Week 2	Week 6	Week 8	End of Study
Lamisil Derm Gel 1%	10/38 (26%)	17/38 (45%)	29/35 (83%)	26/31 (81%)	31/39 (82%)
Vehicle	5/31 (16%)	10/30 (33%)	10/24 (42%)	7/21 (33%)	10/31 (32%)
p-value	0.174	0.225	0.001	0.001	<0.001

Table 22) Mean Total Signs and Symptoms Score at Baseline Compared to each Visit

	Baseline	Day 7	Week 2	Week 6	Week 8	End of Study
Lamisil Derm Gel 1%	6.1	2.3	3.2	4.5	5.0	4.9
Vehicle	5.5	2.0	2.9	2.6	3.2	2.4
p-value	0.799	0.694	0.764	0.174	0.088	0.002

Table 23) Effective Treatment End of Study

	Complete Cure	Cure	* Effective Treatment
Lamisil Derm Gel 1%	15/39 (38%)	10/39 (26%)	25/39 (64%)
Vehicle	5/31 (16%)	3/31 (10%)	5/31 (26%)
p-value	0.019		0.001

Clinical Efficacy and Safety Studies Tinea Pedis

Results Safety

Table 24a) Adverse Events Number and Type

Treatment N	N	Event
Lamisil Derm Gel 1% (51)	16	5 skin, 4 respiratory, 3 joint/otitis, 4 fever/accident
Vehicle (49)	15	7 skin , 2 respiratory, 1 heart, 1 central nervous system, 4 pain/accident

Table 24b

Cutaneous Adverse Events	Lamisil Derm Gel 1% (N)	Vehicle (N)
Dermatitis/acne	1	0
Dermatitis fungal	1	0
Rhagades	0	1
Application site reaction	0	2
Sweat gland disorder	0	2
Skin disorder (unspecifed)	1	2
Pruritus	2	0
Total	5	7

Reviewer's comments: Study SFG 202-E-00 supports the benefit of Lamisil Derm Gel 1% in the treatment of tinea pedis for 7 days, i.e. the active agent was significantly better than vehicle at the end of study and the incidence of adverse events was similar. Clarification: in the adverse events tables, all adverse events were reported whether thought related to study drug or not. Additionally, the incidence of cutaneous adverse events was no greater in the Lamisil Derm Gel 1% group than in the vehicle treated group. (Examples: acne, rash, sweating)

Reviewer's Conclusion: Both studies support the effectiveness of Lamisil Derm Gel 1% in the treatment of tinea pedis. The question is which dosage, i.e. 5 or 7 days would be most effective. There were no interstudy comparisons, both dosage were effective. This author has discussed same with the biometrics reviewer.

Ideally the smallest effective dose should be administered. The label submitted by the sponsor requests the 7 day dosage regimen, this was desired in order to simplify the instructions for the patient and the physician; all the other tinea indications are labeled for 7 days of treatment. From a practical and patient compliance standpoint this seems reasonable; the product is topical, has very limited application (feet < 10% BSA) to the thickest area of skin on the body and an acceptable safety profile.

Note: The sponsor included the 3% gel formulation Study 102-E-00 in consideration of the possibility that the 1% concentration might not demonstrate the desired degree of efficacy. In fact the 1% gel was very effective in treating tinea pedis. At this time, the sponsor has no plans for marketing the 3% concentration for tinea infections.

Clinical Efficacy and Safety Study Tinea Corporis/Cruris

Study SFG 201-E-00 " A randomized, double-blind, placebo controlled, multicenter study of the efficacy and safety of Lamisil Derm Gel 1% compared to placebo once daily for 7 days in subjects with tinea corporis/cruris."

First patient entered: September 19, 1994 Last patient completed: January 17, 1995

Methods: Eighty-three patients were enrolled in 6 centers in South Africa in order to assess the efficacy and safety of Lamisil Derm Gel 1% as compared to vehicle in the treatment of tinea corporis/cruris following once daily application for 7 days. The sponsor defined complete cure as negative mycology and total signs and symptoms score =0; effective treatment was negative mycology and sum of severity scores (erythema, desquamation and pruritus<=2/w individual scores <=1/individual scores vesiculation, incrustation and pustules =0).

Results Efficacy

Table 25) Disposition

	Lamisil Derm Gel 1%	Vehicle
Number of patients entered	40	43
Intent to treat (safety)	39	43
Male to female ratio	23:6	25:8
Age years (mean)	42	36
Age years (range)		
Race (caucasian/black/oriental)	21/0/2/6	26/1/0/6
Discontinuations (protocol violations/other)	2	4
Discontinuations (lost to follow-up)	2	0
Discontinuations (treatment failure)	0	0

Table 26) Number and Percent of Patients with Negative Mycology (culture and KOH)

	Day 7	Week 2	Week 6	Week 8	End of Study
Lamisil Derm Gel 1%	17/29 (59%)	20/27 (74%)	21/24 (88%)	16/19 (84%)	24/29 (83%)
Vehicle	6/33 (18%)	5/33 (15%)	6/33 (18%)	8/30 (27%)	9/33 (27%)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001

Table 27) Total Signs and Symptoms Score at Baseline Compared to each Visit

	Baseline	Day 7	Week 2	Week 6	Week 8	End of Study
Lamisil Derm Gel 1%	7.6	4.4	5.9	6.8	6.6	6.8
Vehicle	8.3	2.8	3.3	3.3	2.3	2.4
p-value	0.549	<0.05	<0.001	<0.001	<0.001	<0.001

Table 28) Effective Treatment End of Study

	Complete Cure	Cure	* Effective Treatment
Lamisil Derm Gel 1%	16/29 (55%)	8/29 (28%)	24/29 (83%)
Vehicle	4/33 (12%)	3/33 (9%)	7/33 (21%)
p-value	<0.001		<0.001

Clinical Efficacy and Safety Study Tinea Corporis/Cruris

Reviewers comments: According to the results of this study, Lamisil Derm Gel 1% is statistically better than vehicle in improving the signs and symptoms of tinea corporis/cruris after 7 days of treatment; in a like manner KOH microscopy is negative in approximately 60% of patients after 7 days. At the end of study, 24 out of 29 Lamisil Derm Gel 1% treated patients were effectively cured versus 7 out of 33 vehicle treated patients.

Results Safety

Table 29a) Adverse Events Number and Type

Treatment N	N	Event
Lamisil Derm Gel 1% (39)	13	6 skin, 2 headache, 1 gastrointestinal, 1 (trauma, flu, abscess, hypertension)
Vehicle (43)	31	21 skin , 5 respiratory, 3 headache, 1 (gout, infection)

Table 29b)

Cutaneous Adverse Events	Lamisil Derm Gel 1% (N)	Vehicle (N)
Dermatitis Contact	1	1
Pruritus	0	5
Rash (erythematous)	0	5
Application site reaction	0	2
Skin Discoloration	3	1
Skin Disorder	1	2
Skin Exfoliation	1	5
Total	6	21

Note: In the Lamisil Derm Gel 1% treatment group only 2 cutaneous adverse events were considered related to study drug.

There were no serious adverse events reported. The incidence of adverse events in the active treatment group was no greater than in the vehicle group, in fact were far less. There were no withdrawals due to adverse events in this or the previous study. Although, the groin skin is thinner and might be expected to be more sensitive, the overall incidence of cutaneous adverse events was no greater in this trial than following application to any other area of skin in the Lamisil Derm Gel 1% treatment groups.

Reviewer's conclusion: The study supports the efficacy and safety of Lamisil Derm Gel 1% in the treatment of tinea corporis/cruris.

Reviewer's final comments: The sponsor has submitted animal toxicity data from Lamisil Derm Gel 1% in addition to supporting data from other formulations which suggest topical application has minimal to absent untoward effects on animals. Additionally, the sponsor has submitted pharmacokinetic data suggesting percutaneous absorption of Lamisil Derm Gel 1% is minuscule, ie AUC <1% of the oral dose. Finally, 5 adequate and well controlled clinical efficacy and safety studies were submitted to support the use of Lamisil Derm Gel 1% in the treatment of tinea versicolor, pedis, corporis and cruris. Lamisil Derm Gel 1% was safe and effective in all studies.

Recommendation: Lamisil Derm Gel 1% should be approved for the above indications with a dosage regimen of once daily for 7 days in patients with tinea versicolor or tinea cruris/corporis and a dosage regimen of once daily for 7 days in the treatment of tinea pedis.

/S/

Ella L. Toombs, MD
Medical Officer

cc
HFD 540
HFD 540/Wilkin
HFD 540/Walker
HFD 540/Kummerer
HFD 540/Vidra
HFD 540/Mainigi
HFD 540/Gao
HFD 540/Tandon

qw 4/29/98 See Team Leader Review.

See Team Leader MOR dated 4/29/9

qw 4/29/98

The sponsor has presented adequate evidence to support the safety and efficacy of Lamisil (terbinafine) DermGel,1% when applied once daily for one week in the treatment of tinea versicolor and tinea pedis.

The sponsor has presented a single trial (SFG 201-E-00) comparing the safety and efficacy of Lamisil (terbinafine) DermGel,1% in the treatment of tinea corporis and tinea cruris. Eighty three patients were enrolled in six centers and received daily application for 7 days. The data are not presented separately for tinea corporis and tinea cruris. The results are a combination of the two indications and the sponsor has not presented individual safety and efficacy results for tinea cruris and corporis. Therefore, the number of patients with tinea cruris is unknown, and the safety profile for use in the inguinal area is unknown.

The overall incidence of cutaneous adverse events was reportedly no greater in trial SFG 201-E-00 (tinea cruris/corporis) than in the studies which applied the drug product at other cutaneous sites. However, no definitive conclusion on the rate of AE's in patients with tinea cruris can be drawn from the overall incidence of AE's occurring in the SFG 201-E-00 study, as the sample size of patients enrolled with tinea cruris is unknown.

Safety in tinea corporis can be extrapolated from studies SFG 203/302-E-00 (tinea versicolor), and efficacy in tinea corporis can be extrapolated from studies SFG 102/202 E-00 (tinea pedis); therefore, the indication of treatment in tinea corporis is approved.

Safety in cannot be extrapolated from the studies presented, therefore, the indication of treatment in is not approved.

/S/

4/29/98

Susan J. Walker, M.D.
Dermatology Team Leader

cc:
HFD-540
HFD-540/DivDir/Wilkin 4/29/98
HFD-540/Derm TL/Walker
HFD-540/MO/Toombs
HFD-540/Mainigi
HFD-540/Vidra
HFD-540/CSO/Kummerer
HFD-735/Biostat TL/Srinivasan
HFD-735/Biostat/Gao
HFD-880/Tandon

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-846

CHEMISTRY REVIEW(S)

APR 29 1998

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-846 **CHEM.REVIEW #**: 3 **REVIEW DATE**: 27-Apr-98

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
NDA 20-846, Original	29-Apr-97	01-May-97	12-May-97
NDA 20-846/BC	03-Apr-98	06-Apr-98	13-Apr-98

NAME & ADDRESS OF APPLICANT:
Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, New Jersey 07936-1080
ATTN: Patricia McGovern
Assistant Director
Drug Regulatory Affairs
Telephone: (973) 503-7384
Fax: (973) 503-6325

DRUG PRODUCT NAME

Proprietary:	Lamisil
Nonproprietary/USAN:	Terbinafine
Code Names/#'s:	SF 86-327b 86-327
Chemical Type/ Therapeutic Classes:	3S Antifungal (topical)

ANDA Suitability Petition/DESI/Patent Status: NOT APPLICABLE!

PHARMACOLOGICAL CATEGORY/INDICATION: Topical treatment of pityriasis versicolor, tinea pedis (athlete's foot), tinea cruris (jock itch) or tinea corporis (ringworm).

DOSAGE FORM:	DermGel
STRENGTHS:	1%
ROUTE OF ADMINISTRATION:	Topical
DISPENSED:	X **Rx** _____ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
(E)-N-(6,6-Dimethyl-2-hepten-4-ynyl)-N-methyl-1-napthalenemethanamine

Empirical Formula:	$C_{21}H_{26}N$
Molecular Formula:	
Molecular Weight:	291.44
CAS No.:	91161-71-6

SUPPORTING DOCUMENTS:
3/5/98 FDA Telefax to J.DeMartino, Novartis.

CONSULTS:
Microbiology

REMARKS/COMMENTS:
A total of eight Informational Requests were presented to this sponsor in Project Management's 3/5/98 telefax with the sponsor's following responses. Each IR and its response are summarized below:

Q1: *Provide information on names, addresses of the drug substance (DS) package/container manufacturer, on possible Type DMFs, on # components/container, on container specifications and on any USP extraction results.*
R1: • Names & addresses of the bag manufacturers:

• HDPE used to manufacture bages is supplied by
LOA dated 10/25/93 is attached authorizing reference to their DMF
• Novartis Specification No.1208, dated 10/8/96,were submitted as the test criteria with these analytical test procedures:
9101-E.04, IR Spectrum (USP/Ph Eur)
9305-E.05, Extractable materials in plastics

• IR extraction results from three individual container batches were within IR limits.
Reviewer Comments: ADEQUATE.

Q2: *Provide a statement on how failed drug product (DP) batches will be reprocessed.*
R2: There will be no reprocessing of failed drug product batches.
Reviewer Comments: ADEQUATE.

Q3a: *Why was a white background selected when evaluating a white gel for globules in the Macroscopic Appearance Test?*
R3a: To qualify the distinction between a "white" and an "off-white" product (Requirement: white to off-white glossy gel). A dark background would not facilitate very slight changes in appearance.
Reviewer Comments:

Q3b: *The two buffer standardising solutions were not adequately described in the pH value Methodology.*
R3b: Buffer Solution pH commercially available from
; tested in accordance to USP.
Buffer Solution pH commercially available from
and tested in accordance to USP.
Reviewer Comments: ADEQUATE.

Q3c: *What was the rationale for only selecting the resolution of isopropyl myristate and benzyl alcohol in the benzyl alcohol assay? Why not include other DermGel components?*

R3c: Since the NDA submission, the benzyl alcohol assay has been improved to include a new system suitability solution. The solution contains the benzyl alcohol, (internal standard), and isopropyl myristate. All unknown peaks came from the isopropyl myristate thus this component is added to determine the resolution of those unknown peaks from peaks of interest such as the benzyl alcohol peak.
Reviewer Comment: ADEQUATE

Q4: *Please provide the reference for Test in NDA*
R4: Test procedure for determining the degradative product is enclosed after Test "Identification and assay of terbinafine base and determination of the degradative products" in Section III B.7.2, pp.3-343 to 3-348, NDA 20-846.
Reviewer Comment: ADEQUATE

Q5: *Dimensions are required for the aluminum tube.*
R5: Tube dimensions were included for the 5g, 15g and 30g tubes.
Reviewer Comment: ADEQUATE.

Q6: *Toxicity data is requested for the*
R6: The safety data submitted were conducted by the That agency's appraisal dound that fulfilled the standards required under Article 31, para.1 of the West German statutory foodstuffs and consumer goods legislation as well as satisfying the requirements of 21 CFR 175.300.
Reviewer Comment: ADEQUATE

Q7: *Specific pivotal clinical trial drug product batches Z050 1294 and Z052 1294 could not be located in NDA Table 12 above or in any of the Release Analysis Tables (Vol.1.3,pp.3-556 & 3-557). Provide the same data for these two pivotal trial batches as listed in your synoptic table (Vol.1.3, p.3-555).*
R7: As explicity stated in 21 CFR 314.50(d)(1)(ii)(b) re: drug product batches used to conduct bioavaility, bioequivalence & primary stability studies have been included in the CMC section on the application. Batches Z050 1294 and Z052 1294 have not been used for those studies and are therefore not documented.
Reviewer Comment: ADEQUATE
Those drug product batches used in ALL primary stability, preclinical and pivotal clinical trials are considered Investigational Formulations therefore could be combined in the Release Analysis Table, Vol.1.3, pp.3-556 & 3-557, with the eight other drug product batches. The three pivotal trial batches noted on page 3-553 with its drug substance lots and specifications have been located separately from the Release Analysis Table and found acceptable.

Q8: Four Informational Requests on Labeling were submitted, e.g.
1) The mock-up product name and generic term should be modified to reflect the recent LNC recommendation of:
LAMISIL (terbinafine) DermGel, 1%*
*equivalent to 1.12% terbinafine hydrochloride

NOTE: The equivalency statement should be no less prominant than the established name. The package insert should bear the same modifications.

R8a: See fax copies of the mock-ups.
Reviewer Comment on 8a: ADEQUATE. Copies of the attached mock-up incorporated this change.

2) The mock-excipients should be listed by alphabetical order.
R8b: See fax copies for these mock-up changes.
Reviewer Comment on 8b: ADEQUATE. Copies of the attached mock-up incorporate this change.

3) Modify "ethanol 11.3% v/v" to read, "ethanol % v/v" or present an explanation why this modification should not be made.
R8c: According to USP monograph, "all statements of percentages of alcohol refer to percentage by volume of ethanol at . The sponsor interpreted that statement to read, ". . . to percentage of volume of ethanol [in the product] at
Reviewer Comment on 8c: ADEQUATE

4) Modify storage conditions from, "Store at or below to "Store at or below or provide an explanation why this modification should not be made.
R8d: No changes were made to the label and no explanation was given.
Reviewer Comment on 8d: ADEQUATE since the lower storage condition cited was well within the stable storage conditions.

CONCLUSIONS & RECOMMENDATIONS:
In response to your original request for a review of N20-846/BC, dated 4/3/98, this minor amendment is RECOMMENDED FOR APPROVAL.

/S/
James D. Vidra, Ph.D.
Review Chemist, HFD-540/HFD-830

Attachment

cc: Orig. NDA# 20-846
HFD-540/Division File
HFD-540/Chem/Vidra
HFD-540/ProjMan/Kummerer
HFD-540/TeamLdr/DeCamp

4/29/98

filename: N20846.BC

540 Kummeter

MAR - 4 1998

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-846 CHEM.REVIEW #: 1 REVIEW DATE: 30-Jan-98

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
NDA 20-846, Original	29-Apr-97	01-May-97	12-May-97
NDA 20-846, NC	03-Sep-97	08-Sep-97	11-Sep-97
NDA 20-846, NC	05-Sep-97	09-Sep-97	11-Sep-97
NDA 20-846, BC	28-Oct-97	30-Oct-97	17-Nov-97

NAME & ADDRESS OF APPLICANT:

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, New Jersey 07936-1080
ATTN: Patricia McGovern
Assistant Director
Drug Regulatory Affairs
Telephone: (201) 503-7384
Fax: (201) 503-6325

DRUG PRODUCT NAME

Proprietary:	Lamisil
Nonproprietary/USAN:	Terbinafine
Code Names/#'s:	SF 86-327b 86-327
Chemical Type/ Therapeutic Classes:	3S Antifungal (topical)

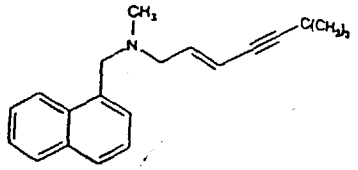
ANDA Suitability Petition/DESI/Patent Status: NOT APPLICABLE!

PHARMACOLOGICAL CATEGORY/INDICATION: Topical treatment of pityriasis versicolor, tinea pedis (athlete's foot), tinea cruris (jock itch) or tinea corporis (ringworm).

DOSAGE FORM:	DermGel
STRENGTHS:	1%
ROUTE OF ADMINISTRATION:	Topical
DISPENSED:	X Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
(E)-N-(6,6-Dimethyl-2-hepten-4-ynyl)-N-methyl-1-napthalenemethanamine

Empirical Formula: $C_{21}H_{26}N$
Molecular Formula:



Molecular Weight: 291.44

CAS No.: 91161-71-6

SUPPORTING DOCUMENTS:

NDA 20-192	DMF
NDA 20-539	DMF
NDA Supplement 20-192/SCS-009	NDA Supplement 20-539/SCS-001

CONSULTS:

(1) Nomenclature & Labeling Committee - Trademark reviewed on 8/18/97 (See APPENDIX #1).

(2) Environmental Exclusion Request (See APPENDIX #2).

REMARKS/COMMENTS:

NDA 20-846 has a 3S classification for a new drug dosage form, LAMISIL DermGel™ (terbinafine emulsion gel), 1%. Terbinafine is an allylamine derivative from a new class of antifungal agents that inhibits Fungal Squalene Epoxidase in the stratum corneum of the skin. DermGel™ is a new oil-in-water emulsion gel formulation filled in 5, 15 and 30 gram aluminum-lined tubes. The terbinafine base is dissolved in the oil phase with the emulsion constrained within a three-dimensional cross-matrix of carbomer. This emulsion-gel formulation completely dissolves the terbinafine. The polymer structure of the emulsion-gel is a very simple one, formed exclusively from carbomer, and encompasses large pockets of water which contain the oil droplets containing the terbinafine.

The proposed shelf-life for this product, when stored below 30°C, is 2 years with the possibility of extension to 3 years. At this time, an Expiry Date of 24 months is recommended for approval.

LAMISIL DermGel™ is indicated for the topical treatment of the following dermatological infections: pityriasis versicolor due to *Malassezia furfur,* and tinea pedis (athlete's foot), tinea cruris (jock itch), or tinea corporis (ringworm) due to *Trichophyton rubrum, Trichophyton mentagrophytes,* or *Epidermophyton floccosum.* Both the drug substance, terbinafine base, and the drug product LAMISIL DermGel™ are manufactured by the Novartis Pharmaceuticals Corporation, Basle, Switzerland.

The following Information Requests are made for LAMISIL DermGel:

1. Provide information on the names and addresses of the drug substance package/container manufacturer(s), on possible Type Drug Master Files, on the number of components per container, on container specifications and on any USP extraction results conducted on this container(s).
2. A statement on how failed drug product batches will be reprocessed.
3. Requests on the following Regulatory Specifications:
   - Why was a white background selected when evaluating a white gel for globules in the Macroscopic Appearance Test?
   - The two buffer standardizing solutions were not adequately described in the pH Value Methodology.
   - What was the rationale for only selecting the resolution of isopropyl myristate and benzyl alcohol in the Benzyl Alcohol Assay? Why not include other DermGel components?
4. The interaction between the Degradative Product and the presents a quantitative accuracy problem not caused by the procedure (Vol.1.3, pp.3-338 & 3-339). Although the primary procedure involves calculations using a second degradant, to determine the amount of a second procedure, Test is

used as a back-up method. Please provide the location/reference for Test in NDA 20-846.
5. Dimensions are required for the aluminum tube.
6. Toxicity data is requested for the
7. Specific pivotal clinical trial Drug Product Batches Z050-1294 and Z052-1294 could not be located in Table 12 above or in any of the Release Analysis Tables (Vol.1.3,pp.3-556 & 3-557). Provide the same data for these two pivotal clinical trial batches as listed in your synoptic table (Vol.1.3,p.3-555).
8. Informational Request on Labeling:
   - If the terbinafine base (M.Wt.291.44) is currently 1% of the LAMISIL DermGel and if terbinafine hydrochloride (M.Wt.327.90) is also at 1% of LAMISIL Creme and LAMISIL Solution, the M.Wt differential between the base and hydrochloride salt is %. Should this molecular weight differential not be reflected in the labeling of all three LAMISIL products? If so, should LAMISIL DermGel read 1% while LAMISIL Solution/LAMISIL Creme read %, or should LAMISIL DermGel read % while LAMISIL Solution/LAMISIL Creme read %? It is recommended the sponsor be notified of this labeling discrepancy.
   - Modify all labeling to delete from the generic drug name, , and from the established name.
   - Modify "ethanol % v/v" to read, "ethanol % v/v" or present an explanation why this modification should not be made.
   - Modify storage conditions from, "Store at or below to "Store at or below or provide an explanation why this modification should not be made.

CONCLUSIONS & RECOMMENDATIONS:
This original NDA 20-846 for the LAMISIL DermGel is RECOMMENDED FOR APPROVAL. A listing of eight Informational Requests associated with this NDA are provided to this sponsor for their eventual reply.

/S/

2/11/98

James D. Vidra, Ph.D.
Review Chemist, HFD-540/HFD-830

cc: Orig. NDA# 20-846
HFD-540/Division File
HFD-540/Chem/Vidra
HFD-540/MO/Toombs
HFD-540/PharmTox/Mainigi
HFD-540/ProjMan/Kummerer
HFD-540/TeamLdr/DeCamp 3/4/98
HFD-830/DivDir/Chen
filename: N20846

3/21/98

APPENDIX #1

Nomenclature and Labeling Committee Comments

Consult (HFD-540)

LAMISIL DermGel terbinafine emulsion gel

LAMISIL is the proprietary name for an approved product and was not evaluated by the Committee.

The term DermGel is an acceptable descriptive term for use with the proprietary name. However, it is not an official term and should not appear to be the established name for this product. The terms "emulsion" and "gel" are both recognized USP dosage form descriptors however, the compound term is not and should not be used as the established name.

The Committee recommends the following presentation be used to portray the different name elements:

LAMISIL DermGel
(terbinafine)
Emulsion gel, 1%

/S/ 8/18/97, Chair
CDER Labeling and Nomenclature Committee

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-846

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

APPENDIX #2

Request for Categorical Exclusion of Environmental Assessment

Patricia McGovern
Assistant Director
Drug Regulatory Affairs

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Tel 973-503-7584
Fax 973-503-6325
Internet:patricia.mcgovern
@pharma.novartis.com

NOVARTIS

NEW CORRESP

September 5, 1997

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

NDA NO. 20-846

LAMISIL® DermGel
(terbinafine emulsion gel)
Emulsion Gel 1%

RESPONSE TO FDA REQUEST

Dear Dr. Wilkin:

Please refer to our pending new drug application for Lamisil® DermGel™ (terbinafine emulsion gel) Emulsion Gel, 1% submitted on April 29, 1997. In response to a request from Dr. Roy Blay, FDA Project Manager for this product, and in accordance with FDA's Revised Policies and Procedures for compliance with the National Environmental Policy Act, Novartis is requesting the withdrawal of the Environmental Assessment included in this application (NDA 20-846, Volume 4, p. 3-948). We are now providing a claim for categorical exclusion from the Environmental Assessment requirements under 21 CFR 25.31(b). In compliance with those requirements, our claim demonstrates that estimated concentration of the active substance, terbinafine, will be below the 1 ppb cut-off level at the point of entry into the environment.

If you have questions or comments concerning this submission, please contact Dr. Joyce Ann Sinno at (908) 277-7044.

Sincerely,

Patricia McGovern

Patricia McGovern
Assistant Director

PM/dmh
cc: Roy Blay, PhD
Attachment
Submitted in Duplicate

NOVARTIS

Lamisil® DermGel™ Emulsion Gel, 1%

ENVIRONMENTAL ASSESSMENT

A claim for categorical exclusion from the Environmental Assessment requirements under 21 CFR 25.31(b) - Action on an NDA, abbreviated application, or a supplement to such applications, or action on an OTC monograph - if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 ppb.

NOVARTIS

Lamisil® DermGel™ Emulsion Gel, 1%

As set forth in 21 CFR Part 25.31(b), action on a New Drug Application is categorically excluded from the requirement to prepare an Environmental Assessment or an Environmental Impact Statement if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be less than 1 part per billion (ppb).

Novartis Pharmaceuticals Corporation has filed a New Drug Application (NDA) for Lamisil® DermGel™. Lamisil® DermGel™ contains the drug substance terbinafine, a synthetic allylamine derivative which exerts its antifungal effect by

Approval is being sought to market a new dosage form of Lamisil® for the topical treatment of the following dermatological infections: pityriasis versicolor due to *Malassezia furfur* (formerly *Pityrosporum ovale*) and tinea pedis (athlete's foot), or tinea corporis (ringwom) due to *Trichophyton rubrum*, *Trichophyton mentagrophytes*, or *Epidermophyton floccosum*, respectively.

Novartis Pharmaceuticals Corporation certifies that NDA #20-846 for Lamisil® DermGel™ Emulsion Gel, 1% qualifies for a categorical exclusion in accordance with 21 CFR Part 25.31(b) as the new dosage form will increase the concentration of the active moiety, terbinafine base; however the concentration of terbinafine base at the point of entry into the environment will be less than 1 ppb. Please refer to confidential Attachments 1 and 2, which support this claim.

Further, Novartis Pharmaceuticals Corporation states that, to the best of its knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment and would thus require the preparation of at least an Environmental Assessment.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-846

PHARMACOLOGY REVIEW(S)

AUG 2 7 1997

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Division of Dermatologic & Dental Drug Products, HFD-540

NDA 20-846 (Original submission 04-29-1997)
Drug: Lamisil[R] DermGel[TM](terbinafine emulsion gel) Emulsion Gel,1%
Sponsor: Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080
Patricia McGovern
(201)503-7384

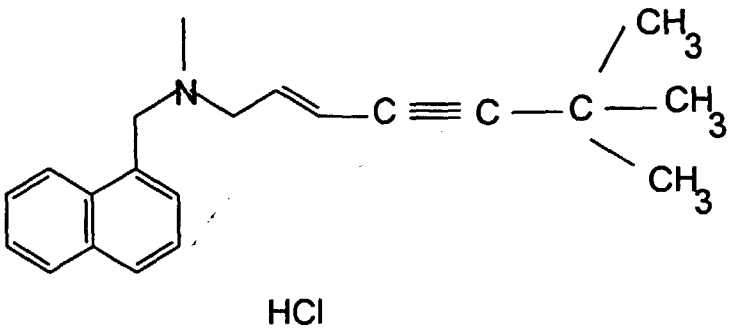
Number of Volumes: Four (4)
Date CDER Received: 04-29-1997
Date Assigned: 05-12-1997
Date of Review: 05-26-1997

Dosage and Route of Administration: Topical, Gel
Category: Antifungal
Indication: Topical treatment of pityriasis versicolor due to Malassezia furfur, and tinea pedis, or tinea corporis due to Trichophyton rubrum, Trichophyton mentagrophytes, or Epidermophyton floccosum.

Review Objective: To evaluate the safety of an already approved drug in a different formulation.

Chemical Name: (E)-N-(6, 6-dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalenemethanamine hydrochloride

Chemical Structure:



Composition:

Ingredients	Grams/100g Drug Product
Terbinafine	1.0
Butylated hydroxytoluene,NF	
Sodium hydroxide, Ph.Eur.	
Benzyl alcohol, NF	
Sorbitan monolaurate, NF	
Carbomer 934P	NF
Polysorbate 20, NF	
Isopropyl myristate, NF	
Ethanol (V/V),	
Water purified, USP	

Related Submissions:

INDs

NDAs

20-192; Lamisil Cream 1% (approved, 12-30-1992)
20-539; Lamisil Tablets (approved, 05-10-1992)
20-749; Lamisil Solution 1%

Background: Over the years, a number of applications have been submitted to support the different antifungal formulations of the active ingredient, terbinafine hydrochloride. To support these applications, the sponsor has extensively tested the safety of this compound in a wide spectrum of animal and *in vitro* studies. These studies were conducted with the tablet, cream, solution, as well as with the proposed 1% Derm Gel formulations. A large number of these studies were reviewed under various INDs and NDAs listed above; the rest are reviewed here.

Index of Studies

1. Testing of pharmacological efficacy in guinea pigs
2. Acute oral toxicity in mice
3. Acute oral toxicity in rats
4. Acute dermal irritation study in rabbits
5. Acute eye irritation in rabbits
6. Four-week dermal study in rabbits

Testing Facility: All toxicity studies (#2-6) were conducted at the

GLP Statements: All toxicity study reports included signed GLP compliance statements.

1. Topical Efficacy of Terbinafine Prepared As Emulsion Gel in Experimental Dermatophytosis of Guinea Pigs (103-122; November, 1992).

Study objective/Design: The efficacy of 0.0039, 0.0156, and 0.0625 percent terbinafine gels in treating experimental dermatophytosis induced by *Trichophyton mentagrophytes* infection in female guinea pigs (200-250g) was evaluated. Terbinafine solutions and ethanol,) at the same concentration levels as the test formulations were used as reference standards. Reportedly, the same reference standards were previously used to check the efficacy of terbinafine cream formulations.

A preshaved site on the lumbar region on the back of each animal received 0.1 mL of inoculum containing 10^6 colony forming units of *T. mentagrophytes*. Two days after the induction of infection, for one week, the infected sites received daily applications of 0.5 mL of the respective test formulations. Each preparation was tested in 6-8 animals. A group of infected but vehicle treated animals served as controls.

Observations/Evaluations: The efficacy of the test formulations was determined mycologically and clinically. The residual infection in the mycotic lesions was assessed by the "hair root invasion test". At postinfection day 11, the hair samples from the infected areas were incubated with dermatophyte test medium on the agar plates for seven days. After incubation, the hair roots were examined microscopically for fungal growth. In the clinical evaluation on postinfection day 11, the intensity of local changes in each drug treated animal was compared with the vehicle treated animals.

Results/Conclusions: Terbinafine emulsion gels were effective in treating experimental trichophytosis with a calculated ED_{50} (cure rates) of 0.008%. A slightly reduced response (ED_{50}=0.0012%) was observed with the standard references. The mycological and clinical

evaluations provided similar results for cure.

2. Lamisil[R] Emulsion Gel 1%: Acute Oral Toxicity in Mice (203-116; September 1992).

3. Lamisil[R] Emulsion Gel 1%: Acute Toxicity in Rats (203-117; September 1992).

Study Design/Procedures:

Animals: ICO,OFI male (26.8±1.5g) and female (23.7±0.5g) mice.
Sprague-Dawley male (171±7g) and female (150±6g) rats.

Dosage(gavage): Mice: 25 mL/kg (250 mg/kg)
Rats: 10 mL/kg (100 mg/kg)

Following a single oral dose of the test material, animals were examined daily for signs of toxicity, morbidity, and mortality. Body weights were determined on postdose days 5, 8, and 15. On day 15, all animals were subjected to gross necropsy examination.

Results: No deaths occurred during the study. There were no changes in body weights, general health, or gross pathology. LD_{50} values in mice and rats exceeded 250, and 100 mg/kg, respectively.

4. Lamisil[R] Emulsion Gel 1%: Acute Dermal Irritation in Rabbits (203-115; November, 1992).

Study Design/Procedures/Evaluations: The skin irritation potential of the test formulation was evaluated in three NZW rabbits (2.5±0.1kg) following a single topical application of 0.5 mL (5mg) material on a preshaved site (6cm^2) on the right flank. The untreated left flank served as a control. Animals were exposed to the test material for 4 hours under occlusion. The dermal reactions were graded (O.E.C.D Guideline 404) at 24, 48, and 72 hours after the treatment.

Results/Conclusions: At the first examination, all animals exhibited a well-defined erythema and slight edema. On the second day, only very slight erythema was observed in all the rabbits. No dermal lesions were observed on the third day. The test formulation was considered a non-irritant.

5. Lamisil[R] Emulsin Gel 1%: Acute Eye Irritation in Rabbits (203-114; September, 1992).

Study Design/Procedures: Three male NZW rabbits (2.8±0.1kg) received 0.1 mL of Lamisil

Emulsion Gel, 1% in the conjunctival sac of the left eye. The untreated right eye served as a control. The eyes were not washed after the treatment. The ocular reactions reactions were scored (Draize) at 1, 24, 48, and 72 hours post-treatment.

Results/Conclusions: Some light redness and chemosis (conjunctival reactions) were observed in all the rabbits at the first examination. No ocular reactions were observed after 24 hours of treatment, indicating that the test formulation was a non-irritant.

6. Four-Week Toxicity Study by Dermal Route in Rabbits with a Two-Week Recovery Period (203-119; December, 1992).

Study Design/Procedures/Evaluations

Animals: Twelve weeks old male and female NZW white rabbits with mean body weight of approximately 2.5 kg were used in this study.

Test Formulations and Group Distribution: Lamisil Gel at 1% (10M+10F), 2% (10M+10F), 3% (15M+15F), and vehicle (15M+15F) groups.

Animals received daily topical applications of 2 g/kg of the test formulation on a 240 cm^2 preshaved site (one site/animal) on the dorsal retro-scapular region for 4 weeks. Blood samples for the determination of levels of plasma drug and its metabolites, and hematologic (10 tests) and serum chemistry (17 tests) parameters were drawn from 5 animals/sex/group on the last day at 0, 2, and 6 hours post-application.

After 4 weeks of treatment, 5 animals of each sex from the 3% gel and vehicle groups were maintained for two-weeks recovery period.

Throughout the treatment and recovery periods, animals were examined daily for clinical signs of toxicity. Body weights and food consumption were determined weekly. Dermal reactions were scored daily prior to the treatment and 24 hours after the last drug application. At the end of the treatment and recovery periods, all the survivors, and animals found dead during the study, were subjected to complete necropsy examination. The weights of the following organs were determined: adrenals, liver, heart, kidneys, ovaries, testes, spleen, and thymus. Histopathologic examinations were conducted on all the macroscopic lesions, skin, and the weighed organs.

Results

Clinical Observations/Mortality: No drug related clinical signs of toxicity were observed during the entire period of the study. The death of one male of the 1% group found dead on treatment day 3, was not considered drug related. This animal exhibited signs of poor physical

condition. No clinical signs of toxicity were observed in a 3% male found dead on treatment day 29.

Dermal Reactions: Dermal irritation first observed on day 5 involved most animals in all the groups. These reactions more prominent in the controls were attributed to ethanol in the formulations (table).

Percent Group Distribution of Animals with Dermal Lesions

TREATMENT PERIOD

	MALES				FEMALES			
Group:	Control	1%	2%	3%	Control	1%	2%	3%
Lesions:								
Well-defined erythema	100	80	100	93	100	80	40	46
Slight edema	93	70	80	86	80	70	70	53
Scabs on back	100	90	100	100	100	90	80	93

RECOVERY PERIOD

Very slight erythema	40	--	--	0	0	--	--	0
Very slight edema	60	--	--	40	20	--	--	0
Scabs	0	--	--	0	0	--	--	0

Body weights/Food consumption: No intergroup differences were observed at any time in the study period.

Hematology/Serum chemistry: No drug related statistically significant intergroup differences were observed.

Gross Pathology/Organ weights/Histopathology: The necropsy examination of the dead male from the 1% gel group revealed redish color lungs with a greyish/whitish zone, a whitish color liver and liquid in the thoracic cavity. The corresponding histopathologic findings included multifocal cell necrosis with hepatic cell hypertrophy, myocarditis with pericarditis, and multifocal epidermatitis. Reportedly, death resulted from factors (acute bronchopneumonia, pleuritis, and pericarditis) of infectious origin. The dead male from 3% group exhibited a hematoma in the cervical region; histopathologic examination revealed perimuscular hemorrhages in the cervical region. This accidental death was related to the blood sampling procedure and or injury in the cage.

At the end of the treatment period, a statistically significant ($p<0.01$ to 0.05) increase in relative kidney (13% in 3% group) and liver (13% in 1% and 2% groups, and 14% in the 3% group) weights was observed in the drug treated males. However, these changes in organ weights were not associated with any relevant histopathologic lesions. No intergroup differences in the organ weights were observed at the end of the recovery period.

The histopathologic examination of the application sites confirmed the signs of dermal irritation (e.g., acanthosis, hyperkeratosis, epidermal cell necrosis etc.,) observed during the daily clinical examinations.

Plasma Drug Levels: At a given sampling time point, the concentrations (ng free base/mL) of the parent drug and its N-demethylated metabolite were found to be dose-related. The mean plasma drug concentration in the males was usually higher than females. However, the reverse was true for the metabolite, indicating a sex- associated difference in the demethylation pathway in the rabbits.

Labeling: The draft submitted by the sponsor has been modified to indicate the values for margin of safety in terms of milligrams of terbinafine base/m^2/day. In addition, the names of various genotoxicity tests conducted by the sponsor are added to the text.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 28-month oral carcinogenicity study in rats, a marginal increase in the incidence of liver tumors was observed in males at the highest dose level, 69 mg/kg/day (in terms of mg/m^2/day equivalent to 41 times the maximum potential exposure at the recommended topical human dose*). There was no dose-related trend, and the mid-dose male rats, 20 mg/kg/day (in terms of mg/m^2/day equivalent to 12 times the maximum potential exposure at the recommended topical human dose*), did not have any liver tumors. No increased incidence in liver tumors was noted in female rats at dose levels up to 97 mg/kg/day (in terms of mg/m^2/day equivalent to 58 times the maximum potential exposure at the recommended topical human dose*), or in male or female mice treated orally for 23 months at doses up to 156 mg/kg/day (in terms of mg/m^2/day equivalent to 47 times the maximum potential exposure at the recommended topical human dose*).

A wide range of oral *in vivo* studies in mice, rats, dogs and monkeys and *in vitro* studies using rat, monkey and human hepatocytes suggest that the development of liver tumors in the high-dose male rats may be associated with peroxisome proliferation and support the conclusion that this is a rat-specific finding.

The results of a variety of *in vitro* (mutations in *E. coli* and *Salmonella*, DNA repair in rat

hepatocytes, mutagenicity in Chinese hamster fibroblasts, chromosome aberration and sister chromatid exchanges in Chinese hamster lung cells), and *in vivo* (chromosome aberration in Chinese hamsters, micronucleus test in mice) genotoxicity tests gave no evidence of a mutagenic or clastogenic potential and demonstrated the absence of tumor-initiating or cell-proliferating activity.

Oral reproduction studies in rats at doses up to 300 mg/kg/day (in terms of mg/m^2/day equivalent to 180 times the maximum potential exposure at the recommended topical human dose*) did not reveal any specific effects on fertility or other reproductive parameters. Intravaginal application of terbinafine hydrochloride at 150 mg/day (in terms of mg/m^2/day equivalent to 202 times the maximum potential exposure at the recommended topical human dose*) in pregnant rabbits did not increase the incidence of abortions, premature deliveries or fetal abnormalities.

Pregnancy

Pregnancy Category B: Oral doses of terbinafine hydrochloride up to 300 mg/kg/day (in terms of mg/m^2/day equivalent to 180 and 202 times the maximum potential exposure at the recommended topical human dose*) during organogenesis in rats and rabbits, respectively, were not teratogenic. Similarly, a subcutaneous study in rats at doses up to 100 mg/kg/day (in terms of mg/m^2/day equivalent to 60 times the maximum potential exposure at the recommended topical human dose*) and a percutaneous study in rabbits, including doses up to 150 mg/kg/day (in terms of mg/m^2/day equivalent to 202 times the maximum potential exposure at the recommended topical human dose*) did not reveal any teratogenic potential. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Lamisil® Solution 1% (terbinafine hydrochloride solution) should be used only if clearly indicated during pregnancy.

* The above comparisons between oral animal doses and the maximum potential exposure at the recommended topical human dose are based upon the application to human skin of 0.1 mg of terbinafine/cm^2 once daily, the assumption of average human cutaneous exposure of 100 cm^2 (assuming the use of 1 gram of Lamisil® Solution/dose), and the theoretical maximum human cutaneous absorption of 100%.

Toxicologist's Discussion and Interpretation of Safety Data

To date, topical 1% cream (interdigital tinea pedis, tinea cruris, tinea corporis) and tablet (onychomycosis) formulations of terbinafine hydrochloride have been approved for marketing. The approval of Lamisil 1% solution for the treatment of athletes foot (tinea pedis), jock itch (tinea cruris), ring worm (tinea corporis), and pityriasis, is pending. To support these products, the sponsor has very extensively tested the safety of terbinafine in a wide spectrum of animal studies and in *in vitro* assays. These studies previously reviewed under various INDs and NDAs

by this reviewer have also very well addressed the safety of the proposed Lamisil Derm Gel 1%. for the topical treatment of pityriasis versicolor (Malassezia furfur), and tinea pedis, tinea cruris, and tinea corporis (Trichophyton rubrum, Trichophyton mentagrophytes, or Epidermophyton floccosum). Additionally, a number of studies were conducted to evaluate the efficacy, oral acute toxicity, primary dermal and ocular irritation potentials, and subchronic dermal toxicity of Lamisil 1% Derm Gel.

In a therapeutic efficacy study in guinea pigs, terbinafine emulsion gel was effective in treating the experimental trichophytosis. Clinically this preparation will be used at a maximum level of once daily for one week. In animal studies, this drug has been tested for much longer duration at much higher dose levels. LD_{50} values in mice and rats exceeded 250, and 100 mg/kg/day, respectively. The proposed human dose is about 0.167 mg/kg/day. In a primary irritation study in rabbits, the drug was well tolerated; and the formulation also did not produce any ocular lesions in a primary eye irritation test in rabbits. In a rabbit cumulative toxicity study, almost all the vehicle and most of the drug treated animals exhibited reversible dermal irritation attributed to ethanol in the test formulations.

On the whole, taking into account its negligible toxicity, based on extensive testing in multiple animal species, and to date, safe world-wide use of terbinafine in cream and tablet forms since 1991, this reviewer has no objection in approving Lamisil 1% Derm Gel for its short term use.

Regulatory Conclusions: This new drug application is approvable, provided the sponsor agrees to the recommended changes in the labeling.

/S/ 08/27/97

Kumar D.Mainigi, Ph.D., M.P.H., DABT
Toxicologist

CC: Original NDA 20-846
HFD-82
HFD-540
MO/Toombs
Pharm/Mainigi
Chem/Vidra
CSO/ Blay
Pharm/Jacobs
Biopharm/Bashaw

Concurrence:
A.Jacobs, TL, HFD-540 8/27/97
J.Wilkin, Dir, HFD-540 8/29/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-846

STATISTICAL REVIEW(S)

MAR 12 1998

STATISTICAL REVIEW AND EVALUATION

NDA: 20-846 /3S
Applicant: Novartis Pharmaceuticals Corp.
Name of Drug: Lamisil® DermGel™ (terbinafine emulsion gel) Emulsion Gel, 1%
Pharm. Class: Antifungal
Route of Administration: Topical
Documents Reviewed: NDA 20-846: Vol. 1, 37-50 (submitted April 29, 1997)
Indication: Topical treatment of the following dermatological infections:
pityriasis versicolor due to Malassezia furfur;
tinea pedis (athlete's foot);
versicolor, or tinea corporis (ringworm)
due to Trichophyton rubrum, trichophyton mantagrophytes
or Epidermophyton floccosum.
Related INDs: IND IND IND IND
IND
Related NDAs: NDA 20-192 (terbinafine hydrochloride cream, 1%), NDA 20-749 (terbinafine hydrochloride solution, 1%), NDA 20-539 (terbinafine hydrochloride tablets)
Medical Officer: Ella Toombs, M. D. (HFD-540)

Table of Contents:

Introduction :

Tinea pedis and tinea corporis/cruris are similar diseases, caused by a common group of dermatophyte pathogens, the majority being due to Trichophyton rubrum. Pityriasis versicolor, a yeast infection, is a chronic disease with a high relapse rate, and has a different disease presentation and pathology.

For the indication of pityriasis versicolor, two pivotal randomized, placebo-controlled studies (SFG 203 and SFG 302) examined the efficacy and safety of Lamisil 1% Emulsion Gel used once daily for one week with seven weeks of blinded follow up.

For the tinea pedis indication, two pivotal double-blind, placebo-controlled studies were performed to evaluate the tolerability and efficacy of Lamisil 1% Emulsion Gel or 3% Gel applied once daily for 5 days (SFG 102) and 1% Gel applied for one week (SFG 202).

For the Tinea corporis/cruris indication, one pivotal double-blind, placebo-controlled study (SFG 201) was performed to evaluate the tolerability and efficacy of Lamisil 1% Emulsion Gel used once daily for one week with seven weeks of blinded follow up.

Study Design : All of the five trials are pivotal, randomized, placebo-controlled, double blind, parallel, multi-center in design.

Table 1. Study designs

Indication	Study	Country(ies)	Duration of treatment	Follow-up period	No. of subjects Enrolled		Enrolled Subjects	
					Lamisil 1% (3%)	Placebo	Age range (mean)	Sex %M %F
Pityriasis versicolor	SFG 203	Sweden	1 week OD	7 weeks	31 (0)	30	(36.8)	50.8% 49.2%
	SFG 302	Norway/Sweden	1 week OD	7 weeks	87 (0)	42	(36.0)	51.9% 48.1%
Tinea pedis	SFG 102	United Kingdom	5 days OD	37 days	30 (28)	27	(39.8)	69.4% 30.6%
	SFG 202	Finland/Belgium	1 week OD	7 weeks	51 (0)	50	(43.3)	66.3% 33.7%
Tinea corporis/cruris	SFG 201	South Africa	1 week OD	7 weeks	40 (0)	43	(37.9)	78.3% 21.7%

In all studies, clinical diagnosis confirmed by positive microscopy was required for study entry for all indications. Culture was also performed in tinea pedis and tinea corporis/cruris studies. Efficacy (clinical and mycological) and safety parameters were assessed at study visits which occurred at specified intervals throughout the study. End of study was defined as the last non-missing post-baseline observation and was the primary endpoint in the analysis. For all three indications, the primary efficacy variable was Effective Treatment. The secondary efficacy variables included: Complete Cure (negative mycology and no signs and symptoms), Microscopy, Culture (in T. pedis and T. corporis/cruris studies only), Mycology (microscopy and culture combined in T. pedis and T. corporis/cruris studies only), Total signs and symptoms score (TSSS,; sum of individual severity scores for the evaluated signs and symptoms of the indication), Clinical Cure, (i.e., no signs and symptoms) and Overall Assessment of Efficacy by investigator (This variable was not in the electronic data submitted by the sponsor). The ITT population was used for all efficacy analyses, and included any subject who was randomized, received at least one application of the study drug, was not Delayed Exclusion (i.e., had negative microscopy or culture at baseline), and had at least one non-missing post-baseline efficacy assessment [microscopy assessment (in tinea pedis and tinea corporis/cruris) or clinical signs and symptoms]. The safety population included all patients who had applied the study drug at least one post-baseline evaluation of one of the safety variables (i.e., adverse events or Overall Assessment of Tolerability by investigator).

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) of 0 or 1. Each sign or symptom was graded on a scale of 0-3, absent, mild, moderate, or severe. Three signs and symptoms were assessed in the pityriasis versicolor studies: erythema, desquamation, and pruritus; TSSS was the sum of the severity scores for these symptoms. The criteria for Complete Cure was met if a subject had negative microscopy results and a TSSS of 0, making it more stringent than Effective Treatment.

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 for 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, which had more stringent criteria than Effective treatment, was defined as negative microscopy, negative culture, and TSSS for erythema, desquamation, pruritus, vesicultion, incrustation and pustules = 0.

Results:

Pityriasis versicolor

Study SFG 203

Efficacy Analysis

Primary Efficacy Variables: The primary efficacy parameter is the Overall Effectiveness (= Effective treatment) . Confirmatory statistical conclusions for the Overall Effectiveness will be done using the outcomes of the assessments at End-of-study (week 8) only, which is defined as the primary endpoint. The "Effective treatment" includes the following two categories of "cure" in the investigator's assessment of clinical response in the CRF:

1. Microscopy shows no hyphae. There are no clinical signs and symptoms. Hypopigmentation may be present.
2. Microscopy shows no hyphae. Mild desquamation, mild pruritus, mild erythema, (total score=1 for these 3 parameters). Hypopigmentation may be present.

All others are considered failures.

Secondary Efficacy Variables : All "Components of Efficacy", i.e., the Assessment of Lesions (individual severity scores for Clinical Signs and Symptoms), the Microscopy of the Target Area , the Quantitative Culture of the Target Area, and the Clinical Response, are secondary efficacy parameters. The total Clinical Score summarizes the Assessment of Lesions for all symptoms, i.e., the sum of the severity scale scores of Erythema, Desquamation, Pruritus, and Others, defines the Total Clinical Score. This is also a secondary efficacy parameter. "Complete cure" was included in the sponsor's submission of the NDA, it was not defined in the original protocol, and was defined in the NDA submission as "negative mycology and no signs and symptoms", which corresponds to the "cure 1" in "clinical response".

The Intent-to-treat (ITT) efficacy analyses will be done upon Intent-to-treat subjects, i.e., subjects who were randomized to either treatment group, were not delayed exclusions, received study medication, and reported Mycological Controlling Sampling measurements in the application skin area prior to and after the first administration of the respective test drug.

Valid subjects population is defined as all ITT subjects having completed the seven days of treatment with Lamisil Derm Gel , reporting valid Mycological Controlling Sampling measurements at Baseline and Week 8, and without reporting any protocol violations or conditions liable to influence the efficacy evaluations.
Subjects whose treatment is stopped prematurely for the following reason are also valid for efficacy analyses:

- The subject's clinical status with respect to the indications worsened any time during the trial (lack of efficacy).

If the treatment was stopped prematurely due to the above reason, the Overall Effectiveness (primary efficacy parameter) of the pertaining subjects will be set to "Ineffective".

Table 2 Patient deposition (SFG203)

	ITT population		Valid population	
	Lamisil (m/f)	Placebo(m/f)	Lamisil (m/f)	Placebo(m/f)
Baseline	28 (14/14)	30 (16/14)	26 (13/13)	29 (15/14)
Week 1	28(14/14)	30(16/14)	26 (13/13)	29 (15/14)
Week 2	28(14/14)	27(14/13)	26 (13/13)	26 (13/13)
Week 6	28(14/14)	20(10/10)	26 (13/13)	19 (9/10)
Week 8	21(10/11)	5(1/4)	21 (10/11)	5 (1/4)

Reviewer's note: It is noted that there were only 5 patients left in the placebo group in Week 8. Hence, the "last observation carried forward" (l.o.c.f.) analysis will be performed for the primary efficacy variable, and all secondary variable analyses will be the l.o.c.f. only.

Table 3 contains the results of the primary efficacy analysis, i.e., the rates of "Effective treatment " in study SFG203. There were no statistically significant difference (p=0.518) in week 8 in either the ITT population or the valid population. This may be due to the high dropout rate in the placebo group. The difference was statistically significant (p=0.001) in both the ITT and the valid population at "End-of-study" (l.o.c.f. analysis), in favor of the test drug, Lamisil Derm Gel 1%. The frequencies at week 1 were listed for labeling purposes.

Table 3 Rates of Effective treatment (SFG203)

		Treatment group		
		Lamisil	Placebo	p**
ITT population				
Week 1	N	28	30	
	Yes	11 (39.3%)	7 (23.3%)	0.193
	No	17 (60.7%)	23 (76.7%)	
Week 8	N	21	5	
	Yes	19 (90.5%)	4(80.0%)	0.518
	No	2 (9.5%)	1(20%)	
l.o.c.f.*	N	28	30	
	Yes	21(75%)	4(13.3%)	0.001
	No	7(25%)	26(86.7%)	
Valid population				
Week 8	N	21	5	
	Yes	19 (90.5%)	4(80.0%)	0.518
	No	2 (9.5%)	1(20%)	
l.o.c.f.	N	26	29	
	Yes	19(73.1%)	4(13.8%)	0.001
	No	7(26.9%)	25(86.2%)	

*Last observation carried forward
**p values were from the Mantel-Haenszel chi-square test.

Table 4 lists the rate of "complete cure" at "EOS" (End-of-study, or l.o.c.f. analysis). The difference was statistically significant (p=0.001) for both the ITT and the valid population, in favor of the Lamisil group. The frequencies at week 1 were listed for labeling purposes.

Table 4 Rates of Complete cure (SFG203)

		Treatment group		
		Lamisil	Placebo	p**
ITT population (week 1)	N	28	30	
	Yes	6 (21.4%)	1 (3.3%)	0.036
	No	22 (78.6%)	29 (96.7%)	
ITT population (l.o.c.f)	N	28	30	
	Yes	20(71.4%)	4(13.3%)	0.001
	No	8(28.6%)	26(86.7%)	
Valid population l.o.c.f.	N	26	29	
	Yes	18(69.2 %)	4(13.8%)	0.001
	No	8(30.7%)	25(86.2%)	

*Last observation carried forward
**p values were from the Mantel-Haenszel chi-square test.

Table 5 lists the rate of negative microscopy at "EOS" (End-of-study, or l.o.c.f. analysis). The difference was statistically significant (p=0.001) for both the ITT and the valid population, in favor of the Lamisil group. The frequencies at week 1 were listed for labeling purposes.

Table 5 Rates of negative microscopy (SFG203)

		Treatment group		
		Lamisil	Placebo	p**
ITT population (week 1)	N	28	30	
	Negative	17 (60.7%)	10 (33.3%)	0.001
	Positive	11 (39.3%)	20 (66.7%)	
ITT population (l.o.c.f)	N	28	29	
	Negative	21(75%)	4(13.8%)	0.001
	Positive	7(25%)	25(86.2%)	
Valid population l.o.c.f.	N	26	29	
	Negative	19(73.1 %)	4(13.8%)	0.001
	Positive	7(26.9%)	25(86.2%)	

*Last observation carried forward
**p values were from the Mantel-Haenszel chi-square test.

Table 6 contains the result of the analysis of "change of total score from baseline", total disease severity score, colony count, and scores of Erythema, Desquamation, Pruritus. The differences between the Lamisil group and the placebo group were statistically significant in "change of total score from baseline" (p=0.0001 for both the ITT and valid populations), total disease severity score (p=0.0001 for both the ITT and valid populations), and scores of Erythema (p=0.0001 for the ITT population and p=0.0003 for the valid population), Desquamation (p=0.0001 for both the ITT and valid populations), Pruritus (p=0.0048 for ITT population, p=0.0097 for the valid population). All were in favor of the Lamisil group. The difference in colony count was not statistically significant (p=0.2306 for ITT population, p=0.4777 for the valid population), but the Lamisil group had numerically higher colony counts.

Table 6 Change of Total score from baseline, Total score, Colony count, Erythema, Desquamation, Pruritus (SFG 203)

	Variable	Treatment	N	Mean	p
ITT population (l.o.c.f.)	Change of Total score from baseline	Lamisil	28	-4.56233422	0.0001
		Placebo	30	-2.17011494	
	Total score	Lamisil	28	0.55172414	0.0001
		Placebo	30	2.78620690	
	Colony Count	Lamisil	28	59.5225464	0.2306
		Placebo	30	47.9241379	
	Erythema	Lamisil	28	0.36167341	0.0001
		Placebo	29	1.23308271	
	Desquamation	Lamisil	28	0.14574899	0.0001
		Placebo	29	1.02631579	
	Pruritus	Lamisil	28	0.03643725	0.0048
		Placebo	29	0.47493734	
Valid population (l.o.c.f.)	Change of Total score from baseline	Lamisil	26	-4.54710744	0.0001
		Placebo	29	-2.21038961	
	Total score	Lamisil	26	0.60991736	0.0001
		Placebo	29	2.68311688	
	Colony Count	Lamisil	26	56.2793388	0.4777
		Placebo	29	49.2597403	
	Erythema	Lamisil	26	0.40330579	0.0003
		Placebo	29	1.21558442	
	Desquamation	Lamisil	26	0.16528926	0.0001
		Placebo	29	1.00909091	
	Pruritus	Lamisil	26	0.04132231	0.0097
		Placebo	29	0.45844156	

Reviewer's comment: According to the protocol, Week 8 was the primary time point for efficacy analyses. However, there were a large number of dropouts in the placebo group due to treatment failures. By Week 8, there were only 5 subjects left in the placebo group. Four of the five subjects left were in the category of "Effective treatment" (i.e., successfully treated). The reviewer felt that it was more appropriate to conduct the "last observation carried forward" analysis (End-of-study analysis). Hence, the results of the analyses for study SFG203 were based on the l.o.c.f. analyses. Study SFG203 showed that the Lamisil Derm Gel 1% treatment group was statistically significantly superior ($p=0.001$) to the placebo group in the treatment of Pityriasis versicolor in both the ITT population and the valid population at "End-of-study" (l.o.c.f. analysis), relative to the primary efficacy variable, Overall Effectiveness (Effective treatment). The Lamisil Derm Gel 1% treatment group was statistically significantly superior to the placebo group ($p=0.001$) in the secondary efficacy variable "complete cure" and "microscopy" at "End-of-study" (l.o.c.f. analysis) in both the ITT population and the valid population. The Lamisil Derm Gel 1% treatment group was statistically significantly superior to the placebo group ($p<0.01$), in the secondary efficacy variable "Change of Total score from baseline" , "Total score", and scores of Erythema, Desquamation , and Pruritus at "End-of-study" (l.o.c.f. analysis) in both the ITT population and the valid population. The Lamisil Derm Gel 1% group had numerically higher colony counts (secondary variable)

than the placebo group, but the differences were not statistically significant (p=0.2306 for the ITT population, p=0.4777 for the valid population).

Study SFG 302

Efficacy Analysis

Primary Efficacy Variables: The primary efficacy parameter is the Overall Effectiveness (= Effective treatment). Overall effectiveness will be classified as "effective" or "ineffective" based on a combination of results of microscopy and the clinical symptom severity scores. The category of "effective" is defined as follows:

- Negative microscopy, and
- total severity score (sum of severity scores for erythema, scaling and prutitis) ≤ 1.

Confirmatory statistical conclusions concerning the efficacy of 1% Lamisil emulsion gel compared with placebo will be made using the evaluation of overall effectiveness at 'End of Study' (defined as 'the last non-missing post-screening/baseline observation up to and including the week 8 (Day 56) visit or at discontinuation from the study.)

Secondary Efficacy Variables :

- microscopy
- severity scores for erythema, scaling and pruritus
- cure (negative microscopy and total severity score =0)
- total severity score

The Intent-to-treat (ITT) population includes subjects who received at least one application of randomized medication, and have at least one post-screening/baseline efficacy measurement (microscopy or severity score of signs and symptoms) in the application skin area.

Valid subjects population is defined as all ITT subjects who received study medication in compliance with the treatment schedule, who reported efficacy assessments at Week 1 (Day 7) and Week 8 (Day 56), and without any protocol violations, liable to influence the evaluation of efficacy (e.g. prior/concomitant topical antifungal medication, etc.).

Compliance with respect to the treatment schedule is defined as a patient who received 6, 7, or 8 applications of study medication (once per day).

Table 7 Patient deposition (SFG302)

	ITT population		Valid population	
	Lamisil (m/f)	Placebo(m/f)	Lamisil (m/f)	Placebo(m/f)
Baseline	87 (42/45)	42 (25/17)	75 (39/36)	37 (23/14)
Week 1	86 (41/45)	41 (25/16)	75 (39/36)	37 (23/14)
Week 2	84 (40/44)	40 (23/17)	71 (36/35)	34 (21/13)
Week 4	86 (40/46)	31 (20/11)	74 (37/37)	26 (18/8)
Week 8	68 (32/36)	22 (15/7)	64 (30/34)	19 (14/5)

Reviewer's note: The "last observation carried forward" (l.o.c.f.) analysis will be performed for the primary efficacy variable (EOS , End-of-study, as defined in the NDA submission), and all secondary variable analyses will be the l.o.c.f. only.

Table 8 contains the results of the primary efficacy analysis, i.e., the rates of "Effective treatment " in study SFG302. The difference was statistically significant (p=0.001) in both the ITT and the valid population at both Week 8 and "End-of-study" (l.o.c.f. analysis), in favor of the test drug, Lamisil Derm Gel 1%. The frequencies at week 1 were listed for labeling purposes.

Table 8 Rates of Effective treatment (SFG302)

		Treatment group		
		Lamisil	Placebo	p**
ITT population				
Week 1	N	85	39	
	Yes	45 (52.9%)	7 (18%)	0.001
	No	40 (47.1%)	32 (82%)	
Week 8	N	56	21	
	Yes	40 (71.4%)	3 (14.3%)	0.001
	No	16 (28.6%)	18 (85.7%)	
l.o.c.f.*	N	87	42	
	Yes	63 (72.4%)	4 (9.5%)	0.001
	No	24 (27.6%)	38 (90.5%)	
Valid population				
Week 8	N	53	18	
	Yes	39 (73.6%)	1 (5.6%)	0.001
	No	14 (26.4%)	17 (94.4%)	
l.o.c.f.	N	75	37	
	Yes	54 (72%)	1 (2.7%)	0.001
	No	21 (28%)	36 (97.3%)	

*Last observation carried forward

**p values were from the Mantel-Haenszel chi-square test

Table 9 lists the rate of "complete cure" at "EOS" (End-of-study, or l.o.c.f. analysis). The difference was statistically significant (p=0.001) for both the ITT and the valid population, in favor of the Lamisil group. The frequencies at week 1 were listed for labeling purposes.

Table 9 Rates of Complete cure (SFG302)

		Treatment group		
		Lamisil	Placebo	p**
ITT population (week 1)	N	85	40	
	Yes	25 (29.4%)	5 (12.5%)	0.040
	No	60 (70.6%)	35 (87.5%)	
ITT population (l.o.c.f)	N	87	42	
	Yes	58 (66.7%)	4 (9.5%)	0.001
	No	29 (33.3%)	38 (90.5%)	
Valid population l.o.c.f.	N	75	37	
	Yes	51 (68%)	1 (2.7%)	0.001
	No	24 (32%)	36 (97.3%)	

*Last observation carried forward
**p values were from the Mantel-Haenszel chi-square test.

Table 10 lists the rate of negative microscopy at "EOS" (End-of-study, or l.o.c.f. analysis). The difference was statistically significant (p=0.001) for both the ITT and the valid population, in favor of the Lamisil group. The frequencies at week 1 were listed for labeling purposes.

Table 10 Rates of negative microscopy (SFG302)

		Treatment group		
		Lamisil	Placebo	p**
ITT population (week 1)	N	85	39	
	Positive	28 (32.9%)	30 (76.9%)	0.001
	Negative	57 (67.1%)	9 (23.1%)	
ITT population (l.o.c.f)	N	75	40	
	Positive	22 (29.3%)	37 (92.5%)	0.001
	Negative	53 (70.7%)	3 (7.5%)	
Valid population l.o.c.f.	N	65	36	
	Positive	19 (29.2%)	35 (97.2%)	0.001
	Negative	46 (70.8%)	1 (2.8%)	

*Last observation carried forward
**p values were from the Mantel-Haenszel chi-square test.

Table 11 contains the result of the analysis of "change of total score from baseline", total disease severity score, and scores of Erythema, Desquamation, Pruritus. The differences between the Lamisil group and the placebo group were statistically significant (p=0.0001) in all measurements in both the ITT and the valid populations, in favor of the Lamisil group.

Table 11 Change of Total score from baseline, Total score, Erythema, Desquamation, Pruritus (SFG 302)

	Variable	Treatment	N	Mean	p
ITT population (l.o.c.f.)	Change of Total score from baseline	Lamisil	87	3.28295423	0.0001
		Placebo	42	1.00639983	
	Total score	Lamisil	87	0.57368586	0.0001
		Placebo	42	2.69704536	
	Erythema	Lamisil	86	0.22059537	0.0001
		Placebo	41	1.01906513	
	Desquamation	Lamisil	86	0.28974745	0.0001
		Placebo	41	1.23571770	
	Pruritus	Lamisil	86	0.06990333	0.0001
		Placebo	41	0.50217112	
Valid population (l.o.c.f.)	Change of Total score from baseline	Lamisil	75	3.26218576	0.0001
		Placebo	37	0.87154933	
	Total score	Lamisil	75	0.59818560	0.0001
		Placebo	37	2.90080050	
	Erythema	Lamisil	74	0.22885274	0.0001
		Placebo	37	1.10348861	
	Desquamation	Lamisil	74	0.29586942	0.0001
		Placebo	37	1.28901406	
	Pruritus	Lamisil	74	0.08120042	0.0001
		Placebo	37	0.50208836	

Reviewer's comment: Study SFG302 showed that the Lamisil Derm Gel 1% treatment group was statistically significantly superior (p=0.001) to the placebo group in the treatment of Pityriasis versicolor in both the ITT population and the valid population at both Week 8 and "End-of-study" (l.o.c.f. analysis), in the primary efficacy variable, Overall Effectiveness (Effective treatment). The Lamisil Derm Gel 1% treatment group was statistically significantly superior to the placebo group (p=0.001) in the secondary efficacy variable "complete cure" and "microscopy" at "End-of-study" (l.o.c.f. analysis) in both the ITT population and the valid population. The Lamisil Derm Gel 1% treatment group was statistically significantly superior to the placebo group (p=0.0001), in the secondary efficacy variable "Change of Total score from baseline" , "Total score", and scores of Erythema, Desquamation , and Pruritus at "End-of-study" (l.o.c.f. analysis) in both the ITT population and the valid population.

The results of SFG203 and SFG302 were pooled and listed in Table 12 for labeling purposes.

Table 12 Combined results for SFG203 and SFG302

		Treatment group		
		Lamisil	Placebo	p**
Effective treatment				
Week 1	N	113	69	
	Yes	56 (49.6%)	14 (20.3%)	0.001
	No	57 (50.4%)	55 (79.7%)	
Week 8	N	77	26	
	Yes	59 (76.6%)	7 (26.9%)	0.001
	No	18 (23.4%)	19 (73.1%)	
l.o.c.f.	N	115	72	
	Yes	84 (73%)	8 (11.1%)	0.001
	No	31 (27%)	64 (88.9%)	
Complete cure				
Week 1	N	113	70	
	Yes	31 (27.4%)	6 (8.6%)	0.002
	No	82 (72.6%)	64 (91.4%)	
Week 8	N	77	26	
	Yes	55 (71.4%)	7 (26.9%)	0.001
	No	22 (28.6%)	19 (73.1%)	
l.o.c.f.	N	115	72	
	Yes	78 (67.8%)	8 (11.1%)	0.001
	No	37 (32.2%)	64 (88.9%)	
Microscopy				
Week 1	N	113	69	
	Positive	39 (34.5%)	50 (72.5%)	0.001
	Negative	74 (65.5%)	19 (27.5%)	
Week 8	N	77	26	
	Positive	17 (22.1%)	19 (73.1%)	0.001
	Negative	60 (77.9%)	7 (26.9%)	
l.o.c.f.	N	115	72	
	Yes	85 (73.9%)	8 (11.1%)	0.001
	No	30 (26.1%)	64 (88.9%)	

*Last observation carried forward

**p values were from the Mantel-Haenszel chi-square test

Tinea pedis

Study SFG 102

Efficacy Analysis

Primary Efficacy Variables: The primary efficacy parameter (= Effective treatment) is the "combined result of efficacy (effective/ineffective) at week 6 which was dichotomized from "clinical response". The

combined result of efficacy is defined as " effective", when clinical response has the value of "complete cure" or "cure"; and "ineffective" for all other values of clinical response. "Complete cure" and "cure" are defined as:

Complete cure: Microscopy and culture negative, no residual clinical signs and symptoms.

Cure: Microscopy and culture negative, residual erythema and/or desquamation and/or pruritus (total score ≤ 2), but no other clinical signs.

Secondary Efficacy Variables : "all the individual components of efficacy" which includes

- microscopy
- mycology culture
- signs and symptoms for erythema, desquamation, pruritus, pustules, incrustation, vesiculation
- total sum of signs and symptoms
- clinical response
- final overall assessment

Reviewer's note: The electronic data submitted by the sponsor did not include information on " final overall assessment". In the sponsor's submission, "clinical response" was not analyzed, instead, "complete cure" was analyzed.

Complete Intention to Treat (CITT) population is defined as all subjects randomized into the study and receiving at least one application of trial medication, having a measurement of mycology at the screening visit, a clinical assessment at the baseline visit, and having at least one post-baseline measurement of mycology, or at least one post-baseline clinical assessment.

Reduced Intention to Treat (ITT) population is defined as all subjects randomized into the study *except screening culture negative subjects* and receiving at least one application of trial medication, having a measurement of mycology at the screening visit, a clinical assessment at the baseline visit, and having at least one post-baseline measurement of mycology, or at least one post-baseline clinical assessment.

Valid subjects population is defined as subjects completing the whole study including treatment and follow-up, being compliant to the treatment regimen, having positive screening mycology tests, valid final mycology testing and a clinical assessment at week 6, and not violating the protocol in any way liable to influence the efficacy outcome.

Reviewer's note: In the electronic data submitted by the sponsor, an "efficacy evaluable population" was identified rather than a "valid population".

Table 13 Patient deposition (SFG102)

	ITT population			Efficacy population		
	Lamisil 1% (m/f)	Lamisil 3% (m/f)	Placebo(m/f)	Lamisil 1% (m/f)	Lamisil 3% (m/f)	Placebo(m/f)
Baseline	22 (16/6)	21 (14/7)	20 (13/7)	22 (16/6)	20 (14/6)	17 (12/5)
Week 1	22 (16/6)	21 (14/7)	20 (13/7)	22 (16/6)	20 (14/6)	17 (12/5)
Week 2	20 (15/5)	19 (12/7)	19 (12/7)	20 (15/5)	18 (12/6)	16 (11/5)
Week 4	20 (15/5)	20 (13/7)	17 (10/7)	19 (14/5)	18(12/6)	14(9/5)
Week 6	19 (13/6)	19 (12/7)	16 (10/6)	18 (13/5)	18(12/6)	13 (9/4)

Table 14 contains the results of the primary efficacy analysis, i.e., the rates of "Effective treatment " in study SFG102. The difference was statistically significant (p=0.001) in both the ITT and the valid population at both Week 6 and "End-of-study" (l.o.c.f. analysis), in favor of the test drug, Lamisil Derm Gel 1% and Lamisil Derm Gel 3%. The Lamisil Derm Gel 1% group had higher rate of "Effective treatment " than the Lamisil Derm Gel 3% group. The frequencies at week 1 were listed for labeling purposes.

Table 14 Rates of Effective treatment (SFG102)

		Treatment group			
		Lamisil 1%	Lamisil 3%	Placebo	p**
ITT population					
Week 1	N	22	21	20	
	Yes	2 (9.1%)	2 (9.5%)	2 (10%)	0.921
	No	20	19	18	
Week 6	N	19	19	16	
	Yes	16 (84.2%)	13 (68.4%)	3 (18.8%)	0.001
	No	3 (15.8%)	6 (31.6%)	13 (81.3%)	
l.o.c.f.*	N	22	21	20	
	Yes	19 (86.4%)	14 (66.7%)	3 (15%)	0.001
	No	3 (13.6%)	7 (33.3%)	17 (85%)	
Efficacy population					
Week 6	N	18	18	13	
	Yes	15 (83.3%)	12 (66.7%)	2 (15.4%)	0.001
	No	3 (16.7%)	6 (33.3%)	11 (84.6%)	
l.o.c.f.	N	22	20	18	
	Yes	19 (86.4%)	12 (60%)	3 (16.7%)	0.001
	No	3 (13.6%)	8 (40%)	15 (83.3%)	

*Last observation carried forward

**p values were from the Mantel-Haenszel chi-square test.

Table 15 lists the rate of "complete cure" at "EOS" (End-of-study, or l.o.c.f. analysis). The difference was statistically significant for both the ITT (p=0.004) and the valid population (p=0.002), in favor of the Lamisil groups. The Lamisil Derm Gel 1% group had higher rate of "Complete cure " than the Lamisil Derm Gel 3% group. The frequencies at week 1 were listed for labeling purposes.

Table 15 Rates of Complete cure (SFG102)

		Treatment group			
		Lamisil 1%	Lamisil 3%	Placebo	p**
ITT population (week 1)	N	22	21	20	
	Yes	0 (0%)	0 (0%)	0 (0%)	1.0
	No	22 (100%)	21 (100%)	20 (100%)	
ITT population (l.o.c.f)	N	22	21	20	
	Yes	10(45.45%)	7 (33.3%)	1 (5.0%)	0.004
	No	12 (55.55%)	14(66.7%)	19 (95.0%)	
Efficacy population l.o.c.f.	N	22	20	18	
	Yes	10 (45.45%)	7 (35%)	0 (0.0%)	0.002
	No	12 (55.55%)	13(65%)	18 (100%)	

*Last observation carried forward
**p values were from the Mantel-Haenszel chi-square test.

Table 16 lists the rate of negative microscopy at "EOS" (End-of-study, or l.o.c.f. analysis). The difference was statistically significant (p=0.001) for both the ITT and the valid population, in favor of the Lamisil groups. The Lamisil Derm Gel 1% group had higher rate of "negative microscopy" than the Lamisil Derm Gel 3% group. The frequencies at week 1 were listed for labeling purposes.

Table 16 Rates of negative microscopy (SFG102)

		Treatment group			
		Lamisil 1%	Lamisil 3%	Placebo	p**
ITT population (week 1)	N	22	21	19	
	Positive	13 (59.1%)	14 (66.7%)	15 (79%)	0.181
	Negative	9 (40.9%)	7 (33.3%)	4 (21%)	
ITT population (l.o.c.f)	N	22	21	20	
	Positive	1 (4.6%)	3 (14.3%)	15 (75%)	0.001
	Negative	21 (95.5%)	18 (85.7%)	5 (25%)	
Efficacy population l.o.c.f.	N	22	20	18	
	Positive	1 (4.45%)	3 (15%)	13 (72.2%)	0.001
	Negative	21 (95.55%)	17 (85%)	5 (27.8%)	

*Last observation carried forward
**p values were from the Mantel-Haenszel chi-square test.

Table 17 lists the rate of negative culture at "EOS" (End-of-study, or l.o.c.f. analysis). The difference was statistically significant (p=0.001) for both the ITT and the valid population, in favor of the Lamisil groups. The Lamisil Derm Gel 1% group had higher rate of "negative culture" than the Lamisil Derm Gel 3% group.

Table 17 Rates of negative culture (SFG102)

		Treatment group			
		Lamisil 1%	Lamisil 3%	Placebo	p**
ITT population (l.o.c.f)	N	22	21	20	
	Positive	0 (0%)	1 (4.8%)	15 (75%)	0.001
	Negative	22 (100%)	20 (95.2%)	5 (25%)	
Efficacy population l.o.c.f.	N	22	20	18	
	Positive	0 (0%)	1 (5)	14 (77.8%)	0.001
	Negative	22 (100%)	19 (95%)	4 (22.2%)	

*Last observation carried forward

**p values were from the Mantel-Haenszel chi-square test.

Table 18 contains the result of the analysis of "change of total score from baseline", total disease severity score, and scores of Erythema, Desquamation, Pruritus. The differences between the Lamisil group and the placebo group were statistically significant in "change of total score from baseline" (Lamisil Derm Gel 1% vs. Placebo: p=0.0032 for ITT population, p=0.0023 for the valid population; Lamisil Derm Gel 3% vs. Placebo: p=0.0085 for ITT population, p=0.0101 for the valid population), total disease severity score (Lamisil Derm Gel 1% vs. Placebo: p=0.0001 for both the ITT and the valid population; Lamisil Derm Gel 3% vs. Placebo: p=0.0001 for both the ITT population and the valid population), and scores of Erythema (Lamisil Derm Gel 1% vs. Placebo: p=0.0066 for ITT population, p=0.0014 for the valid population; Lamisil Derm Gel 3% vs. Placebo: p=0.0080 for ITT population, p=0.0010 for the valid population), Desquamation (Lamisil Derm Gel 1% vs. Placebo: p=0.0001 for both the ITT population and the valid population; Lamisil Derm Gel 3% vs. Placebo: p=0.0001 for both the ITT population and the valid populations), Pruritus (Lamisil Derm Gel 1% vs. Placebo: p=0.0001 for both the ITT population and the valid population; Lamisil Derm Gel 3% vs. Placebo: p=0.0001 for ITT population, p=0.0002 for the valid population). These results were in favor of Lamisil groups.

Table 18 Change of Total score from baseline, Total score, Erythema, Desquamation, Pruritus (SFG 102)

	Variable	Treatment	N	Mean	p
ITT population (l.o.c.f.)	Change of Total score from baseline	Lamisil 1% (A)	22	6.11102246	A vs. C: 0.0032
		Lamisil 3% (B)	21	5.77111698	B vs. C: 0.0085
		Placebo (C)	20	2.83751569	
	Total score	Lamisil 1% (A)	22	0.76543290	A vs. C: 0.0001
		Lamisil 3% (B)	21	1.21750322	B vs. C: 0.0001
		Placebo(C)	20	4.75985171	
	Erythema	Lamisil 1% (A)	22	0.17655903	A vs. C: 0.0066
		Lamisil 3% (B)	21	0.18282192	B vs. C: 0.0080
		Placebo(C)	20	0.69915180	
	Desquamation	Lamisil 1% (A)	22	0.40795623	A vs. C: 0.0001
		Lamisil 3% (B)	21	0.57264784	B vs. C: 0.0001
		Placebo(C)	20	1.61790964	
	Pruritus	Lamisil 1% (A)	22	0.09026070	A vs. C: 0.0001
		Lamisil 3% (B)	21	0.13960577	B vs. C: 0.0001
		Placebo(C)	20	1.06427809	
Efficacy population (l.o.c.f.)	Change of Total score from baseline	Lamisil 1% (A)	22	6.11671790	A vs. C: 0.0023
		Lamisil 3% (B)	20	5.64579362	B vs. C: 0.0101
		Placebo(C)	17	2.93271075	
	Total score	Lamisil 1% (A)	22	0.76707232	A vs. C: 0.0001
		Lamisil 3% (B)	20	1.34689094	B vs. C: 0.0001
		Placebo(C)	17	4.75323841	
	Erythema	Lamisil 1% (A)	22	0.17774103	A vs. C: 0.0014
		Lamisil 3% (B)	20	0.14670805	B vs. C: 0.0010
		Placebo(C)	17	0.81423317	
	Desquamation	Lamisil 1% (A)	22	0.40821125	A vs. C: 0.0001
		Lamisil 3% (B)	20	0.65493792	B vs. C: 0.0001
		Placebo(C)	17	1.62144250	
	Pruritus	Lamisil 1% (A)	22	0.09040643	A vs. C: 0.0001
		Lamisil 3% (B)	20	0.20292618	B vs. C: 0.0002
		Placebo(C)	17	1.04085079	

Reviewer's comment: Study SFG102 showed that the Lamisil Derm Gel 1% and Lamisil Derm Gel 3% treatment groups were statistically significantly superior (p=0.001) to the placebo group in the treatment of Tinea pedis in the primary efficacy variable, Overall Effectiveness (Effective treatment) in both the ITT population and the valid population at both Week 6 and "End-of-study" (l.o.c.f. analysis). The Lamisil Derm Gel 1% and Lamisil Derm Gel 3% treatment groups were statistically significantly superior to the placebo group in the secondary efficacy variable "complete cure" at "End-of-study" (l.o.c.f. analysis) in both the ITT population (p=0.004) and the valid population (p=0.002). The Lamisil Derm Gel 1% and Lamisil Derm Gel 3% treatment groups were statistically significantly superior to the placebo group (p=0.001) in the secondary efficacy variable "microscopy" and "mycology culture" at "End-of-study"

(l.o.c.f. analysis) in both the ITT population and the valid population. The Lamisil Derm Gel 1% and Lamisil Derm Gel 3% treatment groups were statistically significantly superior to the placebo group ($p \leq 0.01$), in the secondary efficacy variable "Change of Total score from baseline" , "Total score", and scores of Erythema, Desquamation , and Pruritus at "End-of-study" (l.o.c.f. analysis) in both the ITT population and the valid population.

Study SFG 202

Efficacy Analysis

Primary Efficacy Variables: The primary efficacy parameter is the Overall Effectiveness (= Effective treatment). Confirmatory statistical conclusions for the Overall Effectiveness will be done using the outcomes of the assessments at week 8 only, which is defined being the primary endpoint. The "Effective treatment" is given the value "effective" if the following five conditions are satisfied:

- Microscopy is negative, and
- culture is negative, and
- sum of severity scores for erythema, desquamation and pruritus < =2, and
- individual severity scores for erythema, desquamation and pruritus < =1, and
- sum of severity scores for pustules, incrustation and vesiculation = 0

All others are considered "ineffective".

Secondary Efficacy Variables :

Complete cure is defined as "yes" if all of the following three conditions are satisfied:

- microscopy is negative, and
- culture is negative, and
- Total score of signs and symptoms = 0;

and defined as "no" otherwise.

The Intent-to-treat (ITT) efficacy analyses will be done upon Intent-to-treat subjects, i.e., subjects who were randomized to either treatment group, were not delayed exclusions, received study medication, and reported Mycological Controlling Sampling measurements in the application skin area prior to and after the first administration of the respective test drug.

Valid subjects population is defined as all ITT subjects having completed the seven days of treatment with Lamisil Derm Gel , reporting valid Mycological Controlling Sampling measurements at Baseline and Week 8, and without reporting any protocol violations or conditions liable to influence the efficacy evaluations.

Subjects whose treatment is stopped prematurely for the following reason are also valid for efficacy analyses:

- The subject's clinical status with respect to the indications worsened any time during the trial (lack of efficacy).

If the treatment was stopped prematurely due to the above reason, the Overall Effectiveness (primary efficacy parameter) of the pertaining subjects will be set to "Ineffective".

Table 19 Patient deposition (SFG202)

	ITT population		Efficacy population	
	Lamisil 1% (m/f)	Placebo(m/f)	Lamisil 1% (m/f)	Placebo(m/f)
Baseline	41 (28/13)	32 (16/16)	32 (21/11)	23 (13/10)
Week 1	38 (26/12)	32 (17/15)	30 (20/10)	24 (14/10)
Week 2	38 (26/12)	30 (15/15)	30 (20/10)	22 (12/10)
Week 6	37 (24/13)	26 (12/14)	28 (18/10)	20 (10/10)
Week 8	36 (25/11)	22 (11/11)	31 (21/10)	18 (18/8)

Table 20 contains the results of the primary efficacy analysis, i.e., the rates of "Effective treatment " in study SFG202. The difference was statistically significant in week 8 in the ITT population (p=0.023) but not the valid population (p=0.062). The dropout of subjects before week 8, which reduced the sample size and hence the power, seems to have caused the difference in treatment effects to be non-significant for the valid population at week 8. The difference was statistically significant in both the ITT (p=0.002) and the valid population (p=0.01) at "End-of-study" (l.o.c.f. analysis), in favor of the test drug, Lamisil 1%. The frequencies at week 1 were listed for labeling purposes.

Table 20 Rates of Effective treatment (SFG202)

		Treatment group		
		Lamisil	Placebo	p**
ITT population				
Week 1	N	38	32	
	Yes	3 (7.9%)	3 (9.4%)	0.827
	No	35 (92.1%)	29 (90.6%)	
Week 8	N	33	21	
	Yes	20 (60.6%)	6 (28.6%)	0.023
	No	13 (39.4%)	15 (71.4%)	
l.o.c.f.*	N	39	31	
	Yes	25 (64.1%)	8 (25.8%)	0.002
	No	14 (35.9%)	23 (74.2%)	
Valid population				
Week 8	N	28	17	
	Yes	18 (64.3%)	6 (35.3%)	0.062
	No	10 (35.7%)	11 (64.7%)	
l.o.c.f.	N	30	23	
	Yes	20 (66.7%)	7 (30.4%)	0.01
	No	10 (33.3%)	16 (69.6%)	

*Last observation carried forward

**p values were from the Mantel-Haenszel chi-square test

Table 21 lists the rate of "complete cure" at "EOS" (End-of-study, or l.o.c.f. analysis). The difference was statistically significant for the ITT population (p=0.041) but not the valid population (p=0.103). The smaller sample size of the valid population, which results in less power, seems to have caused the difference in treatment effects to be non-significant for the valid population. In both populations, the Lamisil group had numerically higher rates of "Complete cure". The frequencies at week 1 were listed for labeling purposes.

Table 21 Rates of Complete cure (SFG202)

		Treatment group		
		Lamisil	Placebo	p**
ITT population (week 1)	N	38	32	
	Yes	0 (0%)	1 (3.1%)	0.276
	No	38 (100%)	31 (96.9%)	
ITT population (l.o.c.f)	N	39	31	
	Yes	15 (38.5%)	5 (16.1%)	0.041
	No	24 (61.5%)	26 (83.9%)	
Valid population l.o.c.f.	N	30	23	
	Yes	13 (43.3%)	5 (21.7%)	0.103
	No	17 (56.7%)	18 (78.3%)	

*Last observation carried forward
**p values were from the Mantel-Haenszel chi-square test.

Table 22 lists the rate of negative microscopy at "EOS" (End-of-study, or l.o.c.f. analysis). The difference was statistically significant for both the ITT (p=0.001) and the valid population (p=0.003), in favor of the Lamisil group. The frequencies at week 1 were listed for labeling purposes.

Table 22 Rates of negative microscopy (SFG202)

		Treatment group		
		Lamisil	Placebo	p**
ITT population (week 1)	N	38	32	
	Positive	28 (73.7%)	24 (75%)	0.901
	Negative	10 (26.3%)	8 (25%)	
ITT population (l.o.c.f)	N	39	31	
	Positive	7 (18%)	19 (61.3%)	0.001
	Negative	32 (82.1%)	12 (38.7%)	
Valid population l.o.c.f.	N	30	23	
	Positive	6 (20%)	14 (60.8%)	0.003
	Negative	24 (80%)	9 (39.1%)	

*Last observation carried forward
**p values were from the Mantel-Haenszel chi-square test.

Table 23 contains the result of the analysis of "change of total score from baseline", total score, and scores of Erythema, Desquamation, Pruritus. The differences between the Lamisil group and the placebo group were statistically significant in "change of total score from baseline" (p=0.0001 for the ITT and

p=0.0022 for the valid populations), total disease severity score (p=0.0004 for the ITT and p=0.0037 for the valid populations), and scores of Erythema (p=0.0110 for the ITT population and p=0.0445 for the valid population), Desquamation (p=0.0001 for the ITT population and p=0.0003 for the valid populations), Pruritus (p=0.0065 for ITT population, p=0.0296 for the valid population). All in favor of the Lamisil group.

Table 23 Change of Total score from baseline, Total score, Erythema, Desquamation, Pruritus (SFG 202)

	Variable	Treatment	N	Mean	p
ITT population (l.o.c.f.)	Change of Total score from baseline	Lamisil	39	4.95712131	0.0001
		Placebo	31	2.12062863	
	Total score	Lamisil	39	1.14501185	0.0004
		Placebo	31	3.23998301	
	Erythema	Lamisil	39	0.32169791	0.0110
		Placebo	31	0.83746283	
	Desquamation	Lamisil	39	0.58327947	0.0001
		Placebo	31	1.57312757	
	Pruritus	Lamisil	39	0.13984055	0.0065
		Placebo	31	0.65029024	
Valid population (l.o.c.f.)	Change of Total score from baseline	Lamisil	30	4.64267490	0.0022
		Placebo	23	2.40764117	
	Total score	Lamisil	30	1.01708823	0.0037
		Placebo	23	2.83502317	
	Erythema	Lamisil	30	0.28193215	0.0445
		Placebo	23	0.76455382	
	Desquamation	Lamisil	30	0.50790626	0.0003
		Placebo	23	1.44420197	
	Pruritus	Lamisil	30	0.12216902	0.0296
		Placebo	23	0.50003357	

Reviewer's comment: Study SFG202 showed that the Lamisil Derm Gel 1% treatment group was statistically significantly superior to the placebo group in the treatment of Tinea pedis in the primary efficacy variable, Overall Effectiveness (Effective treatment) in both the ITT population (p=0.002) and the valid population (p=0.01) at "End-of-study" (l.o.c.f. analysis), in the ITT population (p=0.023) at week 6, but not in the valid population (p=0.062 at week 6). The Lamisil Derm Gel 1% treatment group was statistically significantly superior to the placebo group in the secondary efficacy variable "complete cure" at "End-of-study" (l.o.c.f. analysis) in the ITT population (p=0.041) but not the valid population (p=0.103). The Lamisil Derm Gel 1% treatment group was statistically significantly superior to the placebo group in the secondary efficacy variable "microscopy" at "End-of-study" (l.o.c.f. analysis) in both the ITT population (p=0.001) and the valid population (p=0.003). The Lamisil Derm Gel 1% treatment group was statistically significantly superior to the placebo group (p<0.05), in the secondary efficacy variable "Change of Total score from baseline", "Total score", and scores of Erythema, Desquamation, and Pruritus at "End-of-study" (l.o.c.f. analysis) in both the ITT population and the valid population.

Tinea corporis/cruris

Study SFG 201

Efficacy Analysis

Primary Efficacy Variables: The primary efficacy parameter is the Overall Effectiveness (= Effective treatment). Confirmatory statistical conclusions for the Overall Effectiveness will be done using the outcomes of the assessments at End-of-study (week 8) only, which is defined being the primary endpoint. The "Effective treatment" is given the value "effective" if the following five conditions are satisfied:

- Microscopy is negative, and
- culture is negative, and
- sum of severity scores for erythema, desquamation and pruritus < =2, and
- individual severity scores for erythema, desquamation and pruritus < =1, and
- sum of severity scores for pustules, incrustation and vesiculation = 0

All others are considered "ineffective".

Secondary Efficacy Variables :

Complete cure is defined as "yes" if the following three conditions are satisfied:

- microscopy is negative, and
- culture is negative, and
- Total score of signs and symptoms = 0;

and defined as "no" otherwise.

Clinical cure is defined as "yes" if total score of signs and symptoms = 0 and "no" otherwise.
Recurrence is defined as "yes" if effective treatment = no at EOS and if effective treatment = yes at any preceding realigned visit, and "no" if effective treatment = yes at EOS and if effective treatment = yea at any preceding realigned visit, and "missing" otherwise. Other secondary efficacy variables include microscopy, culture, mycology, total score, clinical response.

The Intent-to-treat (ITT) efficacy analyses will be done upon Intent-to-treat subjects, i.e., subjects who were randomized to either treatment group, were not delayed exclusions, received study medication, and reported Mycological Controlling Sampling measurements in the application skin area prior to and after the first administration of the respective test drug.

Valid subjects population is defined as all ITT subjects having completed the seven days of treatment with Lamisil, reporting valid Mycological Controlling Sampling measurements at Baseline and Week 8, and without reporting any protocol violations or conditions liable to influence the efficacy evaluations.

Subjects whose treatment is stopped prematurely for the following reason are also valid for efficacy analyses:

- The subject's clinical status with respect to the indications worsened any time during the trial (lack of efficacy).

If the treatment was stopped prematurely due to the above reason, the Overall Effectiveness (primary efficacy parameter) of the pertaining subjects will be set to "Ineffective".

Table 24 Patient deposition (SFG201)

	ITT population		Valid population	
	Lamisil (m/f)	Placebo(m/f)	Lamisil (m/f)	Placebo(m/f)
Baseline	29 (23/6)	33 (25/8)	27 (21/6)	30 (23/7)
Week 1	29 (23/6)	33 (25/8)	27 (21/6)	30 (23/7)
Week 2	29 (23/6)	33 (25/8)	27 (21/6)	30 (23/7)
Week 6	29 (23/6)	33 (25/8)	27 (21/6)	30 (23/7)
Week 8	28 (22/6)	32 (25/7)	27 (21/6)	30 (23/7)

Table 25 contains the results of the primary efficacy analysis, i.e., the rates of "Effective treatment " . The difference was statistically significant (p=0.001) in both the ITT and the valid population at both Week 8 and "End-of-study" (l.o.c.f. analysis), in favor of the test drug, Lamisil Derm Gel 1%. The frequencies at week 1 were listed for labeling purposes.

Table 25 Rates of Effective treatment (SFG201)

		Treatment group		
		Lamisil	Placebo	p**
ITT population				
Week 1	N	29	33	
	Yes	8 (27.6%)	2 (6.1%)	0.023
	No	21 (72.4%)	31 (93.9%)	
Week 8	N	19	30	
	Yes	16 (84.2%)	6 (20%)	0.001
	No	3 (15.8%)	24 (80%)	
l.o.c.f.	N	29	33	
	Yes	24 (82.8%)	7 (21.2%)	0.001
	No	5 (17.2%)	26 (78.8%)	
Valid population				
Week 8	N	18	28	
	Yes	16 (88.9%)	6 (21.4%)	0.001
	No	2 (11.1%)	22 (78.6%)	
l.o.c.f.	N	27	30	
	Yes	24 (88.9%)	7 (23.3%)	0.001
	No	3 (11.1%)	23 (76.7%)	

*Last observation carried forward

**p values were from the Mantel-Haenszel chi-square test.

Table 26 lists the rate of "complete cure" at "EOS" (End-of-study, or l.o.c.f. analysis). The difference was statistically significant for both the ITT and the valid population (p=0.001), in favor of the Lamisil Derm Gel 1% group. The frequencies at week 1 were listed for labeling purposes.

Table 26 Rates of Complete cure (SFG201)

		Treatment group		
		Lamisil	Placebo	p**
ITT population (week 1)	N	29	33	
	Yes	1 (3.45%)	1 (3%)	0.927
	No	28 (96.55%)	32 (97%)	
ITT population (l.o.c.f)	N	29	33	
	Yes	16 (55.2%)	4 (12.1%)	0.001
	No	13 (44.8%)	29 (87.9%)	
Valid population l.o.c.f.	N	27	30	
	Yes	16 (59.3%)	4 (13.3%)	0.001
	No	11 (40.7%)	26 (86.7%)	

*Last observation carried forward
**p values were from the Mantel-Haenszel chi-square test.

Table 27 lists the rate of negative microscopy at "EOS" (End-of-study, or l.o.c.f. analysis). The difference was statistically significant for both the ITT and the valid population (p=0.001), in favor of the Lamisil group. The frequencies at week 1 were listed for labeling purposes.

Table 27 Rates of negative microscopy (SFG201)

		Treatment group		
		Lamisil	Placebo	p**
ITT population (week 1)	N	29	33	
	Positive	9 (31%)	23 (69.7%)	0.003
	Negative	20 (69%)	10 (30.3%)	
ITT population (l.o.c.f)	N	29	33	
	Positive	3 (10.3%)	20 (60.6%)	0.001
	Negative	26 (89.7%)	13 (39.4%)	
Valid population l.o.c.f.	N	29	33	
	Positive	2 (7.4%)	19 (63.3%)	0.001
	Negative	25 (92.6%)	11 (36.7%)	

*Last observation carried forward
**p values were from the Mantel-Haenszel chi-square test.

Table 28 contains the result of the analysis of "change of total score from baseline", total disease severity score, and scores of Erythema, Desquamation, Pruritus. The differences between the Lamisil group and the placebo group were statistically significant in "change of total score from baseline" (p=0.0001 for both the ITT and the valid populations), total disease severity score (p=0.0001 for both the ITT and the valid populations), and scores of Erythema (p=0.0001 for the ITT population and p=0.0002 for the valid population), Desquamation (p=0.0001 for both the ITT population and the valid populations), Pruritus

(p=0.0001 for both the ITT population and the valid populations). All results were in favor of the Lamisil group.

Table 28 Change of Total score from baseline, Total score, Erythema, Desquamation, Pruritus (SFG 201)

	Variable	Treatment	N	Mean	p
ITT population (l.o.c.f.)	Change of Total score from baseline	Lamisil	29	6.85506665	0.0001
		Placebo	33	2.38701952	
	Total score	Lamisil	29	0.80466736	0.0001
		Placebo	33	5.86197019	
	Erythema	Lamisil	29	0.17701063	0.0001
		Placebo	33	1.17995697	
	Desquamation	Lamisil	29	0.31028737	0.0001
		Placebo	33	1.87551406	
	Pruritus	Lamisil	29	0.17576086	0.0001
		Placebo	33	1.60321630	
Valid population (l.o.c.f.)	Change of Total score from baseline	Lamisil	27	7.13559942	0.0001
		Placebo	30	2.29170787	
	Total score	Lamisil	27	0.59831871	0.0001
		Placebo	30	5.53001502	
	Erythema	Lamisil	27	0.13413743	0.0002
		Placebo	30	1.06499286	
	Desquamation	Lamisil	27	0.25048733	0.0001
		Placebo	30	1.83324177	
	Pruritus	Lamisil	27	0.12426901	0.0001
		Placebo	30	1.61039080	

Reviewer's comment: Study SFG201 showed that the Lamisil Derm Gel 1% treatment group was statistically significantly superior (p=0.001) to the placebo group in the treatment of Tinea corporis/cruris in the primary efficacy variable, Overall Effectiveness (Effective treatment) in both the ITT population and the valid population at both week 8 and "End-of-study" (l.o.c.f. analysis). The Lamisil Derm Gel 1% treatment group was statistically significantly superior (p=0.001) to the placebo group in the secondary efficacy variable "complete cure" and "microscopy" at "End-of-study" (l.o.c.f. analysis) in both the ITT population and the valid population. The Lamisil Derm Gel 1% treatment group was statistically significantly superior to the placebo group ($p \leq 0.0002$), in the secondary efficacy variable "Change of Total score from baseline" , "Total score", and scores of Erythema, Desquamation , and Pruritus at "End-of-study" (l.o.c.f. analysis) in both the ITT population and the valid population.

Integrated safety:

Table 29 lists the frequencies of subject-reported adverse events by treatment group. The percentage of subjects in the placebo group who reported adverse events during the trial for was statistically significantly (p=0.001) more than those for the Lamisil groups.

Table 29 Number of Subjects Reporting Adverse Events (all studies)

	Treatment group						
	Lamisil 1% (N=239)		Lamisil 3% (N=28)		Placebo (N=192)		p*
	N	%	N	%	N	%	
Subjects with adverse events	72	30.1%	10	35.7%	95	49.5%	0.001
Subjects with serious adverse events	0	0%	0	0%	2	1%	0.105

*p values were from the Mantel-Haenszel chi-square test

Table 30 lists the frequencies of reported adverse events by body system and treatment groups. The placebo group had higher percentages of adverse events than the Lamisil groups in the Skin and appendage system ($p<0.001$). The differences in the reporting of the adverse events in other body systems were not statistically significant for the treatment groups.

Table 30 Number of Subjects Reporting All-Causalities Adverse Events (all studies)

	Treatment group						
	Lamisil 1% (N=239)		Lamisil 3% (N=28)		Placebo (N=192)		p*
Body system	N	%	N	%	N	%	
Application site disorders	2	0.8%	1	3.6%	6	3.1%	0.086
Body as a whole-general disorders	10	4.2%	0	0%	10	5.2%	0.627
Cardiovascular disorders-general	1	0.4%	0	0%	0	0%	0.352
Central and peripheral nerve system	4	1.7%	2	7.1%	3	1.6%	0.978
Gastro-intestinal system disorders	2	0.8%	0	0%	1	0.5%	0.677
Hearing and vestibular disorders	2	0.8%	1	3.6%	0	0%	0.309
Metabolic and nutritional disorders	0	0%	0	0%	1	0.5%	0.253
Musculoskeletal System	4	1.7%	0	0%	2	1%	0.555
Myo-, endo-, pericardial and valve disorders	0	0%	0	0%	1	0.5%	0.253
Psychiatric disorders	1	0.4%	0	0%	1	0.5%	0.880
Reproductive disorders - female	0	0%	0	0%	1	0.5%	0.253
Resistance mechanism disorders	1	0.4%	0	0%	0	0%	0.352
Respiratory system disorders	10	4.2%	2	7.1%	5	2.6%	0.404
Skin and appendage disorders	46	19.2%	5	17.9%	83	43.2%	<0.001
Special senses other , disorders	1	0.4%	0	0%	0	0%	0.352
Urinary system disorders	1	0.4%	0	0%	0	0%	0.352
Vascular (extracardiac) disorders	1	0.4%	0	0%	0	0%	0.352

*p values were from the Mantel-Haenszel chi-square test

Table 31 lists the frequencies of reported treatment-related adverse events by body system and treatment groups. The placebo group had higher percentages of adverse events than the Lamisil groups in the Skin and appendage system ($p=0.004$). The differences in the reporting of the adverse events in other body systems were not statistically significant for the treatment groups.

Table 31 Number of Subjects Reporting Treatment-Related Adverse Events (all studies)

	Treatment group						
	Lamisil 1% (N=239)		Lamisil 3% (N=28)		Placebo (N=192)		p*
Body system	N	%	N	%	N	%	
Application site disorders	2	0.8%	1	3.6%	6	3.1%	0.086
Body as a whole-general disorders	1	0.4%	0	0%	4	2.1%	0.102
Skin and appendage disorders	13	5.4%	2	7.1%	26	13.5%	0.004
Special senses other , disorders	1	0.4%	0	0%	0	0%	0.352

*p values were from the Mantel-Haenszel chi-square test

Reviewer's comments : The differences in reported adverse events between the placebo group and the Lamisil groups were generally not statistically significant. In cases where statistically significant differences existed, the Lamisil groups had less reported adverse events than the placebo group.

Reviewer's Summary and Conclusion (which may be conveyed to the sponsor):

Pityriasis versicolor: Studies SFG203 and SFG302 demonstrated that the Lamisil Derm Gel 1% treatment was statistically significantly more effective than placebo in treating Pityriasis versicolor. (SFG203: Tables 3, 4, 5; SFG302: Tables 8, 9, 10).

Tinea pedis: Studies SFG102 and SFG202 demonstrated that the Lamisil Derm Gel 1% treatment was statistically significantly more effective than placebo in treating Tinea pedis. (SFG102: Tables 14, 15, 16; SFG202: Tables 20, 21, 22).

Tinea corporis/cruris: Study SFG201 demonstrated that the Lamisil Derm Gel 1% treatment was statistically significantly more effective than placebo in treating Tinea corporis/cruris. (Tables 25, 26, 27).

Thus, the results of the analyses of the studies, done by this reviewer, provided statistical evidence to show that Lamisil Derm Gel 1% is superior to placebo in the treatment of Pityriasis versicolor, Tinea pedis, and Tinea corporis/cruris.

The integrated safety analysis done by this reviewer demonstrated that the differences in reported adverse events between Lamisil groups and the placebo group were generally not statistically significant (Tables 29, 30, 31).

/S/ 03/12/98

Ping Gao, Ph.D.
Mathematical Statistician, DOB IV

March 12, '98

Concur: Rajagopalan Srinivasan, Ph.D.
Team Leader, DOB IV

HFD 540
NDA 20-846
HFD-540/Dr. Wilkin
HFD-540/Dr. Walker
HFD-540/Dr. Toombs
HFD-540/Ms. Kummerer
HFD-725/Dr. Huque
HFD-725/Dr. Srinivasan
HFD-725/Dr. Gao
HFD-344/Dr. Carreras
Chron.

This review contains 28 pages.
MS word/c: \nda\20-846\20-846.doc\Mar. 10, 1998; Ping Gao /(301)-827-2083

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-846

MICROBIOLOGY REVIEW(S)

DF-N-20-846

APR 17 1998

REVIEW FOR HFD-540

OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805
Microbiologist's Review # 2 of NDA 20-846
April 15, 1998

A. 1. **APPLICATION NUMBER:** NDA 20-846

APPLICANT: Novartis
59 Route 10
East Hanover, NJ 07936-1080

2. **PRODUCT NAME:** Lamisil® DermGel™

3. **DOSAGE FORM:** Terbinafine emulsion gel (1%) topical.

4. **METHOD OF STERILIZATION:** None

5. **PHARMACOLOGICAL CATAGORY and/or PRINCIPLE INDICATION:** Terbinafine is an antifungal and the proposed indication for the drug product is for the topical treatment of pityriasis due to *Malassezia furfur*, and tinea infections..

6. **DRUG PRIORITY CLASSIFICATION:** S

B. 1. **DATE OF INITIAL SUBMISSION:** April 29, 1997

2. **DATE OF AMENDMENT:** <u>April 3, 1998</u>

3. **DATE OF CONSULT:** May 12, 1997 April 7, 1998

4. **RELATED DOCUMENTS:** (none)

5. **ASSIGNED FOR REVIEW:** May 15, 1997 April 13, 1998

C. **REMARKS:** Lamisil® DermGel™ is the third formulation of Lamisil that has been developed by Novartis. Lamisil Cream 1% (NDA 20-192) was approved on 12/30/92, and Lamisil Solution 1% (NDA 20-749) was submitted to the FDA on 10/16/96.

Microbiologist's Review #1 yielded two deficiencies which were forwarded (via FAX) to the applicant on March 5, 1998. The applicant's corresponding responses to these deficiencies are the subject of this review.

D. CONCLUSIONS:

The application is recommended for approval for issues concerning microbiology drug product quality. Specific comments are provided in section "E. REVIEW NOTES".

/S/

4/15/98

Neal Sweeney, Ph.D.

PTK 4/17/98

cc:

Original NDA 20-846
HFD-540/ Division File
HFD-540/CSO/R.Blay/S. Kummerer
HFD-805/Consult File/N. Sweeney

Drafted by: Neal Sweeney, April 15, 1998
R/D initialed by P. Cooney, April 15, 1998

Blaj 540

OCT 17 1997

REVIEW FOR HFD-540

OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805
Microbiologist's Review # 1 of NDA 20-846
October 16, 1997

A. 1. **APPLICATION NUMBER:** NDA 20-846

APPLICANT: Novartis
59 Route 10
East Hanover, NJ 07936-1080

2. **PRODUCT NAME:** Lamisil® DermGel™

3. **DOSAGE FORM:** Terbinafine emulsion gel (1%) topical.

4. **METHOD OF STERILIZATION:** None

5. **PHARMACOLOGICAL CATAGORY and/or PRINCIPLE INDICATION:** Terbinafine is an antifungal and the proposed indication for the drug product is for the topical treatment of pityriasis due to *Malassezia furfur*, and tinea infections..

6. **DRUG PRIORITY CLASSIFICATION:** S

B. 1. **DATE OF INITIAL SUBMISSION:** April 29, 1997

2. **DATE OF CONSULT:** May 12, 1997

3. **RELATED DOCUMENTS:** (none)

4. **ASSIGNED FOR REVIEW:** May 15, 1997

C. **REMARKS:** Lamisil® DermGel™ is the third formulation of Lamisil that has been developed by Novartis. Lamisil Cream 1% (NDA 20-192) was approved on 12/30/92, and Lamisil Solution 1% (NDA 20-749) was submitted to the FDA on 10/16/96.

D. CONCLUSIONS:

The application is approvable for issues concerning drug product microbial limits and preservative effectiveness testing, provided the applicant commit to include both preservative effectiveness and microbial limits testing in the stability commitment protocol. Additionally preservative effectiveness acceptance criteria should be part of the drug product specification.

/S/

10/16/97

Neal Sweeney, Ph.D. date 10/17/97

cc:

Original NDA 20-846
HFD-540/ Division File
HFD-540/CSO/R.Blay
HFD-805/Consult File/N. Sweeney

Drafted by: Neal Sweeney, October 16, 1997
R/D initialed by P. Cooney, October 16, 1997

FEB 2 1998

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

Requester:	Susan Kummerer, CSO HFD-540
Date of Request:	11-20-97
Reason for Request:	Clinical Microbiology Review of antifungal activity
IND/NDA Number:	NDA # 20-846
Review Date:	1-16-98
Submission/Type:	Original NDA
Document Date:	4-29-97
CDER Date:	4-29-97
Assigned Date:	11-25-97
Applicant:	Novartis Pharmaceuticals Corp. Drug Regulatory Affairs 59 Route 10 East Hanover, NJ 07936-1080
Contact Person:	Patricia McGovern, Assistant Director Drug Regulatory Affairs 59 Route 10 East Hanover, NJ 07936 Phone: (973) 503-7384

Drug Product Name:

Proprietary:	Lamisil® DermGel™
Nonproprietary/USAN:	Terbinafine emulsion gel
Code Names/#'s:	None
Chemical Type:	Allylamine derivative
Therapeutic Class:	3S

ANDA Suitability Petition/DESI/Patent Status:
Not Applicable

Pharmacological Category/Indication:
Antifungal—Allylamine derivative/Topical treatment of Tinea pedis, tinea cruris, or tinea corporis due to *Trichophyton rubrum, Trichophyton mentagrophytes,* or *Epidermophyton floccosum,* and pityriasis versicolor due to *Malassezia furfur*

Dosage Form:	DermGel
Strength(s):	1%
Route of Administration:	Topical
Dispensed:	__X__ Rx ____ OTC

Supporting Documents:
DMF:
NDA: 20192, 20539
IND:

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, 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® DermGel™(each gram contains 10 mg of terbinafine in an emulsion gel), 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% emulsion gel is being supported by five clinical trials in four indications. Table 1 lists these five studies. All five are considered pivotal and placebo controlled studies.

TABLE 1. List of pivotal studies in claimed indications.

Indication	Study[a]	Location	Duration of Treatment	Follow-up Period	No. of Subjects Enrolled: Enrolled	Lamisil 1% (3%)	Placebo	Enrolled Subjects: Age Range (Mean)	Sex %M %F
Pityriasis versicolor	SFG 203	Sweden	1 wk OD	7 wks	61	31	30	[redacted] (36.8)	50.8 49.2
	SFG 302	Norway/ Sweden	1 wk OD	7 wks	129	87	42	[redacted] (36.0)	51.0 48.1
Tinea pedis	SFG 102	UK	5 days OD	37 days	85	30 (28)	27	[redacted] (39.8)	69.4 30.6
	SFG 202	Finland/ Belgium	1 wk OD	7 wks	101	51	50	[redacted] (43.3)	66.3 33.7
Tinea Corporis/ Cruris	SFG 201	South Africa	1 wk OD	7 wks	83	40	43	[redacted] (37.9)	78.3 21.7

[a] All studies are placebo-controlled, randomized, double-blind, parallel group, multicenter in design

All five studies follow similar study designs and subject inclusion criteria. The protocols required that each subject have 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 efficacy was measured by assessment of clinical signs and symptoms, mycological results and overall assessment of efficacy by the investigator. A total of 459 patients were enrolled. Of these, 267 were randomized to Lamisil and 192 to placebo. This resulted in a total of 453 subjects for safety analysis: 262 Lamisil subjects and 191 placebo subjects.

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.

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.

a. Pityriasis versicolor

Table 2 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 115 Lamisil and 72 placebo treated subjects were included in the pooled ITT population for this indication. Three Lamisil-treated subjects and no placebo-treated subjects were excluded from the pooled ITT population, the reason for exclusion was "no efficacy follow-up."

TABLE 2. Rates for Effective Treatment, Complete Cure and Negative Microscopy at end of study SFG 203 and SFG 302 (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
SFG 203	75% (21/28)	14% (4/29)	< 0.001	71% (20/28)	14% (4/29)	< 0.001	75% (21/28)	14% (4/29)	< 0.001
SFG 302	73% (63/86)	10% (4/41)	<0.001	67% (58/86)	10% (4/41)	< 0.001	74% (64/86)	10% (4/41)	< 0.001
Pooled	74% (84/114)	11% (8/70)	ND	68% (78/114)	11% (8/70)	ND	75% (85/114)	11% (8/70)	N/D

Note: End of study is the last non-missing post-baseline observation.
CMH indicates the Cochran-Mantel-Haenszel test (adjusted for center) for treatment comparisons.
(n/N) = number of responders for variable/number of subjects evaluated for variable.
ND = not done

At End of Study, Lamisil was shown to be statistically significantly ($p \leq 0.001$) 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 (the maximum possible score was 9). In the pooled Lamisil group, the mean TSSS at the End of Study was 0.6 compared to 2.7 for the pooled placebo group. Effective Treatment required, in addition to negative microscopy, a TSSS ≤ 1. This TSSS represents a notable decrease in clinical severity from baseline, indicates minimal clinical manifestations of the infection, and thus provides a valuable and meaningful clinical indicator of a successful outcome not achieved by the placebo group.

The microscopy evaluation showed that Lamisil was significantly superior to placebo ($p < 0.001$) at End of Study for both studies.

The recurrence rate at the End of Study was 7%(8/84) for the Lamisil pooled group compared to

30%(6/20) in the placebo group.

For Effective Treatment, Complete Cure, and Negative Microscopy statistically significant differences in favor of Lamisil compared to placebo occurred by week 1 and continued through the End of Study evaluations, depending on the study. The response rates were progressive, thus the sponsor proposes that the patients should be informed that full therapeutic benefit may only be seen several weeks after end of treatment.

b. Tinea pedis and corporis/cruris

A total of 186 subjects were enrolled in two tinea pedis studies of whom 133 (82 Lamisil; 51 placebo) were included in the pooled ITT population. The most common reason for exclusion from the ITT population was delayed exclusion (negative baseline culture) which accounted for 51 subjects (27% in the pooled group). The data for two subjects, one in each treatment group, were excluded from the ITT population because of "no efficacy follow-up". In the tinea corporis/cruris study, 83 subjects were enrolled, of whom 62 (29 Lamisil, 33 placebo) were included in the pooled ITT population. The most common reason for exclusion from the ITT population was delayed exclusion , which accounted for 10 subjects in each treatment group; the data for one subject in the Lamisil treatment group was excluded because of "no efficacy follow-up".

Table 3 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 two tinea pedis studies, at End of Study, Lamisil was shown to be statistically significantly ($p \leq 0.001$) superior to placebo in all three of these measures of efficacy. The efficacy results observed at End of Study in the tinea corporis/cruris study ($p<0.001$) for Effective Treatment are consistent with the results shown in the two tinea pedis studies.

In the two tinea pedis studies, the mean TSSS at baseline ranged from 6.1 to 7.0 (the maximum possible score was 18). Most subjects had baseline TSSS of 5-7. At End of Study, in the two studies, the mean TSSS for the Lamisil 1% treatment group was significantly reduced ($p<0.05$) compared to the placebo group. The mean TSSS at baseline and End of Study in the tinea corporis/cruris study parallel those seen in the tinea pedis studies. The primary efficacy variable, required, in addition to Negative Mycology, a TSSS ≤ 2. According to the sponsor this TSSS represents a notable decrease in clinical severity from baseline, indicates minimal clinical manifestations of the infection, and thus provides a valuable and meaningful clinical indicator of successful outcome.

TABLE 3. End of Study rates for Effective Treatment, Complete Cure and Negative Mycology in tinea pedis and tinea corporis/cruris (ITT population).

Study	Effective Treatment				Complete Cure				Negative Mycology			
	LAM 1% 5 days % (n/N)	LAM 1% 1 wk % (n/N)	PBO % (n/N)	p-Value CMH Test	LAM 1% 5 days % (n/N)	LAM 1% 1 wk % (n/N)	PBO % (n/N)	p-Value CMH Test	LAM 1% 5 days % (n/N)	LAM 1% 1 wk % (n/N)	PBO % (n/N)	p-Value CMH Test
Tinea pedis												
SFG 102	86% (19/22)	–	15% (3/20)	<0.001	45% (10/22)	–	5% (1/20)	0.002	95% (21/22)	–	15% (3/20)	<0.001
SFG 202	–	64% (25/39)	26% (8/31)	0.001	–	38% (15/39)	16% (5/31)	0.019	–	82% (32/39)	32% (10/31)	<0.001
Pooled	86% (19/22)	64% (25/39)	22% (11/51)	ND	45% (10/22)	38% (15/39)	12% (6/51)	ND	95% (21/22)	82% (32/39)	25% (13/51)	ND
Tinea corporis/cruris												
SFG 201	–	83% (24/29)	21% (7/33)	<0.001	–	55% (16/29)	12% (4/33)	<0.001	–	90% (26/29)	39% (13/33)	<0.001

Note: End of Study is last non-missing post-baseline observation.
CMH indicates the Cochran-Mantel-Haenszel test (adjusted for center) for treatment comparisons
LAM = Lamisil Emulsion Gel
PBO = placebo (vehicle)
D = not done
- = not applicable
(n/N) = number of responders for variable/number of subjects evaluated for variable

Table 4 presents the response rates at End of Study by organism at baseline for the two tinea pedis studies.

TABLE 4. Response rates (%, n/N) at End of Study by organism at baseline (tinea pedis studies pooled) (ITT population)

Organism	Effective Treatment			Negative Mycology		
	LAM 5 days % (n/N)	LAM 1 wk % (n/N)	PBO % (n/N)	LAM 5 days % (n/N)	LAM 1 wk % (n/N)	PBO % (n/N)
Pooled: SFG 202 and SFG 102						
T. rubrum	86% (12/14)	60% (18/30)	18% (7/40)	93% (13/14)	80% (24/30)	20% (8/40)
T. mentagrophytes	86% (6/7)	71% (5/7)	44% (4/9)	100% (7/7)	86% (6/7)	56% (5/9)
E. floccosum	100% (1/1)	100% (2/2)	0% 0/1	100% (1/1)	100% (2/2)	0% (0/1)

Note: Of the 133 ITT patients, only 111 patients are included in this table; Lamisil 1% (61 patients) and placebo (50 patients). Patients from the 3% Lamisil group (21 patients) are not included and one patient from the placebo group is not included (organism isolated at baseline was not specified).
Note: End of Study is last non-missing post-baseline observation. LAM = Lamisil Emulsion Gel, 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 all but one of the infections observed at baseline in the tinea pedis studies. The majority of isolates were *Trichophyton rubrum* (84/111). Although the number of organisms isolated at baseline was small for *Trichophyton mentagrophytes* (23/111) and *Epidermophyton floccosum* (4/111), all three organisms responded well to Lamisil treatment (Table 4). Lamisil Effective Treatment rates at End of Study by organism at baseline were: *Trichophyton rubrum* 68% (30/44), *Trichophyton mentagrophytes* 79% (11/14) and *Epidermophyton floccosum* 100% (3/3). The eradication rates by organism for these studies were: *Trichophyton rubrum* 84% (37/44), *Trichophyton mentagrophytes* 93% (13/14) and *Epidermophyton floccosum* 100% (3/3).

Table 5 presents the response rates at End of Study by organism at baseline for the tinea corporis/cruris study.

TABLE 5. Response rates (%, n/N) at End of Study by organism at baseline (tinea corporis/cruris study SFG 201) (ITT population)

	Effective Treatment		Negative Mycology	
Organism	**LAM 1% 1 wk % (n/N)**	**PBO % (n/N)**	**LAM 1% 1 wk % (n/N)**	**PBO % (n/N)**
T. rubrum	81% (22/27)	14% (4/29)	81% (22/27)	21% (6/29)
T. mentagrophytes	100% (1/1)	NA	100% (1/1)	NA
E. floccosum	100% (1/1)	100% (2/2)	100% (1/1)	100% (2/2)
M. canis	NA	0% (0/1)	NA	0% (0/1)
T. violaceum	NA	100% (1/1)	NA	100% (1/1)

Note: End of Study is last non-missing post-baseline observation.
LAM = Lamisil Emulsion Gel, PBO = placebo (vehicle)
(n/N) = number of responders for variable/number of subjects evaluated for variable
NA = not applicable; no patient with this organism

In the tinea corporis/cruris studies, the organisms were present in proportions which were similar to the tinea pedis studies at baseline, the majority being *Trichophyton rubrum* (56/62). Lamisil Effective Treatment at End of Study for *Trichophyton rubrum* was 81% (22/27) versus 14% (4/26) with placebo, which concur with the tinea pedis results. Again, the number of subjects who presented with *Trichophyton mentagrophytes, Epidermophyton floccosum, Microsporum canis* and *Trichophyton. violaceum* in the tinea corporis/cruris study was small.

The sponsor states that the clinical response rates for Lamisil-treated subjects with tinea pedis and

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 has 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 current policy of this Division (DAIDP, HFD-520) 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 resent clinical isolates tested in more than one laboratory. The MIC_{90} for these isolates must be reasonably low.. Consequently, only those organisms involved in pityriasis versicolor, tinea pedis, tinea cruris, and tinea corporis may potentially be placed in the *in vitro* microbiology section of the package insert for the 1% Emulsion Gel formulation. Table 6 summarizes the causative agents of tinea pedis, corporis and cruris.

TABLE 6. 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/ Onychomycosis
Dermatophytid molds								
Trichophyton rubrum	X	X[a]	X	X	X	X	X	X
Trichophyton tonsurans		X	X			X	X	X
Trichophyton mentagrophytes	X	X	X	X		X	X	X
Trichophyton violaceum	X	X	X			X		X
Trichophyton verrucosum	X	X	X	X	X		X	X
Trichophyton schoenleinii		X	X					X
Trichophyton concentricum			X		X			
Epidermophyton floccosum			X	X			X	X
Microsporum canis	X	X	X		X			X
Microsporum audouinii		X	X					
Microsporum gypseum	X	X	X		X			
Microsporum nanum		X[a]	X[a]					
Microsporum distortum		X						
Microsporum ferrugineum		X						

Organism	Tinea Barbae	Tinea Capitis	Tinea Corporis	Tinea Cruris	Tinea Faciei	Tinea Manum	Tinea Pedis	Tinea unguium/ Onychomycosis
Nondermatophytid molds								
Scopulariopsis brevicaulis								X
Scytalidium spp.								X
Acremonium spp.								X
Fusarium spp.								X
Hendersonula spp.								X
Yeast								
Candida albicans								X
Candida parapsilosis								X[a]
Candida krusei								X[a]
Candida tropicalis								X[a]

[a] It is rarely the causative agent of the indicated dermatophytosis.

It is evident from table 5 and the pivotal studies summarized above, that dermatophytes are the most common cause of the tineas for which the sponsor is seeking approval.

Table 7 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 7. ***In vitro*** **susceptibility profile of terbinafine hydrochloride.**

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

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

Microbiologist's comments: Each organism will be discussed separately bellow.

Microbiologist's comments: The list should be written in an alphabetical order. If any of these organisms are not granted by the reviewing medical officer then they will be omitted from this list.

4. PACKAGE INSERT

The **Microbiology** subsection of the package insert should be rewritten as follows:

Microbiology

CONCLUSION & RECOMMENDATIONS:

The application is approvable form the clinical microbiology viewpoint under section 505 (b) of the Act. The sponsor should be notified to revise the Microbiology subsection of the package insert as indicated on page 13 of this review.

/S/

Sousan S. Altaie, Ph. D.
Clinical Microbiology Review Officer

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/S. Kummerer

Concurrence Only:
HFD-540/Dir/J Wilkin
HFD-520/SMicro/A Sheldon
1/30/98
2/3/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-846

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JAN 7 1998

Clinical Pharmacology/Biopharmaceutics Review

NDA: 20-846 SUBMISSION DATE: 4/29/97

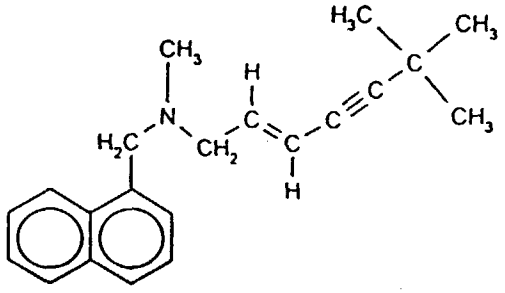
PRODUCT: Lamisil® DermGel™
Terbinafine 1% Topical Emulsion Gel

SPONSOR: Novartis
Pharmaceutical Corp. REVIEWER: Veneeta Tandon, Ph.D.

Review of a NDA

I. Background

Terbinafine is a synthetic allylamine antifungal compound which has been shown to exert its antifungal effect by inhibiting squalene epoxidase, a key enzyme in ergosterol biosynthesis. This action leads to a deficiency of ergosterol and to corresponding accumulation of squalene within the fungal cell. Lamisil® DermGel™ is indicated for the topical treatment of the following dermatological infections: pityriasis versicolor due to *Malassezia furfur*, and tinea pedis (athlete's foot), tinea cruris (jock itch) or tinea corporis (ringworm) due to *Trichophyton rubrum, Trichophyton mentagrophytes, or Epidermophyton floccosum.*



Chemically, terbinafine is (E)-N-(6,6-Dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalenemethanamine and is highly lipid soluble which is thought to account for the preferential uptake into the skin.

Lamisil® DermGel™ is the third topical formulation of Lamisil® that has been developed by Novartis. Lamisil® Cream 1% was approved on December 30, 1992 (NDA 20-192) for the treatment of tinea pedis and tinea corporis/cruris. An NDA for Lamisil® Solution 1% for the treatment of tinea pedis, tinea corporis/cruris and pityriasis versicolor (NDA 20-749) was approved on October 17, 1997. In addition Lamisil® Tablets was approved on May 10, 1996 (NDA 20-539).

Lamisil® DermGel™ has been formulated to provide the physician with an additional formulation treatment option and has the reported advantage in treating large surface areas of the body, as well as hairy areas in the body where cream would be inconvenient, messy or otherwise unacceptable.

II. Recommendation

The plasma concentrations of terbinafine after once daily topical application of 1% Lamisil® DermGel™ was about 37 times lower than that observed after once a day oral administration of 250 mg terbinafine in patients. The absolute bioavailability was estimated to be < 5%. In normal volunteers, the plasma concentrations were about 45 times lower after topical application of the Gel as compared to the oral administration. A comparative study of the dermatopharmacokinetics of the Gel vs . the Cream dosage form indicates that the Gel penetrates the stratum corneum as well as the cream. After 5 days of the treatment, the AUC after the Gel application was significantly higher than that of the Cream ($p<0.001$) and the C_{max} was also greater for the Gel ($0.001 \leq p<0.01$), however, no significant difference in absorption was observed after 7 days of application of the Gel and the cream. The $t_{1/2}$ was 27.2 hours after the application of the gel and 35.2 hours after that of the cream.

The sponsor has adequately investigated the in-vivo pharmacokinetics of terbinafine and has compared the dermal penetration to that of the 1% cream dosage form. From the pharmacokinetic standpoint the sponsor has demonstrated that the systemic absorption is increased in the diseased skin, but is markedly inferior to that of the oral tablet. The pharmacokinetic information provided is satisfactory and the application is approvable, provided the labeling issues are resolved.

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III. Formulation

The to be marketed formulation is as follows:

Components	Amounts for 100 gm of drug product
Terbinafine Base, Sandoz	1.0 g
Butylated hydroxytoluene, NF	g
Sodium Hydroxide, Ph.Eur	g
Benzyl Alcohol, NF	g
Sorbitan Monolaurate, NF	g
Carbomer 974P, NF	g
Polysorbate 20, NF	g
Isopropyl Myristate, NF	g
ethanol	g
Water purified, USP	8

IV. Analytical Methods

V. Summary of In-Vivo Pharmacokinetic Trials

Study No. SFW 409-E-00

Determination of plasma concentration of terbinafine after repeated applications as a Lamisil® 1% Emulsion gel to the normal skin in healthy volunteers.

A total of 12 normal Caucasians subjects (6M/6F) completed the trial. The study medication was applied once daily for seven consecutive days onto a skin surface area representing 20% of the body surface area. The surface of application in this study is 25

times that used the study with 1% cream and 1% solution. mg of emulsion gel containing mg of terbinafine was applied per cm^2 of the skin. Body surface area was calculated using Dubois and Dubois equation: $BSA(m^2)= 0.007184 \times Height\ (cm)^{0.725} \times Weight\ (kg)^{0.425}$. Total amount of gel applied daily in grams was 4 x BSA (m^2). Subjects received a mean daily application of 67.5 ± 5.5 mg of terbinafine. The subjects were asked to wash their body surface with soap and water one hour prior to each application. The treated area was not to be covered till one hour after the application.
Plasma concentration of terbinafine were quatifiable from 2-4 hours post application for 4 subjects and from 10 hours onwards for all subjects. The individual plasma concentrations along with study summary is attached in Appendix I (pages 15-19). Due to very low plasma levels, only the concentrations measured on Day 7 were used for the pharmacokinetic evaluation.

The pharmacokinetic parameters of terbinafine at Day 7 are summarized in the table below:

Parameter	Mean	SD	Range
T_{max} (h)	7.33	3.45	
C_{max} (ng/ml)	3.82	2.05	
AUC_{0-24} (h.ng/ml)	62.55	46.54	

With regard to the mean AUC of 2306.7 h.ng/ml after intravenous administration of 80 mg of terbinafine in healthy volunteers, the absolute bioavailability can be estimated to < 5% (Data from a "Single rising intravenous dose tolerability study of Lamisil in healthy male subjects *Document* 303-617). The plasma concentrations of terbinafine, after repeated once daily application of 55-77 mg topical terbinafine were about 45 times lower than those observed after repeated once a day oral administration of 250 mg terbinafine. The AUC is < 1% of that seen following repeated oral administration of the marketed 250 mg tablet to healthy volunteers for 28 days (terbinafine mean AUC of 10,481 ng.h/ml)

Pharmacokinetics of metabolite

The individual plasma concentrations of the metabolite of terbinafine is attached in Appendix I (page 18). At Day 1 all the plasma concentrations were below the LOQ except for one subject. At day 7, 6/12 subjects had a few quantifiable concentrations. No pharmacokinetic assessment was possible on these data.

Comment

- This study is adequately designed and all relevant information in has been provided.
- Due to a low number of subjects in this study, a meaningful gender analysis was not possible, although, the data did not show any trend in the males or females.

Study No. SFW 410-E-00

Determination of plasma concentration of terbinafine after repeated applications as a Lamisil® 1% Emulsion gel to the diseased skin inpatients with Tinea cruris/Corporis.

This study was also carried out in 12 patients (6M/6F). Terbinafine was applied once a day for 7 consecutive days as 1% Lamisil® Emulsion gel on diseased area(s) of skin as well as 2.5 cm wide margin of healthy skin around the lesion(s). The inclusion criteria for the patients was that the total area of the diseased skin should have a surface of 20-500 cm^2 and must not be oozing. The mean daily amount of terbinafine applied ranged from 20.4 to 92.1 mg. The amount of gel applied was determined by weighing the tube and gloves before and after the application procedure. The evening before the first application patients body was thoroughly washed using soap and water. The treated site was again washed prior to the next application. The application site was allowed to dry for 15 minutes after which the patient was allowed to dress.

Due to very low concentrations of the drug and metabolite on Day 1, only the concentrations measured on Day 7 were used in the pharmacokinetic evaluation. Individual plasma concentrations are shown in Appendix I (page 22). The noncompartmental pharmacokinetic parameters of terbinafine at Day 7 are summarized in the table below, the inconsistent nature of the plasma concentration data did not allow for calculation of $t_{1/2}$:

Parameter	Mean	SD	Range
T_{max} (h)	7.83	7.11	
C_{max} (ng/ml)	2.48	1.85	
AUC_{0-24} (h.ng/ml)	40.54	36.30	
AUC_{0-24} weighted (h.ng/ml)*	41.51	27.68	

*weighted by the actual individual dose applied on Day 7

With regard to the mean AUC of 2306.7 h.ng/ml after intravenous administration of 80 mg of terbinafine in healthy volunteers, the absolute bioavailability can be estimated to <5%. The plasma concentrations of terbinafine, after repeated once daily application of 21-92 mg topical terbinafine were about 37 times lower than those observed after repeated once a day oral administration of 250 mg terbinafine.

Pharmacokinetics of metabolite

The individual plasma concentrations of the metabolite of terbinafine is attached in Appendix I (page 23). At Day 1 all the plasma concentrations were below the LOQ. At day 7, 2/12 subjects had a few quantifiable concentrations. No pharmacokinetic assessment was possible on these data.

Comments

- Normalizing the data for normal volunteers and patients for similar body surface area coverage, it appears that the Cmax and AUC were approximately 24 fold higher in the

patients. However, since Lamisil® Oral tablets are available, which produce even higher levels, this is not of any clinical importance.

- A discrepancy between the study conducted in normal volunteers and the patients is that the normal volunteers were not allowed to wear clothes till 1 hour after the application of the test medication, whereas the patients were allowed to cover the area after 15 minutes of the application of the test medication. This adds up to the difficulty in comparing the results from the study conducted in normal volunteers versus patients.

Study # SFG 205-E-00

A study to investigate the skin pharmacokinetics of Lamisil® 1% emulsion gel compared to Lamisil® 1% cream in healthy subjects, following a single application on one, five or seven consecutive days.

This study was designed to determine whether increasing the number of applications of 1% emulsion gel and 1% cream increases the concentrations of terbinafine in the stratum corneum, whether single applications for 1, 5 or 7 consecutive days results in levels of terbinafine being detected for longer periods at higher concentrations for the same period in the skin and following cessation of treatment and, whether there are differences in tissue levels or duration between the Gel and the Cream. 36 healthy Caucasian volunteers (3 M/ 3F per treatment regimen) completed this study. 0.5 gm of either the gel or the cream were applied on each visit to two areas on the back each measuring 5x3 inches. Skin biopsies were taken at intervals. Results are shown in detail in Appendix I (pages 25-30).

In this study the skin concentration has been calculated twice, once with a LOQ of 0.18 ng/cm^2 and then by raising the LOQ to 2 ng/cm^2. The later approach was considered more acceptable based on ± 15% CV for the 2 ng/ cm^2 standard. This change in the LOQ greatly affected the $t_{1/2}$ values. The % decrease in $t_{1/2}$ ranged from % (1% cream, day 7) to % (1% Emulsion gel, day 5).

For each 2.5 micron thick skin biopsy, the total stratum corneum concentration was calculated by adding the terbinafine concentrations across the five stratum corneum levels. If any of the five level concentrations were missing (e.g. due to contamination), the total stratum corneum concentration was set to missing. The results show that penetration occurs down to level 5, with the highest concentration found in level 1 and 2. Results show that the mean terbinafine concentrations in total stratum corneum were still detectable after stopping 1 day of treatment with Lamisil® Gel and Cream, and up to 168 hours (7 days) in all subjects in the 5-day and 7-day Lamisil® Gel group and 7-day Cream group. Terbinafine levels were only detectable for up to 96 hours after stopping the 5 days treatment with the Cream.

The pharmacokinetic parameters were, the AUC over 7 days after the last application, the C_{max} over the 7 days after the last application, the T_{max} after the last application, the elimination rate constant and the $t_{1/2}$ measured from the last application. The results are summarized in the Table below. The asterix (*) AUC, C_{max} and $t_{1/2}$ values

are obtained with the LOQ of < 0.18 ng/cm2 and have been provided in the table below for comparison purposes.

Mean Total Stratum Corneum Pharmacokinetic Parameters						
	Lamisil Gel			Lamisil Cream		
	1 day	5 days	7 days	1 day	5 days	7 days
No. of subjects	6	6	6	6	6	6
AUC $_{0-t}$ (ng.hr/cm^2)(sd)	8238(962)	9821(594)	12279(619)	7214(960)	8180(280)	11478(221)
*AUC $_{0-t}$ (ng.hr/cm^2)(sd)	8295(956)	10287(551)	12650(626)	7271(951)	8480(268)	11754(256)
C_{max} (ng/cm^2) (sd)	638 (54.1)	891(93.5)	908.8(91)	717.7(76.7)	746(54.1)	944(105.9)
*C_{max} (ng/cm^2) (sd)	638 (54.1)	891(93.5)	908.8(91)	717.7(76.7)	746(54.1)	944(105.9)
$t_{1/2}$ (hours) (sd)	n/a	17.2(3.0)	27.2(5.1)	n/a	14.4(2.4)	35.2(9.2)
*$t_{1/2}$ (hours) (sd)		36.5 (5.5)	47.2(3.0)		21.3(1.5)	44.1(3.4)

T_{max} is not presented due to lack of variability-it was always 4 hours
n/a= not applicable due to insufficient data,
LOQ of terbinafine concentrations <2.0 ng/cm^2, * <0.18 ng/cm^2

Statistical comparisons were done on logarithmically transformed AUC and Cmax. Results are summarized in the Table below,

Comparisions of Pharmacokinetic Parameters				
		AUC 0-t	Cmax	t1/2
Lamisil® Gel vs. Cream	1 day	**	n.s.	n/a
	5 days	***	**	n.s.
	7 days	n.s.	n.s.	*
Lamisil® Gel	1 day vs. 5 days	***	***	n/a
	1 day vs. 7 days	***	***	n/a
	5 days vs. 7 days	***	n.s.	**
Lamisil® Cream	1 day vs. 5 days	*	n.s.	n/a
	1 day vs. 7 days	***	***	n/a
	5 days vs. 7 days	***	***	***

***p<0.001,**0.001≤p<0.01, *0.01≤p<0.05, (*) 0.05≤p<0.1, n.s. = not significant
n/a= not applicable due to insufficient data,
LOQ for terbinafine concentrations < 2.0 ng/cm^2

For AUC and C_{max}, estimates of the pairwise geometric mean ratios were calculated, together with 95% confidence intervals for the ratios. For $t_{1/2}$, estimates of the pairwise mean differences were calculated, together with 95% confidence intervals for the mean differences.

The results indicate that increasing the number of applications of Gel and Cream increases the concentration of terbinafine in the stratum corneum as well as the duration at which detectable concentrations of terbinafine are found. A greater AUC_{0-t} and C_{max}

values for terbinafine in the total stratum corneum were reached after 1 and 5 days of treatment with Lamisil 1% Emulsion Gel compared to 1% Lamisil cream. The elimination half life was significantly longer for the Gel after 5 days treatment as compared to the Cream.

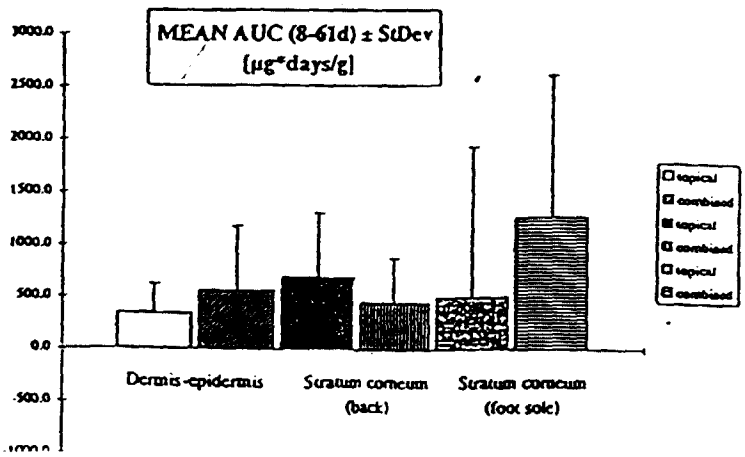
Study # SFG 101-E-00

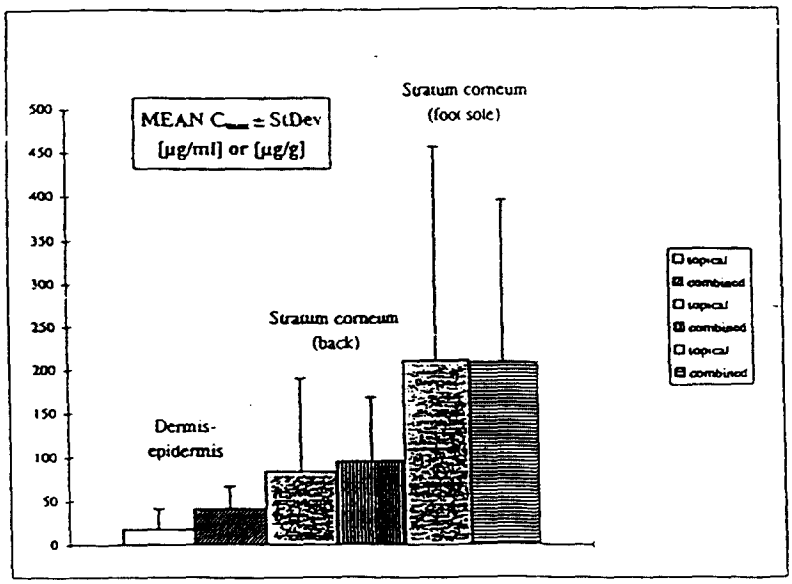
Randomized double-blind parallel-group study on healthy male subjects, with emulsion gel topically applied for 1 week in combination with either 1-week orally administered Lamisil or placebo.

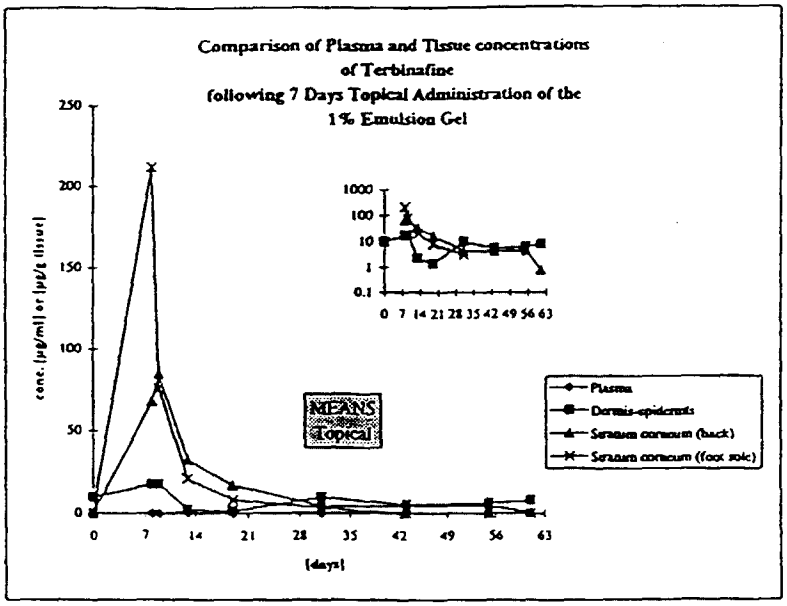
This study was designed to investigate whether topically applied Lamisil 1% Derm Gel, co-administered with terbinafine 250 mg/day orally (both for 1 week) results in higher tissue levels of terbinafine than topically applied Derm Gel alone. 24 healthy Caucasian males (12 per treatment regimen) completed this study. Details of the study design is given in the Appendix on pages 31-39. The treatment duration was 7 days, followed by 54 days post treatment period during which the skin and plasma pharmacokinetics were investigated. Lamisil Emulsion Gel was to be applied to the soles of the subjects feet and to the whole of their back once daily and tablet was to be taken once daily in the morning. Pharmacokinetic variables were derived from terbinafine levels measured in the tissue (foot-sole, back) and plasma samples taken. AUC was calculated individually for the period between Day 8 and 61.
The results are summarized in the table below. Details are provided in the Appendix 1 (pages 31-39)

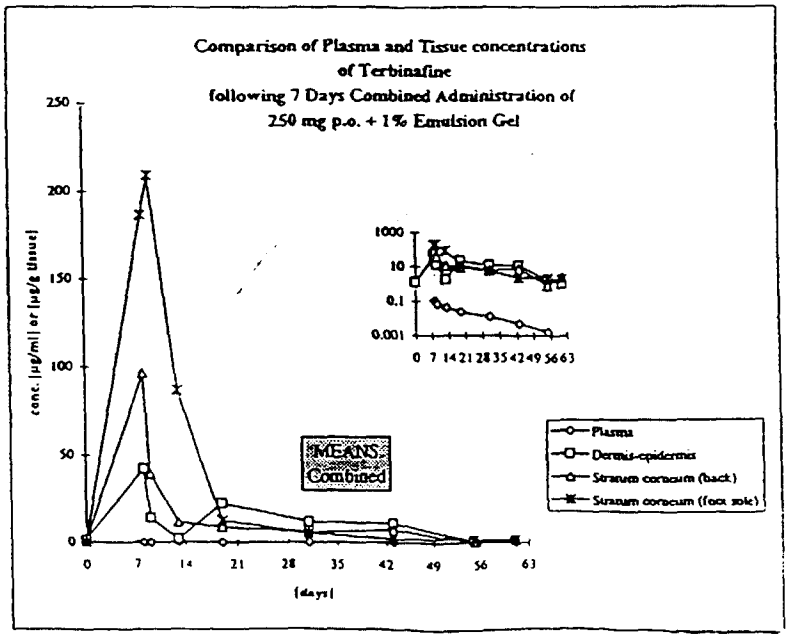
Tissue	Treatment	AUC(8-61d) ± SD µg.days/g	Cmax ± SD µg/mL	Tmax days
Plasma	Topical	0	0	0
Plasma	Combined	0.9 ± 0.6	0.106 ± 0.056	8
Dermis-epidermis	Topical	336.8 ± 553.1	17.6 ± 24.0	9
Dermis-epidermis	Combined	559.8 ± 585.1	42.2 ± 25.1	8
Stratum- (back)	Topical	703.1 ± 412.0	84.6 ± 107	9
Stratum- (back)	Combined	457.0 ± 318.0	96.4 ± 74	8
Stratum-(foot sole)	Topical	507.8 ± 494.6	2117.7 ± 244.1	8
Stratum-(foot sole)	Combined	1277.8 ± 1060.7	209.2 ± 186.2	9

The mean AUC and C_{max} in the different tissues is shown in the bar and line diagram below.




MEAN C = StDev
[µg/ml] or [µg/g]
Stratum corneum
(foot sole)
Stratum corneum
(back)
Dermis-
epidermis
500
450
400
350
300
250
200
150
100
50
0
topical
combined
topical
combined
topical
combined


Comparison of Plasma and Tissue concentrations
of Terbinafine
following 7 Days Topical Administration of the
1% Emulsion Gel
conc. [µg/ml] or [µg/g tissue]
[days]
MEANS
Topical
Plasma
Dermis-epidermis
Stratum corneum (back)
Stratum corneum (foot sole)


Comparison of Plasma and Tissue concentrations
of Terbinafine
following 7 Days Combined Administration of
250 mg p.o. + 1% Emulsion Gel
conc. [µg/ml] or [µg/g tissue]
[days]
MEANS
Combined
Plasma
Dermis-epidermis
Stratum corneum (back)
Stratum corneum (foot sole)

No terbinafine was measurable in *plasma samples* from subjects who were treated topically with oral placebo co-adminsitration. I believe this is due to the higher LOQ in plasma for this study as compared to the others (9.3 ng/ml vs 1 ng/ml in the other studies) Subjects who received once a day 250 mg orally + topical treatment with 1% gel were all systemically exposed to terbinafine. Highest levels were 1 day after the stop of medication (Day 8). In none of the samples from day 61 was terbinafine measurable. The individual concentrations with figures are shown in the Appendix on pages 32-33.

The highest mean concentration from the *stratum corneum from the back* was measured on day 8 for the combined treatment and day 9 for the topical treatment. The mean peak concentrations were 84.6 ± 107 and 96.4 ± 74 μg/g for the topical and combined, respectively. The inter-individual variability (CV%) was high between 65 and 293%. 11 out of 24 subjects had detectable levels of terbinafine on day 61, 10 of these were on combined treatment. The individual concentrations are shown on page 34 of the Appendix.

When compared to stratum corneum from the back, terbinafine appeared to be about 2 times higher concentrated in *stratum corneum from the foot soles*. The mean peak levels of 211.7 ± 244.1 and 209.2 ± 186.2 μg/g were found 1 and 2 days after the cessation of drug application for the topical and combined, respectively. The inter-individual variability (CV%) was high between 65 and 346%. The variabilities are shown graphically in the figure above.

The terbinafine measurements in *dermis-epidermis* were impaired by the blank back ground observed in all samples at study baseline (day 0). Overall mean of this blank interference (15 μg/g) was substracted from all individual concentrations. The inter-individual variability (CV%) was high between %. Due to the back ground interference this data does not carry much significance.

Terbinafine levels appear to be higher in the combined treatment, with the exception in the case of stratum corneum from the back. Due to the high inter-subject variability it is difficult to obtain the statistical significance of these findings. The mean peak concentrations (C_{max}) in each tissue is similar when comparing the topical with the combined application. This suggests that the topical application of the gel contributes mainly to the levels of drug found in the skin. An apparent difference could only be found in the mean AUC, being higher with combined treatment with the exception of the stratum corneum from the back, suggesting that the combined treatment extends the time for the maintenance of fungicidal concentrations in the skin.

Comments

- Due to high inter-subject variability and use of subjects with normal skin, it is difficult to draw any significance from this study. No labeling claims have been made from this study.

VI. Conclusions

Terbinafine is currently available as an 250 mg oral tablet and as 1% cream. A 1% spray dosage form has also been very recently approved. The sponsor has adequately demonstrated in-vivo pharmacokinetics of the 1% emulsion gel dosage form and compared it to that of the cream formulation. No additional pharmacokinetic information is required for approval. However, some labeling suggestions have been outlined below.

VII. Labeling Comments

Metabolism

It is unknown whether or not there is significant skin metabolism of topically applied terbinafine. Radiolabeled studies with oral dosage forms indicate that terbinafine is highly metabolized into a number of inactive metabolites which undergo conjugation and excretion into the urine. The primary metabolite seen in the urine (10% of the oral dose) is N-demethyl terbinafine. After topical application of Lamisil® DermGel™, 2/12 patients and 6/12 healthy volunteers had detectable levels of the N-demethyl metabolite in the plasma at day 7, with maximum concentration being 0.99 ng/mL and 2.57 ng/mL, respectively.

Elimination

Based on series of studies, the total stratum corneum half life of terbinafine when absorbed through the skin is ~14-35 hours, depending on the topical dosage form of terbinafine. In a study comparing the Lamisil® DermGel™ with the Lamisil Cream 1% dosage form, the total stratum corneum $t_{1/2}$ for terbinafine after Day 7 application of Lamisil® DermGel™ was 27.2 h vs. 35.2 h for Lamisil Cream 1% ($p < 0.05$). Approximately 75% of cutaneously absorbed terbinafine is eliminated in the urine, predominately as metabolites.

- For consistency the "Nursing Mothers" section should be identical to that recently proposed for Lamisil® Spray 1%.

/S/ 1/7/98

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Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D. Edb 1/7/98

NDA
CC: [redacted] 20-846 (orig)
HFD-540/Div File
HFD-540/CSO/Kummer
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-344(Viswanathan)
CDR ATTN: B.Murphy

AE

APPENDIX I

NDA/IND#: 20-846 Volume 1.8

Study Type: Bioavailability *Study* # SFW 409-E-00

Study Title: Determination of plasma concentration after repeated application to normal skin.

Study Site	
Clinical Site	*Analytical Site*

Study Design								
Single Dose	*Multiple Dose*	*Washout Period*	*Cross - over*	*Parallel*	*Other Design*	*Fasted/ Fed*	*FDA Diet*	*No. of fasted hrs.*
	X				Open, not controlled			

Subject Category					
Normal	*Patients*	*Young*	*Elderly*	*Renal*	*Hepatic*
X					

Subject Type			
Males		*Females*	
Age	*Weight*	*Age*	*Weight*
(Av 26)	kg (Av 63.8)	(Av 26)	kg (Av 63.8)

Subject Treatment Group			
Group No.	*Total No.*	*Males*	*Females*
	12	6	6

Treatment Group	*Dose*	*Dosage Form*	*Strength*	*Lot #*
All	once daily-7 dys	Emulsion Gel	1%	Z050 1294
	(67.5 mg/d)			

Sampling Times

Plasma (8 ml) **Day 1→ 0, 2, 4 10 & 24 hrs, Day 4→ 0 hrs, Day 7→ 0, 2, 4, 6, 10, 14, 24 & 48 hrs**

Assay Method: *Assay Sensitivity:* 1ng/ml Terbinafine, 0. 5ng/ml SDZ86621

Assay Accuracy:[Nominal / measured / % accuracy]; [1 / 0.95 / -5.1]; [5 / 4.99 / -0.1]; [200 / 191/ -4.4] for terbinafine.

[1 / 0.89 / -11]; [5 / 4.74 / -5.3]; [200 / 181.87 /-.91] for SDZ 86-621.

Labeling Claims from this Study: On Day 1, terbinafine was found in the plasma of eleven out of twelve subjects at 10 hours (mean of 2.2±1.36 ng/mL, limit of quantification-1 ng/mL). On Day 7 all subjects has quantifiable terbinafine levels. The highest measured plasma terbinafine concentration was ng/mL. The AUC_{0-24} on Day 7 was 62.6 ng.h/mL. This is 0.6% of the AUC_{0-24} in healthy subjects following 250 mg PO for 28 days (10,481 ng.h/mL).

BODY SURFACE AREA AND WEIGHT OF LAMISIL GEL (g) IN HEALTHY MALE AND FEMALE VOLUNTEERS

Subject number	Body surface area (m^2)	Amount of Gel to apply (g)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Mean
										5.72
										6.37
										6.64
										6.70
										6.74
										6.03
										7.51
										6.85
										7.71
										7.03
										6.79
										6.96
N	12	12	12	12	12	12	12	12	12	12
MEDIAN	1.744	6.976	6.78	6.84	6.69	6.79	6.795	6.815	6.835	6.77
MEAN	1.736	6.946	6.74	6.80	6.69	6.72	6.73	6.80	6.79	6.75
STD	0.143	0.573	0.57	0.58	0.57	0.56	0.55	0.56	0.54	0.55
STDERR	0.041	0.165	0.17	0.17	0.16	0.16	0.16	0.16	0.16	0.16
MIN										5.72
MAX										7.71
L.95% CL.	1.655	6.621	6.414	6.476	6.366	6.409	6.425	6.481	6.490	6.441
U.95% CL.	1.817	7.270	7.063	7.128	7.011	7.040	7.043	7.113	7.098	7.067

INDIVIDUAL PHARMACOKINETIC PARAMETERS OF TERBINAFINE (SF 86-327) AT DAY 7
after topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days
to the nornal skin in 12 healthy volunteers

Subject Nr	Cmax [ng/ml]	tmax [h]	AUC[0-24h] [h.ng/ml]
N	12	12	12
MEAN	3.82	7.33	62.55
SD	2.05	3.45	46.54
SEM	0.59	0.99	13.43
CV [%]	53.76	47.00	74.41
MEDIAN	3.39	6.00	55.18
MINIMUM			
MAXIMUM			

INDIVIDUAL PLASMA CONCENTRATIONS [ng/ml] OF TERBINAFINE (SF 86-327)
after repeated topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days
to the normal skin in 12 healthy volunteers
(Values below the limit of quantification (1 ng/ml) were set to zero)

Subject Nr/Time(h)	Mean Daily Dose [mg] terbinafine	0.00	2.00	4.00	10.00	24.00	72.00
		Day 1					Day 4
N	12	12	12	12	12	12	12
MEAN	67.54	0.00	0.32	0.33	2.22	1.28	1.03
SD	5.54	0.00	0.59	0.78	1.36	0.91	1.18
SEM	1.60	0.00	0.17	0.22	0.39	0.26	0.34
CV [%]	8.20	N.C.	184.92	234.07	61.10	71.17	114.12
MEDIAN	67.65	0.00	0.00	0.00	1.69	1.48	0.70
MINIMUM							
MAXIMUM							

N.C.: not calculated

INDIVIDUAL PLASMA CONCENTRATIONS [ng/ml] OF TERBINAFINE (SF 86-327)
after repeated topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days
to the normal skin in 12 healthy volunteers
(Values below the limit of quantification (1 ng/ml) were set to zero)

Subject Nr/Time(h)	144.00	146.00	148.00	150.00	154.00	158.00	168.00	192.00	312.00
	Day 7								Day 14
N	12	12	12	12	12	12	12	12	11
MEAN	1.57	1.98	2.71	3.54	3.21	2.74	1.79	0.72	0.21
SD	1.61	1.95	2.60	2.10	2.15	2.27	1.39	0.91	0.47
SEM	0.47	0.56	0.75	0.61	0.62	0.65	0.40	0.26	0.14
CV [%]	103.02	98.43	95.98	59.19	67.11	82.68	77.59	126.56	222.83
MEDIAN	1.38	1.78	2.15	3.08	2.80	2.44	1.51	0.00	0.00
MINIMUM									
MAXIMUM									

* = Missing sample

INDIVIDUAL PLASMA CONCENTRATIONS [ng/ml] OF THE DEMETHYLATED METABOLITE SDZ 86-621
after topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days
to the normal skin in 12 healthy volunteers
(Values below the limit of quantification (0.5 ng/ml) were set to zero)

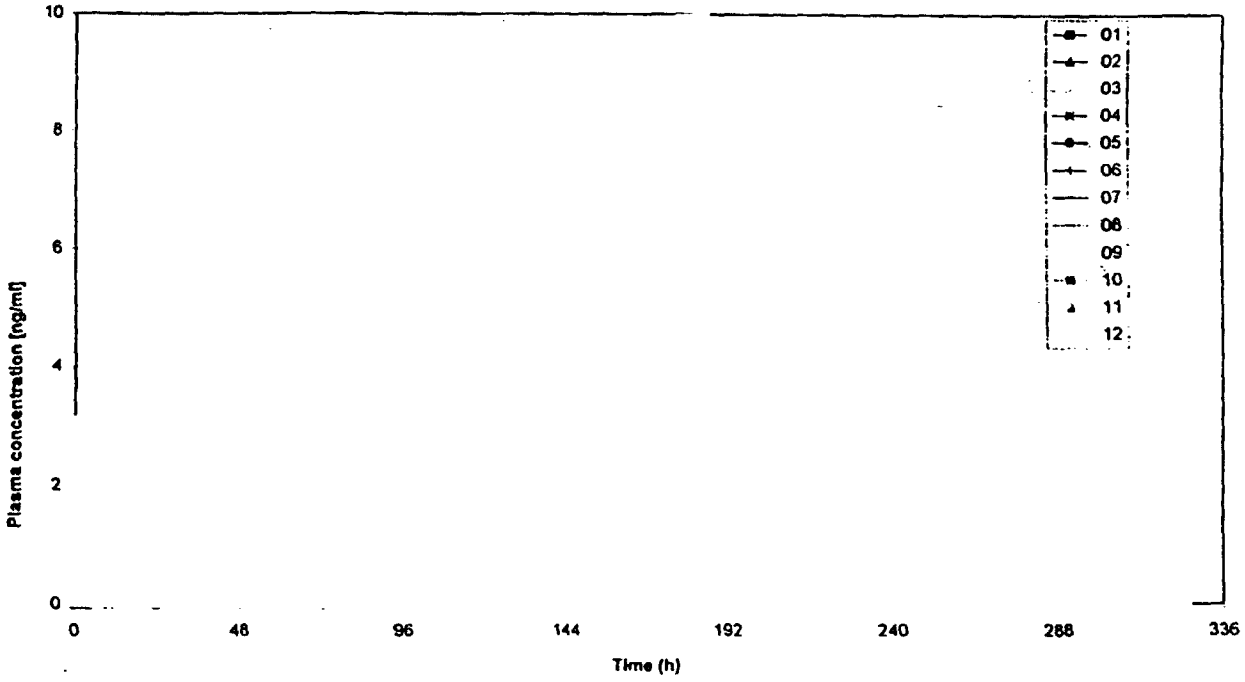
Subject Nr/Time(h)	Mean Daily Dose	0.0	2.0	4.0	10.0	24.0	72.0
	[mg] terbinafine	Day 1					Day 4

INDIVIDUAL PLASMA CONCENTRATIONS [ng/ml] OF THE DEMETHYLATED METABOLITE SDZ 86-621
after topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days
to the normal skin in 12 healthy volunteers
(Values below the limit of quantification (0.5 ng/ml) were set to zero)

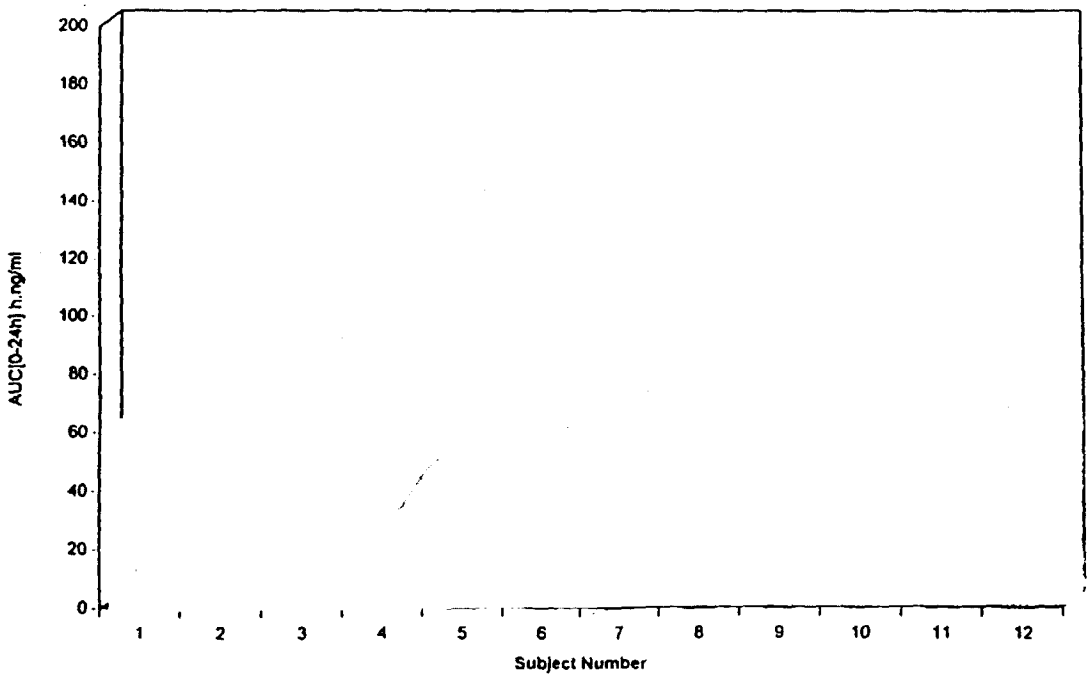
Subject Nr/Time(h)	144.0	146.0	148.0	150.0	154.0	158.0	168.0	192.0	312.0
	Day 7								Day 14
N	12	12	12	12	12	12	12	12	11
MEAN	0.21	0.26	0.31	0.39	0.35	0.43	0.26	0.11	0.00
SD	0.55	0.68	0.76	0.81	0.77	0.61	0.54	0.39	0.00
SEM	0.16	0.20	0.22	0.23	0.22	0.18	0.15	0.11	0.00
CV [%]	257.94	265.84	241.17	206.90	220.68	141.13	204.36	346.41	N.C.
MEDIAN	0.00	0.00	0.00	0.00	0.00	0.25	0.00	0.00	0.00
MINIMUM									
MAXIMUM									

* = Missing sample
N.C.: not calculated

Synoptic view of individual plasma concentrations (ng/ml) of terbinafine (SF 86-327)
after repeated topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days
to the normal skin in 12 healthy volunteers
(Values below the limit of quantification (1 ng/ml) were set to zero)



Individual area under the curve (AUC[0-24h]) [h.ng/ml] of terbinafine (SF 86-327) at Day 7
after repeated topical applications of a 1% Lamisil Emulsion gel once daily
for 7 consecutive days to the normal skin in 12 healthy volunteers



NDA/IND#: 20-846 Volume 1.9

Study Type: Bioavailability *Study* # SFW 410-E-00

Study Title: Determination of plasma concentration after repeated application to diseased skin.

Study Site	
Clinical Site	*Analytical Site*

Study Design								
Single Dose	*Multiple Dose*	*Washout Period*	*Cross - over*	*Parallel*	*Other Design*	*Fasted/ Fed*	*FDA Diet*	*No. of fasted hrs.*
	X				Open, not controlled			

Subject Category					
Normal	*Patients*	*Young*	*Elderly*	*Renal*	*Hepatic*
	X				

Subject Type			
Males		*Females*	
Age	*Weight*	*Age*	*Weight*
(Av 51)	kg (Av 72.0)	(Av 43)	kg (Av 72.0)

Subject Treatment Group			
Group No.	*Total No.*	*Males*	*Females*
	12	6	6

Treatment Group	*Dose*	*Dosage Form*	*Strength*	*Lot #*
All	once daily for 7d	Emulsion Gel	1%	Z050 1294
	varied due to			
	diseased area			

Sampling Times

Plasma (8 ml) **Day 1→ 0, 2, 4 10 & 24 hrs, Day 4→ 0 hrs, Day 7→ 0, 2, 4, 6, 10, 14, 24 & 48 hrs**

Assay Method: *Assay Sensitivity:* 1ng/ml Terbinafine, 0. 5ng/ml SDZ86621

Assay Accuracy:[Nominal / measured / %accuracy]; [1 / 1 / 0.1]; [5 /4.75 / 5]; [200 / 213.82 /6.9] for terbinafine

[1 /0.91 / 9.5]; [5 / 4.66 / 6.7]; [200 /200.65 / 2.8] for the metabolite

Labeling Claims From Study: In a study of 12 patients with tinea cruris/corporis, Lamisil DermGel 1% was applied once daily for 7 days to diseased area(s) as well as a 2.5 cm margin of healthy skin. Mean daily application ranged from 20.4 to 92.1 mg. Terbinafine plasma levels were detected in 6 of 12 patients on Day 1 and the maximum level was ng/mL. Terbinafinne plasma levels were measurable in 10 of 12 patients on Day 7 and the maximum concentration was ng/mL. The AUC_{0-24} on Day 7 was 40.5 ng.h/mL

SUBJECT CHARACTERISTICS OF MALE AND FEMALE PATIENTS WITH TINEA CRURIS/CORPORIS

Patient No.	Sex	Age [years]	Weight [kg]	Height [cm]
	Female			
	Female			
	Female			
	Female			
	Male			
	Female			
	Male			
	Male			
	Male			
	Male			
	Female			
	Male			
N	6 Males	12	12.0	12
Median	6 Females	48	74.2	167
Arith.Mean		47	72.0	168
StDev		12	7.4	6
CV [%]		26	10.3	3
SEM		4	2.1	2
Minimum				
Maximum				
L.95%Conf.Lim		39	67.3	165
U.95%Conf.Lim		55	76.7	172

ACTUAL WEIGHT [g] OF 1% LAMISIL^{R} EMULSION GEL APPLIED TO THE DISEASED SKIN IN MALE AND FEMALE PATIENTS WITH TINEA CRURIS/CORPORIS

Patient No.	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Total Amount	Mean
									2.2
									6.0
									9.2
									3.7
									2.2
									2.1
									4.0
									2.4
									3.4
									2.0
									2.1
									3.5

ACTUAL AMOUNT OF TERBINAFINE [mg] APPLIED AS 1% LAMISIL^{R} EMULSION GEL TO THE DISEASED SKIN IN MALE AND FEMALE PATIENTS WITH TINEA CRURIS/CORPORIS

Patient No.	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Total Amount	Mean
									22.0
									60.1
									92.1
									37.3
									21.9
									20.9
									40.1
									23.6
									34.1
									20.4
									21.3
									34.7

INDIVIDUAL PLASMA CONCENTRATIONS [ng/ml] OF TERBINAFINE (SF 86-327)
after repeated topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days
to the diseased skin in 12 patients with Tinea Cruris/Corporis
(Values below the limit of quantification (1 ng/ml) were set to zero)

Subject Nr/Time(h)	Mean Daily Dose [mg] terbinafine	0.00	2.00	4.00	10.00	24.00	72.00
		Day 1					Day 4
N	12	12	12	12	12	12	12
MEAN	35.71	0.30	0.14	0.38	0.41	0.80	
SD	21.29	0.69	0.48	0.73	0.79	1.14	
SEM	6.15	0.20	0.14	0.21	0.23	0.33	
CV[%]	59.63	234.78	346.41	192.57	191.89	142.11	
MEDIAN	28.85	0.00	0.00	0.00	0.00	0.00	
MINIMUM							
MAXIMUM							

INDIVIDUAL PLASMA CONCENTRATIONS [ng/ml] OF TERBINAFINE (SF 86-327)
after repeated topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days
to the diseased skin in 12 patients with Tinea Cruris/Corporis
(Values below the limit of quantification (1 ng/ml) were set to zero)

Subject Nr/Time(h)	144.00	146.00	148.00	150.00	154.00	158.00	168.00	192.00	312.00
	Day 7						Day 8	Day 9	Day 14
N	12	12	12	12	12	12	12	12	12
MEAN	1.66	1.58	1.68	1.99	2.03	1.91	0.98	0.52	0.14
SD	1.66	1.50	1.37	1.78	1.80	1.76	1.40	0.79	0.48
SEM	0.48	0.43	0.39	0.52	0.52	0.51	0.40	0.23	0.14
CV[%]	99.60	94.90	81.60	89.80	88.40	91.90	142.98	153.25	346.41
MEDIAN	1.18	1.58	1.62	1.86	2.11	1.70	0.00	0.00	0.00
MINIMUM									
MAXIMUM									

INDIVIDUAL PHARMACOKINETIC PARAMETERS OF TERBINAFINE (SF 86-327) at Day 7
after topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days
to the diseased skin in 12 patients with Tinea Cruris/Corporis

Patient Nr	Cmax [ng/ml]	tmax [h]	AUC[0-24h] [h.ng/ml]	Dose of terbinafine [mg] at Day 7	AUC[0-24h] weighted* [h.ng/ml]
N	12	12	12	12	12
Mean	2.48	7.83	40.54	36.00	41.51
SD	1.85	7.11	36.30	21.06	27.68
SEM	0.53	2.05	10.48	6.08	7.99
CV(%)	74.50	90.70	89.50	58.50	66.70
MEDIAN	2.48	6.00	42.54	28.00	47.85
MINIMUM					
MAXIMUM					

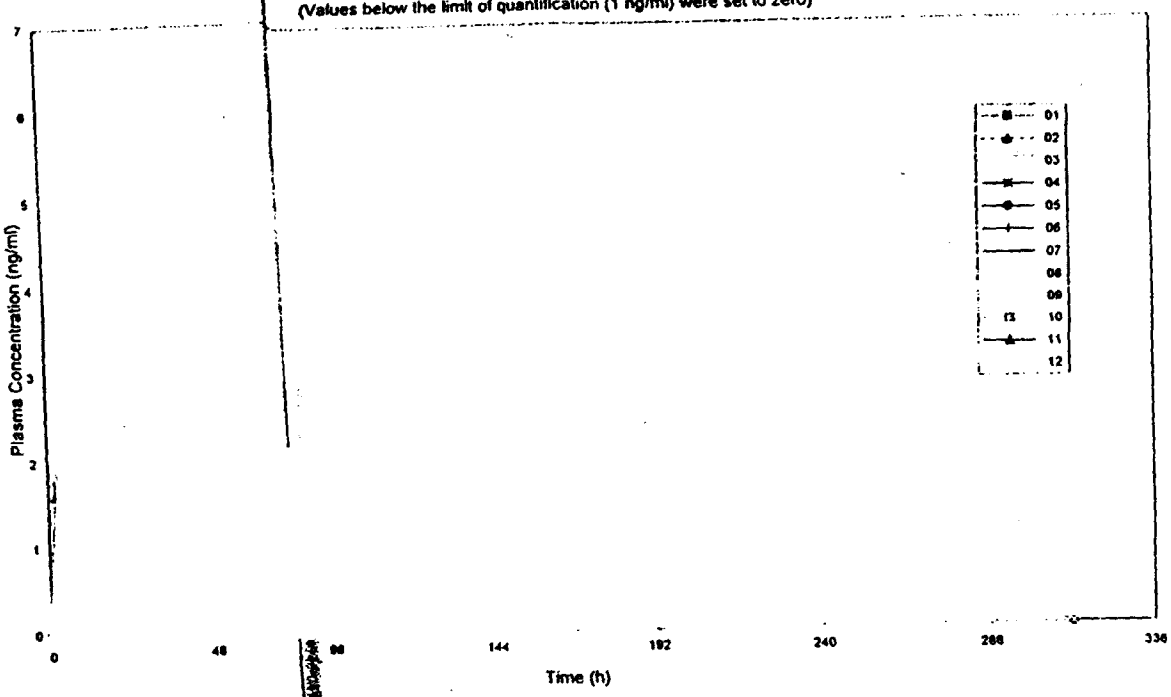
* weighted by the actual individual dose at day 7 relative to the mean dose at day 7

INDIVIDUAL PLASMA CONCENTRATIONS [ng/ml] OF THE DEMETHYLATED METABOLITE SDZ 86-621
after topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days
to the diseased skin in 12 patients with Tinea Cruris/Corporis
(Values below the limit of quantification (0.5 ng/ml) were set to zero)

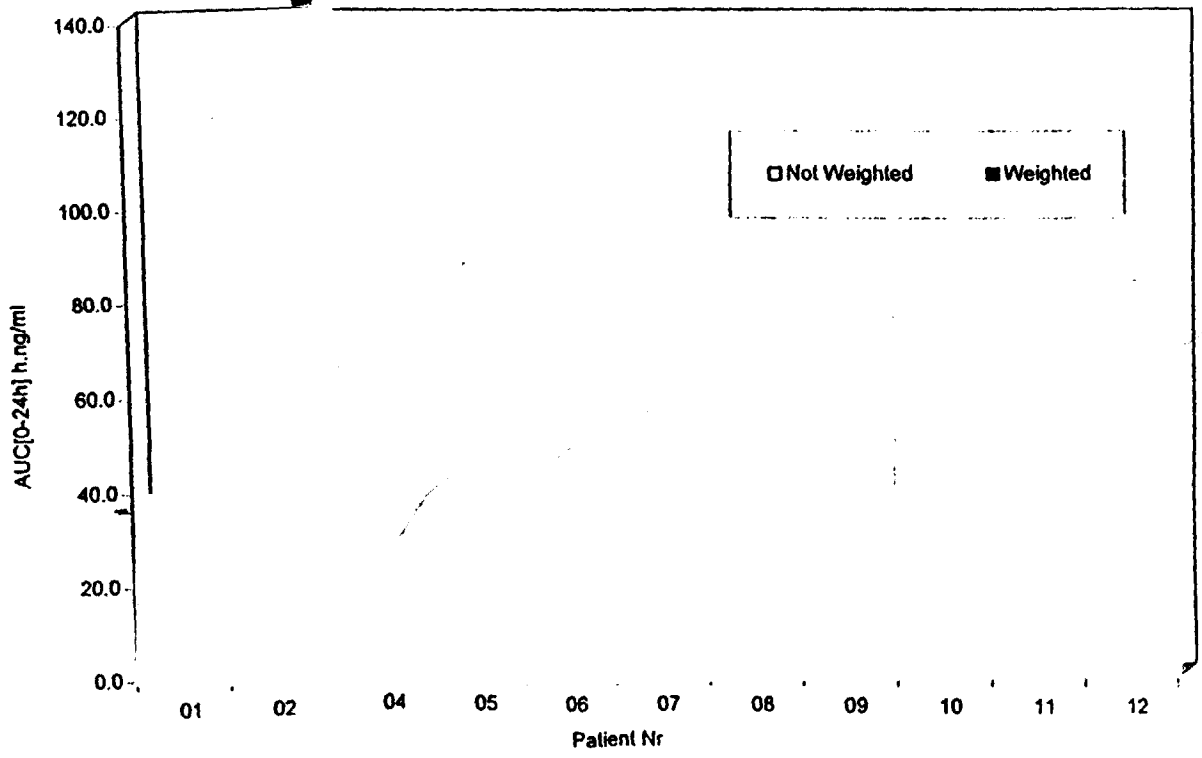
Subject Nr/Time (h)	Mean Daily Dose [mg] terbinafine	0.00	2.00	4.00	10.00	24.00	72.00
		Day 1					Day 4

Subject Nr/Time (h)	144.00	146.00	148.00	150.00	154.00	158.00	168.00	192.00	312.00
	Day 7						Day 8	Day 9	Day 14

Synoptic view of individual plasma concentrations [ng/ml] of terbinafine (SF 86-327) after repeated topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days to the diseased skin in 12 patients with Tinea Cruris/Corporis (Values below the limit of quantification (1 ng/ml) were set to zero)



Individual under the curve (AUC[0-24h]) [h.ng/ml] of terbinafine (SF 86-327) at Day 7 after repeated topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days to the diseased skin in 12 patients with Tinea Cruris/Corporis (Weighted AUC [0-24h] with regards to the mean dose administered at Day 7)



NDA/IND#: 20-846 Volume 1.10

Study Type: Bioavailability *Study* # SFG 205-E-00

Study Title: Bioavailability comparison of terbinafine 1% gel vs. 1% cream.

Study Site	
Clinical Site	*Analytical Site*

Study Design								
Single Dose	*Multiple Dose*	*Washout Period*	*Cross - over*	*Parallel*	*Other Design*	*Fasted/ Fed*	*FDA Diet*	*No. of fasted hrs.*
	X			X	Open, not controlled	NA		

Subject Category					
Normal	*Patients*	*Young*	*Elderly*	*Renal*	*Hepatic*
X					

Subject Type			
Males		*Females*	
Age	*Weight*	*Age*	*Weight*
	kg		kg

Subject Treatment Group			
Group No.	*Total No.*	*Males*	*Females*
gel-1 day	6	3	3
gel-5 days	6	3	3
gel-7 days	6	3	3
cream-1 day	6	3	3
cream-5 days	6	3	3
cream-7 days	6	3	3

Treatment Group	*Dose*	*Dosage Form*	*Strength*	*Lot #*
gel -1, 5, 7 days	0.5 gm	Emulsion Gel	1%	Z028 1291
cream-1,5,7 days	0.5 gm	Cream	1%	Z064 0690

Skin Sampling Times

Day 1(all) prior to dosing and 4, 8, 12, 24, 48, 72, 96 and 168 hrs (7 days) after last dose

Day 3&5 prior to dosing on days 3&5and 4, 8, 12, 24, 48, 72, 96 and 168 hrs after last dose on day 5

Day 7 prior to dosing and 4, 8, 12, 24, 48, 72, 96 and 168 hrs (7 days) after last dose

Assay Method: *Assay Sensitivity:*7.3 ng/ssb (0.18ng/cm^2)

Assay Accuracy:[Nominal/measured/%accuracy]; [12.5/ 12.67 / 7.5]; [250 / 260.82 / 10.6]; [1000 / 1113.52 / 6.3] for terbinafine

Labeling Claims: The total stratum corneum AUC_{0-t} for Lamisil® DermGel™ was significantly greater ($p < 0.05$) than that seen for Lamisil Cream 1% after 1 and 5 days of application. After 7 days of application there was no difference in AUC_{0-t} between the formulations. The total stratum corneum $t_{1/2}$ for terbinafine after Day 7 application of Lamisil® DermGel™ was 27.2 h vs. 35.2 h for Lamisil Cream 1% ($p < 0.05$).

Summary of Level 1 Stratum Corneum Pharmacokinetic Parameters: AUC 0-t (ng.hr/cm2)
(Population: Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	6	6	6	6	6	6
Mean	3238.100	3780.403	4807.130	3376.447	3533.783	5446.440
Median	3358.790	3817.760	4732.290	3385.890	3556.210	5517.820
s.d.	490.4198	280.9984	443.7165	345.7646	228.9598	287.7103
Minimum						
Maximum						

Comparison		Geometric Mean Ratio	95% Confidence Interval	p-value	
Lamisil Gel vs. Cream:	1 day	0.95	(0.85, 1.07)	0.409	
	5 days	1.07	(0.95, 1.20)	0.258	
	7 days	0.88	(0.78, 0.99)	0.036	*
Lamisil Gel:	1 day vs. 5 days	0.85	(0.75, 0.96)	0.008	**
	1 day vs. 7 days	0.67	(0.59, 0.75)	<0.001	***
	5 days vs. 7 days	0.79	(0.70, 0.89)	<0.001	***
Lamisil Cream:	1 day vs. 5 days	0.95	(0.85, 1.07)	0.414	
	1 day vs. 7 days	0.62	(0.55, 0.70)	<0.001	***
	5 days vs. 7 days	0.65	(0.58, 0.73)	<0.001	***

Summary of Level 1 Stratum Corneum Pharmacokinetic Parameters: Cmax (ng/cm2)
(Population: Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	6	6	6	6	6	6
Mean	242.778	357.865	356.580	281.547	290.965	357.613
Median	238.950	360.960	353.820	283.665	284.980	338.670
s.d.	32.9948	43.3623	43.5101	35.2779	31.5027	51.1255
Minimum						
Maximum						

Comparison		Geometric Mean Ratio	95% Confidence Interval	p-value	
Lamisil Gel vs. Cream:	1 day	0.86	(0.75, 1.00)	0.046	*
	5 days	1.23	(1.06, 1.42)	0.007	**
	7 days	1.00	(0.86, 1.16)	0.985	
Lamisil Gel:	1 day vs. 5 days	0.68	(0.59, 0.78)	<0.001	***
	1 day vs. 7 days	0.68	(0.59, 0.79)	<0.001	***
	5 days vs. 7 days	1.00	(0.87, 1.16)	0.961	
Lamisil Cream:	1 day vs. 5 days	0.97	(0.83, 1.12)	0.627	
	1 day vs. 7 days	0.79	(0.68, 0.91)	0.002	**
	5 days vs. 7 days	0.82	(0.71, 0.94)	0.008	**

Summary of Level 1 Stratum Corneum Pharmacokinetic Parameters: t1/2 (hrs)
Population: (Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	n/a	5	6	n/a	6	6
Mean		19.38	33.42		20.14	43.21
Median		19.43	35.54		19.53	46.19
s.d.		1.862	14.138		3.971	9.261
Minimum						
Maximum						

Comparison		Mean Difference	95% Confidence Interval	p-value	
Lamisil Gel vs. Cream:	1 day	n/a	n/a	n/a	
	5 days	-0.75	(-12.09, 10.59)	0.891	
	7 days	-9.79	(-20.60, 1.02)	0.073	(*)
Lamisil Gel:	1 day vs. 5 days	n/a	n/a	n/a	
	1 day vs. 7 days	n/a	n/a	n/a	
	5 days vs. 7 days	-14.04	(-25.38, -2.70)	0.018	*
Lamisil Cream:	1 day vs. 5 days	n/a	n/a	n/a	
	1 day vs. 7 days	n/a	n/a	n/a	
	5 days vs. 7 days	-23.08	(-33.89, -12.27)	<0.001	***

Summary of Level 2 Stratum Corneum Pharmacokinetic Parameters: AUC 0-t (ng.hr/cm2)
(Population: Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	6	6	6	6	6	6
Mean	2384.973	2373.490	3061.137	2065.163	2284.827	3025.800
Median	2438.690	2327.750	3126.340	2027.370	2305.510	3023.180
s.d.	256.2306	225.7166	216.5734	348.0628	93.5922	70.3278
Minimum						
Maximum						

Comparison		Geometric Mean Ratio	95% Confidence Interval	p-value	
Lamisil Gel vs. Cream:	1 day	1.16	(1.04, 1.31)	0.012	*
	5 days	1.04	(0.92, 1.16)	0.539	
	7 days	1.01	(0.90, 1.13)	0.865	
Lamisil Gel:	1 day vs. 5 days	1.00	(0.89, 1.13)	0.949	
	1 day vs. 7 days	0.78	(0.69, 0.87)	<0.001	***
	5 days vs. 7 days	0.77	(0.69, 0.87)	<0.001	***
Lamisil Cream:	1 day vs. 5 days	0.89	(0.80, 1.00)	0.056	(*)
	1 day vs. 7 days	0.67	(0.60, 0.76)	<0.001	***
	5 days vs. 7 days	0.75	(0.67, 0.85)	<0.001	***

Summary of Level 2 Stratum Corneum Pharmacokinetic Parameters: Cmax (ng/cm2)
(Population: Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	6	6	6	6	6	6
Mean	201.240	222.120	247.383	183.200	212.162	265.695
Median	199.175	221.100	249.135	185.325	207.850	259.970
s.d.	20.2538	35.8433	22.4068	23.9846	24.3447	29.4006
Minimum						
Maximum						

Comparison		Geometric Mean Ratio	95% Confidence Interval	p-value	
Lamisil Gel vs. Cream:	1 day	1.10	(0.96, 1.27)	0.173	
	5 days	1.04	(0.90, 1.20)	0.567	
	7 days	0.93	(0.81, 1.07)	0.322	
Lamisil Gel:	1 day vs. 5 days	0.91	(0.79, 1.05)	0.196	
	1 day vs. 7 days	0.81	(0.71, 0.94)	0.006	**
	5 days vs. 7 days	0.89	(0.77, 1.03)	0.107	
Lamisil Cream:	1 day vs. 5 days	0.86	(0.75, 0.99)	0.041	*
	1 day vs. 7 days	0.69	(0.60, 0.79)	<0.001	***
	5 days vs. 7 days	0.80	(0.69, 0.92)	0.003	**

Summary of Level 2 Stratum Corneum Pharmacokinetic Parameters: t1/2 (hrs)
Population: (Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	n/a	6	6	n/a	3	6
Mean		18.45	30.68		26.25	44.99
Median		18.79	27.33		23.45	45.19
s.d.		2.365	9.713		5.645	13.545
Minimum						
Maximum						

Comparison		Mean Difference	95% Confidence Interval	p-value	
Lamisil Gel vs Cream:	1 day	n/a	n/a	n/a	
	5 days	-7.79	(-21.72, 6.13)	0.254	
	7 days	-14.31	(-25.68, -2.94)	0.017	*
Lamisil Gel:	1 day vs. 5 days	n/a	n/a	n/a	
	1 day vs. 7 days	n/a	n/a	n/a	
	5 days vs. 7 days	-12.23	(-23.59, -0.86)	0.037	*
Lamisil Cream:	1 day vs. 5 days	n/a	n/a	n/a	
	1 day vs. 7 days	n/a	n/a	n/a	
	5 days vs. 7 days	-18.74	(-32.67, -4.82)	0.011	*

Summary of Level 3 Stratum Corneum Pharmacokinetic Parameters: AUC 0-t (ng.hr/cm2)
(Population: Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	6	6	6	6	6	6
Mean	1379.030	1776.780	2148.860	1001.947	1346.963	1831.763
Median	1297.940	1754.870	2148.130	1057.850	1340.290	1837.350
s.d.	189.7754	106.1386	141.8106	168.5783	93.9240	126.2773
Minimum						
Maximum						

Comparison		Geometric Mean Ratio	95% Confidence Interval	p-value
Lamisil Gel vs. Cream:	1 day	1.38	(1.22, 1.57)	<0.001 ***
	5 days	1.32	(1.16, 1.50)	<0.001 ***
	7 days	1.17	(1.04, 1.33)	0.014 *
Lamisil Gel:	1 day vs. 5 days	0.77	(0.68, 0.87)	<0.001 ***
	1 day vs. 7 days	0.64	(0.56, 0.72)	<0.001 ***
	5 days vs. 7 days	0.83	(0.73, 0.94)	0.004 **
Lamisil Cream:	1 day vs. 5 days	0.74	(0.65, 0.83)	<0.001 ***
	1 day vs. 7 days	0.54	(0.48, 0.61)	<0.001 ***
	5 days vs. 7 days	0.74	(0.65, 0.83)	<0.001 ***

Summary of Level 3 Stratum Corneum Pharmacokinetic Parameters: Cmax (ng/cm2)
(Population: Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	6	6	6	6	6	6
Mean	116.935	156.533	160.283	126.903	134.757	193.892
Median	116.715	154.475	157.105	127.580	136.215	190.560
s.d.	10.4637	19.4843	20.5212	21.2251	11.8680	19.1028
Minimum						
Maximum						

Comparison		Geometric Mean Ratio	95% Confidence Interval	p-value
Lamisil Gel vs. Cream:	1 day	0.93	(0.81, 1.07)	0.306
	5 days	1.16	(1.00, 1.33)	0.043 *
	7 days	0.82	(0.72, 0.95)	0.009 **
Lamisil Gel:	1 day vs. 5 days	0.75	(0.65, 0.86)	<0.001 ***
	1 day vs. 7 days	0.73	(0.63, 0.84)	<0.001 ***
	5 days vs. 7 days	0.98	(0.85, 1.13)	0.735
Lamisil Cream:	1 day vs. 5 days	0.93	(0.81, 1.08)	0.325
	1 day vs. 7 days	0.65	(0.56, 0.75)	<0.001 ***
	5 days vs. 7 days	0.70	(0.60, 0.80)	<0.001 ***

Summary of Level 3 Stratum Corneum Pharmacokinetic Parameters: t1/2 (hrs)
Population: (Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	n/a	5	6	n/a	1	2
Mean		24.78	31.64		31.39	37.09
Median		26.23	29.86		31.39	37.09
s.d.		3.625	8.999			16.686
Minimum						
Maximum						

Comparison		Mean Difference	95% Confidence Interval	p-value
Lamisil Gel vs. Cream:	1 day	n/a	n/a	n/a
	5 days	n/a	n/a	n/a
	7 days	n/a	n/a	n/a
Lamisil Gel:	1 day vs. 5 days	n/a	n/a	n/a
	1 day vs. 7 days	n/a	n/a	n/a
	5 days vs. 7 days	-6.86	(-16.62, 2.91)	0.147
Lamisil Cream:	1 day vs. 5 days	n/a	n/a	n/a
	1 day vs. 7 days	n/a	n/a	n/a
	5 days vs. 7 days	n/a	n/a	n/a

Summary of Level 4 Stratum Corneum Pharmacokinetic Parameters: AUC 0-t (ng.hr/cm2)
(Population: Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	6	6	6	6	6	6
Mean	763.220	1151.623	1406.537	522.427	658.677	858.347
Median	771.720	1159.440	1401.800	560.800	646.930	857.610
s.d.	51.8302	170.0573	84.0143	160.9439	72.8074	51.2350
Minimum						
Maximum						

Comparison		Geometric Mean Ratio	95% Confidence Interval	p-value	
Lamisil Gel vs. Cream:	1 day	1.54	(1.25, 1.89)	<0.001	***
	5 days	1.74	(1.41, 2.15)	<0.001	***
	7 days	1.64	(1.33, 2.02)	<0.001	***
Lamisil Gel:	1 day vs. 5 days	0.67	(0.54, 0.82)	<0.001	***
	1 day vs. 7 days	0.54	(0.44, 0.67)	<0.001	***
	5 days vs. 7 days	0.81	(0.66, 1.00)	0.051	(*)
Lamisil Cream:	1 day vs. 5 days	0.76	(0.61, 0.93)	0.011	*
	1 day vs. 7 days	0.58	(0.47, 0.71)	<0.001	***
	5 days vs. 7 days	0.76	(0.62, 0.94)	0.014	*

Summary of Level 4 Stratum Corneum Pharmacokinetic Parameters: Cmax (ng/cm2)
(Population: Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	6	6	6	6	6	6
Mean	76.433	97.782	98.718	81.513	70.760	97.277
Median	74.375	104.550	99.815	88.760	69.860	92.605
s.d.	7.3986	15.6803	13.1155	25.0984	10.0487	12.4564
Minimum						
Maximum						

Comparison		Geometric Mean Ratio	95% Confidence Interval	p-value	
Lamisil Gel vs. Cream:	1 day	0.99	(0.78, 1.25)	0.913	
	5 days	1.38	(1.08, 1.75)	0.011	*
	7 days	1.01	(0.80, 1.29)	0.906	
Lamisil Gel:	1 day vs. 5 days	0.79	(0.62, 1.00)	0.051	(*)
	1 day vs. 7 days	0.78	(0.61, 0.99)	0.040	*
	5 days vs. 7 days	0.99	(0.78, 1.25)	0.907	
Lamisil Cream:	1 day vs. 5 days	1.10	(0.86, 1.40)	0.427	
	1 day vs. 7 days	0.80	(0.63, 1.01)	0.064	(*)
	5 days vs. 7 days	0.73	(0.57, 0.92)	0.011	*

Summary of Level 4 Stratum Corneum Pharmacokinetic Parameters: t1/2 (hrs)
Population: (Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	n/a	3	6	n/a	n/a	n/a
Mean		28.32	40.43			
Median		27.08	40.11			
s.d.		3.154	4.379			
Minimum						
Maximum						

Comparison		Mean Difference	95% Confidence Interval	p-value	
Lamisil Gel vs. Cream:	1 day	n/a	n/a	n/a	
	5 days	n/a	n/a	n/a	
	7 days	n/a	n/a	n/a	
Lamisil Gel:	1 day vs. 5 days	n/a	n/a	n/a	
	1 day vs. 7 days	n/a	n/a	n/a	
	5 days vs. 7 days	-12.12	(-18.92, -5.32)	0.004	**
Lamisil Cream:	1 day vs. 5 days	n/a	n/a	n/a	
	1 day vs. 7 days	n/a	n/a	n/a	
	5 days vs. 7 days	n/a	n/a	n/a	

Table 3.6.2.1
Summary of Level 5 Stratum Corneum Pharmacokinetic Parameters: AUC 0-t (ng.hr/cm2)
(Population: Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	6	6	6	6	6	6
Mean	472.910	738.527	855.657	248.180	355.987	315.473
Median	484.880	718.300	844.760	251.520	344.480	322.500
s.d.	158.5715	103.8373	188.2127	87.2868	38.4823	22.409
Minimum						
Maximum						

Comparison		Geometric Mean Ratio	95% Confidence Interval	p-value	
Lamisil Gel vs. Cream:	1 day	1.92	(1.42, 2.60)	<0.001	***
	5 days	2.07	(1.53, 2.80)	<0.001	***
	7 days	2.66	(1.97, 3.60)	<0.001	***
Lamisil Gel:	1 day vs. 5 days	0.61	(0.45, 0.83)	0.002	**
	1 day vs. 7 days	0.54	(0.40, 0.72)	<0.001	***
	5 days vs. 7 days	0.88	(0.65, 1.18)	0.375	
Lamisil Cream:	1 day vs. 5 days	0.66	(0.49, 0.89)	0.008	**
	1 day vs. 7 days	0.74	(0.55, 1.00)	0.052	(*)
	5 days vs. 7 days	1.13	(0.83, 1.52)	0.431	

Summary of Level 5 Stratum Corneum Pharmacokinetic Parameters: Cmax (ng/cm2)
(Population: Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Day (N=6)
N	6	6	6	6	6	6
Mean	48.645	58.210	52.612	44.535	37.352	29.54
Median	51.145	54.860	52.925	41.670	37.955	27.17
s.d.	14.0936	8.4314	11.1038	18.8379	5.5071	6.00
Minimum						
Maximum						

Comparison		Geometric Mean Ratio	95% Confidence Interval	p-value	
Lamisil Gel vs. Cream:	1 day	1.15	(0.83, 1.58)	0.383	
	5 days	1.56	(1.13, 2.15)	0.008	**
	7 days	1.77	(1.29, 2.44)	<0.001	***
Lamisil Gel:	1 day vs. 5 days	0.81	(0.59, 1.12)	0.197	
	1 day vs. 7 days	0.91	(0.66, 1.25)	0.552	
	5 days vs. 7 days	1.12	(0.81, 1.54)	0.478	
Lamisil Cream:	1 day vs. 5 days	1.10	(0.80, 1.52)	0.531	
	1 day vs. 7 days	1.41	(1.02, 1.93)	0.038	*
	5 days vs. 7 days	1.27	(0.92, 1.75)	0.134	

Summary of Level 5 Stratum Corneum Pharmacokinetic Parameters: t1/2 (hrs) (Page 6 of 6)
Population: (Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Day (N=6)
N	n/a	n/a	5	n/a	n/a	n/a
Mean			53.25			
Median			50.41			
s.d.			11.911			
Minimum						
Maximum						

Comparison		Mean Difference	95% Confidence Interval	p-value
Lamisil Gel vs. Cream:	1 day	n/a	n/a	n/a
	5 days	n/a	n/a	n/a
	7 days	n/a	n/a	n/a
Lamisil Gel:	1 day vs. 5 days	n/a	n/a	n/a
	1 day vs. 7 days	n/a	n/a	n/a
	5 days vs. 7 days	n/a	n/a	n/a
Lamisil Cream:	1 day vs. 5 days	n/a	n/a	n/a
	1 day vs. 7 days	n/a	n/a	n/a
	5 days vs. 7 days	n/a	n/a	n/a

NDA/IND#: 20-846 Volume 1.11

Study Type: Bioavailability *Study* # SFG 205-E-00

Study Title: Bioavailability comparison of terbinafine 1% gel with oral placebo vs. 1% gel co-administered with oral tablets.

Study Site	
Clinical Site	*Analytical Site*
	Not mentioned

Study Design								
Single Dose	*Multiple Dose*	*Washout Period*	*Cross-over*	*Parallel*	*Other Design*	*Fasted/ Fed*	*FDA Diet*	*No. of fasted hrs.*
	X (for 1 week)			X	randomized double-blind	NA		

Subject Category					
Normal	*Patients*	*Young*	*Elderly*	*Renal*	*Hepatic*
X					

Subject Type			
Males		*Females*	
Age	*Weight*	*Age*	*Weight*

Subject Treatment Group			
Group No.	*Total No.*	*Males*	*Females*
gel+oral placebo	12	12	
gel+oral tablet	12	12	

Treatment Group	*Dose*	*Dosage Form*	*Strength*	*Lot #*
gel+oral placebo	50-60 mg/day		1%+ placebo	Z028 1991 & 016 0992
gel+oral tablet			1% +250 mg	Z028 1991 & 016 0992

Plasma & Tissue Sampling Times

Day 0 and Days 1, 2, 6, 12, 24, 36, 48 and 54 after cessation of application

Assay Method: *Assay Sensitivity:* 9.3ng/ml for plasma, 24.9ng/10mg for dermis-epidermis, 2.8 ng/10mg for stratum corneum from the back and 47ng/10mg for stratum corneum from the footsoles.

Assay Accuracy:[Nominal/measured/% CV]; [715/668/5]; [186/192/6]; [24.88/24.7/8/3] for terbinafine in plasma. [373/356/14]; [124/95/10.6]; 12.44/12.94/24.1]; [4.35/6.63/12.8] for terbinafine in biopsies %CV (131) high for lower concentrations in stratum (foot sole); %CV <12.9 for all samples.

Labeling claims from this study: None from this study.

TABLE 1

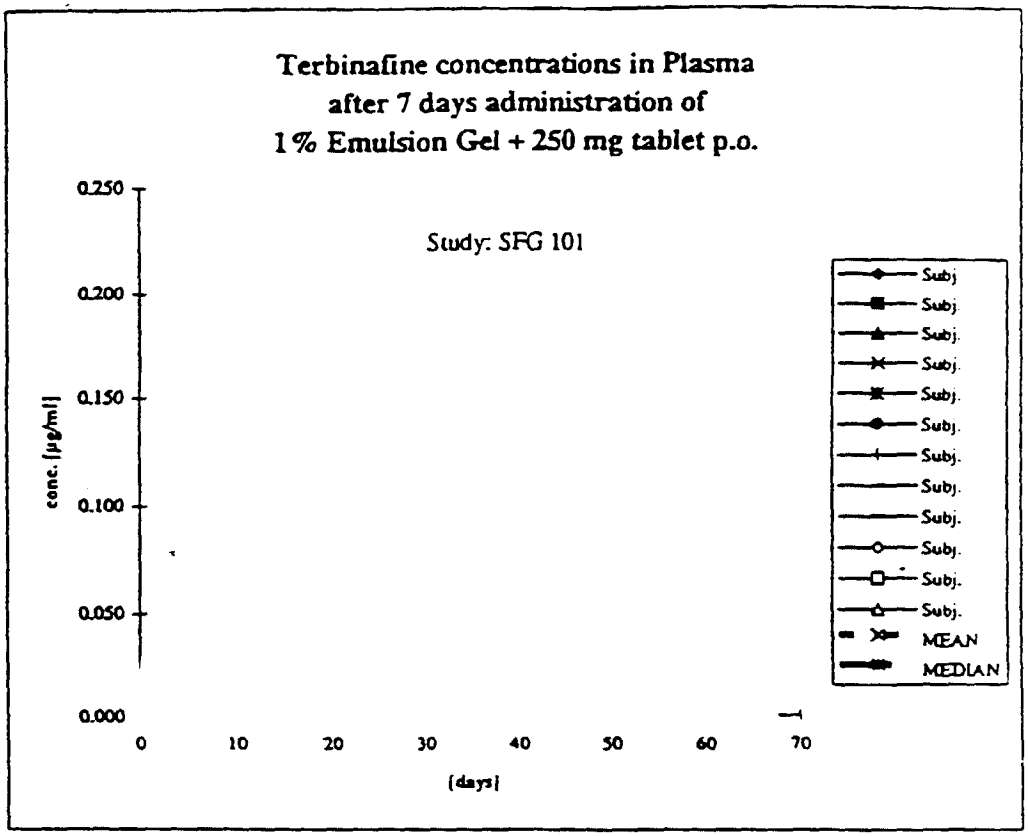
Study: SFG 101

Terbinafine concentrations in Plasma after 7 days administration of 1% Emulsion Gel or 250 mg p.o. + 1% Gel

Time [days] ->	0	8	9	13	19	31	43	55	61
Subject No:	[µg/ml]								
[redacted]									
Topical:	empty values: no sample or sample loss								
MEAN	0	0	0	0	0	0	0	0	0
StDEV									
CV[%]									
MEDIAN	0	0	0	0	0	0	0	0	0
Combined:									
[redacted]	0	0.106	0.071	0.043	0.024	0.012	0.005	0.002	0.000
StDEV	0	0.056	0.041	0.022	0.014	0.011	0.007	0.004	0.000
CV[%]	0	52.4	57.7	50.4	59.3	87.9	158.6	222.8	#DIV/0!
MEDIAN	0	0.179	0.089	0.062	0.037	0.013	0.000	0.000	0.000

	Topical	Combined
MEAN AUC(8-61d) [µg*days/ml]	0	0.9
Cmax of the MEAN [µg/ml]	0	0.106
tmax of the MEAN [days]		8
MEDIAN AUC(8-61d) [µg*days/ml]	0	0.9

FIGURES 1 AND 2



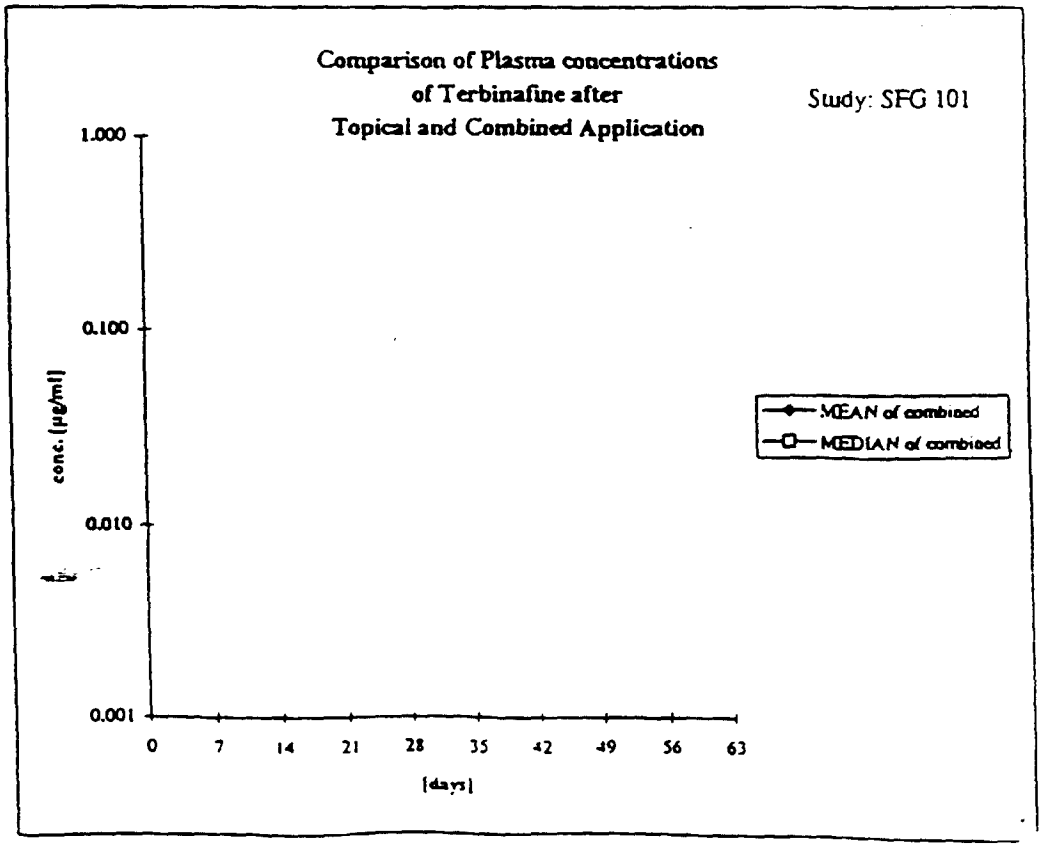
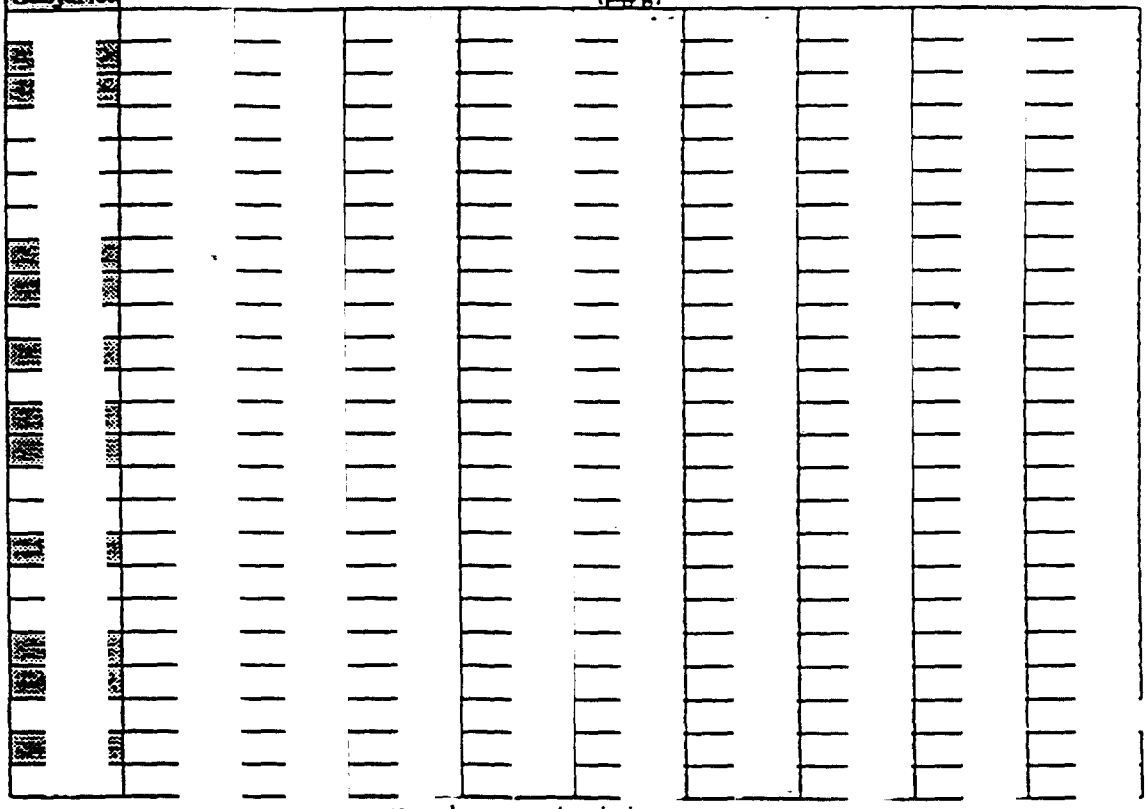


TABLE 2

Study: SFG 101 Terbinafine concentrations in Stratum corneum (from the back) after 7 days administration of 1% Emulsion Gel or 250 mg p.o. + 1% Gel

(* Subject 7 excluded from statistics)

Day ->	0	8	9	13	19	31	43	55	61
Subj.-No.	conc. [µg/g]								



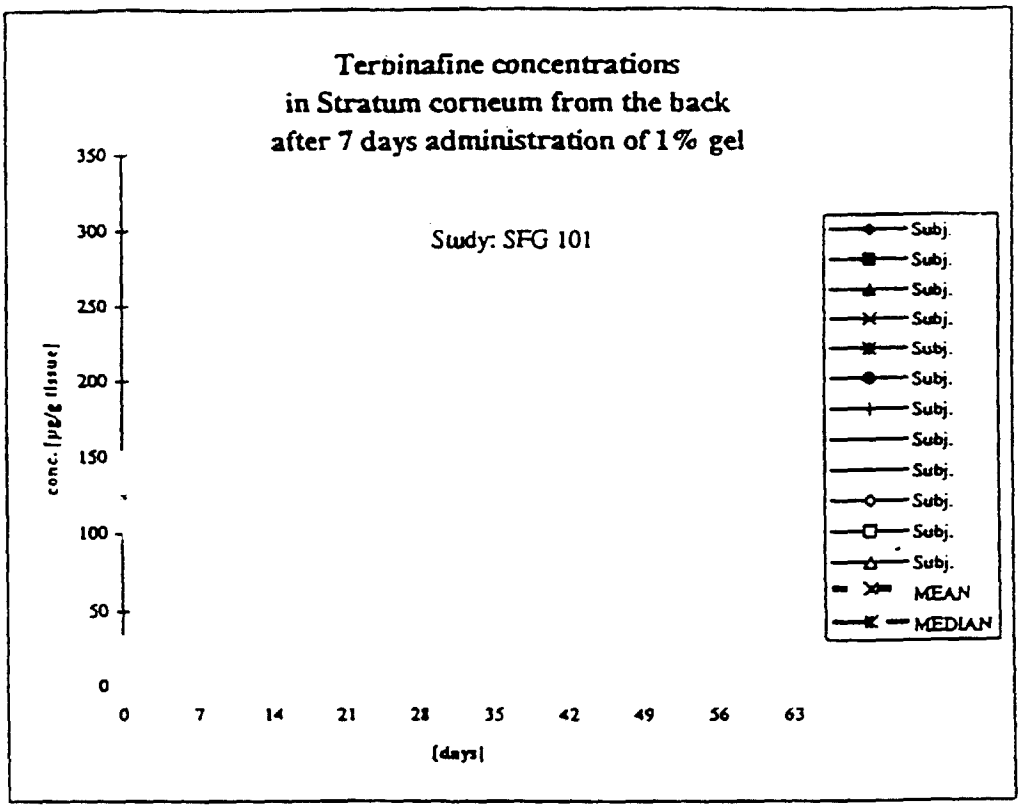
empty values: sample missing

Topical:									
MEAN	0	67.9	84.6	32.2	16.9	4.3	4.1	4.6	0.8
StDev	0	73	107	32	25	10	12	12	2
CV[%]	0	107	126	100	146	230	293	269	218
MEDIAN	0	44.7	33.8	20.8	4.5	0.6	0.5	0.0	0.0

Combined:									
MEAN	0	96.4	39.1	11.5	8.8	5.9	7.4	0.8	2.4
StDev	0	74	26	10	20	13	19	2	4
CV[%]	#DIV/0!	77	65	91	222	226	259	226	168
MEDIAN	0	78.6	28.4	9.2	1.2	1.0	0.0	0.0	0.7

	Topical	Combined
MEAN AUC(8-61d) [µg*days/g]	703.1	457.0
Cmax (µg/g) of the MEAN	85	96
tmax (days) of the MEAN	9	8
MEDIAN AUC (8-61d) [µg*days/g]	706.6	370.0
N	12	11

FIGURES 3 AND 4



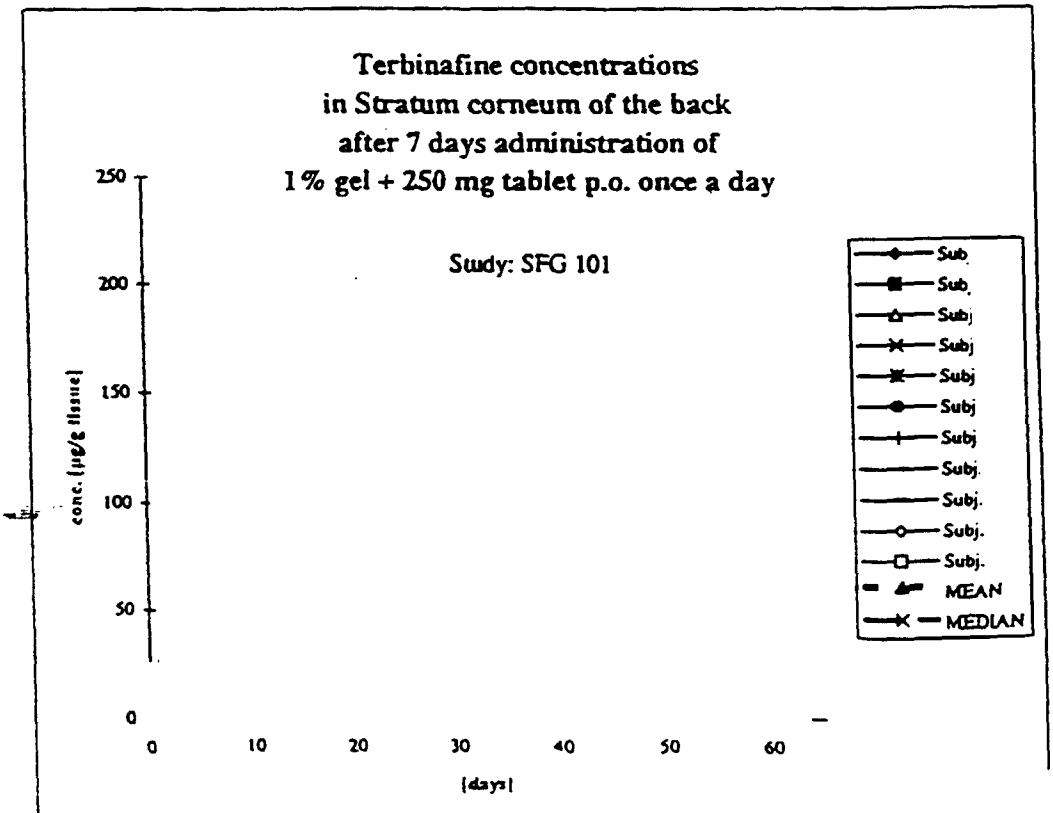


TABLE 3

Study: SFG 101 **Terbinafine concentrations in Stratum corneum (from the foot sole) after 7 days administration of 1% Emulsion Gel or 250 mg p.o. + 1% Gel**

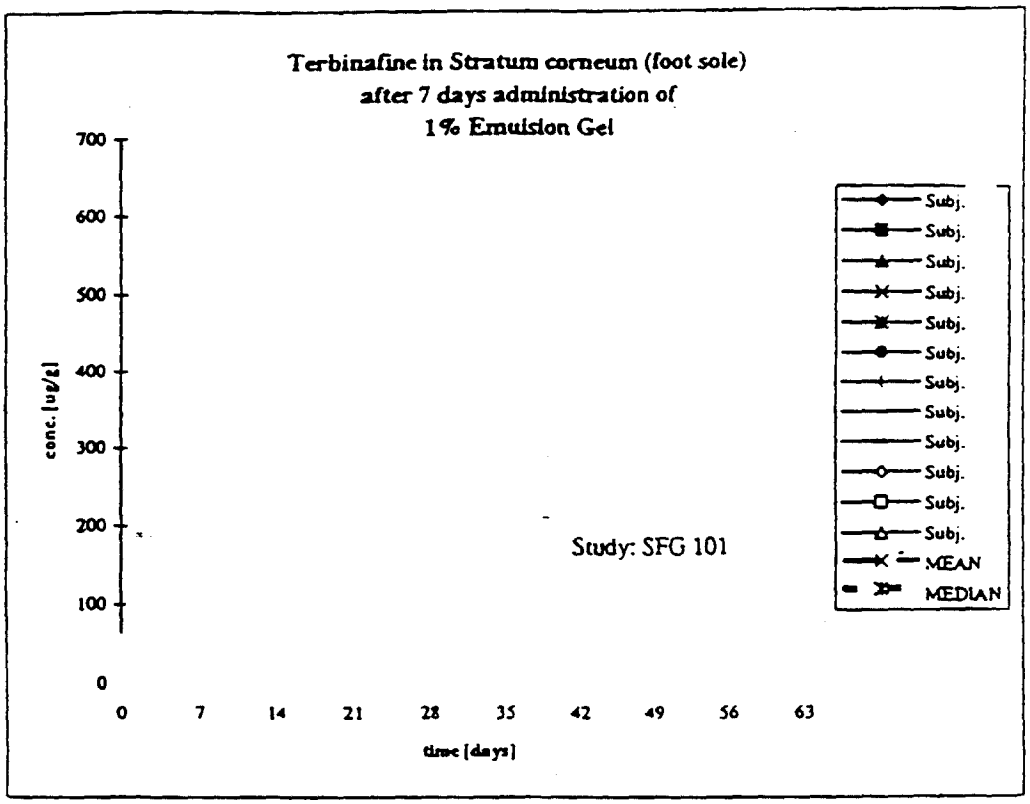
Day ->	0	8	9	13	19	31	43	55	61
Subj. No.				conc. [µg/g]					
[redacted]									

empty values: no sample available

Topical:									
MEAN	0	211.7	75.9	20.7	8.0	3.0	0.0	0.0	0.0
StDEV	0	244.1	93.2	19.4	14.3	4.7	0.0	0.0	0.0
CV(%)	0	115.3	122.8	93.4	178.2	154.4	0.0	0.0	0.0
MEDIAN	0	123.0	38.8	15.5	0.0	0.0	0.0	0.0	0.0
Combined:									
MEAN	0	186.2	209.2	86.7	12.6	5.3	2.2	2.1	1.9
StDEV	0	121.8	186.2	127.0	20.1	7.4	4.4	7.4	3.6
CV(%)	0	65.4	89.0	146.4	159.6	138.5	203.1	346.4	186.7
MEDIAN	0	156.8	109.2	40.6	0.0	0.0	0.0	0.0	0.0

	Topical	Combined
MEAN AUC (8-61d) [µg*days/g]	507.8	1277.8
Cmax [µg/g] of the MEAN	211.7	209.2
tmax [days] of the MEAN	8	9
MEDIAN AUC (8-61d) [µg*days/g]	386.8	914.3
N	12	12

FIGURES 5 AND 6



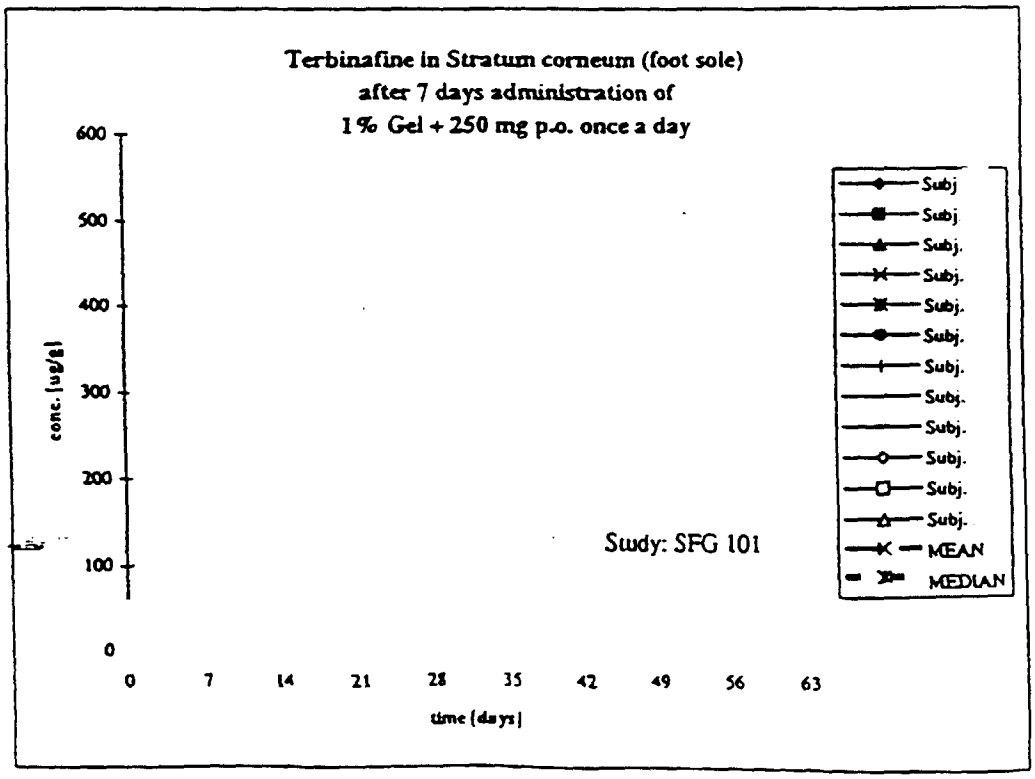


TABLE 4

Study: SFG 101

Terbinafine concentrations in Dermis-epidermis
after 7 days administration of
1% Emulsion Gel or 250 mg p.o. + 1% Gel

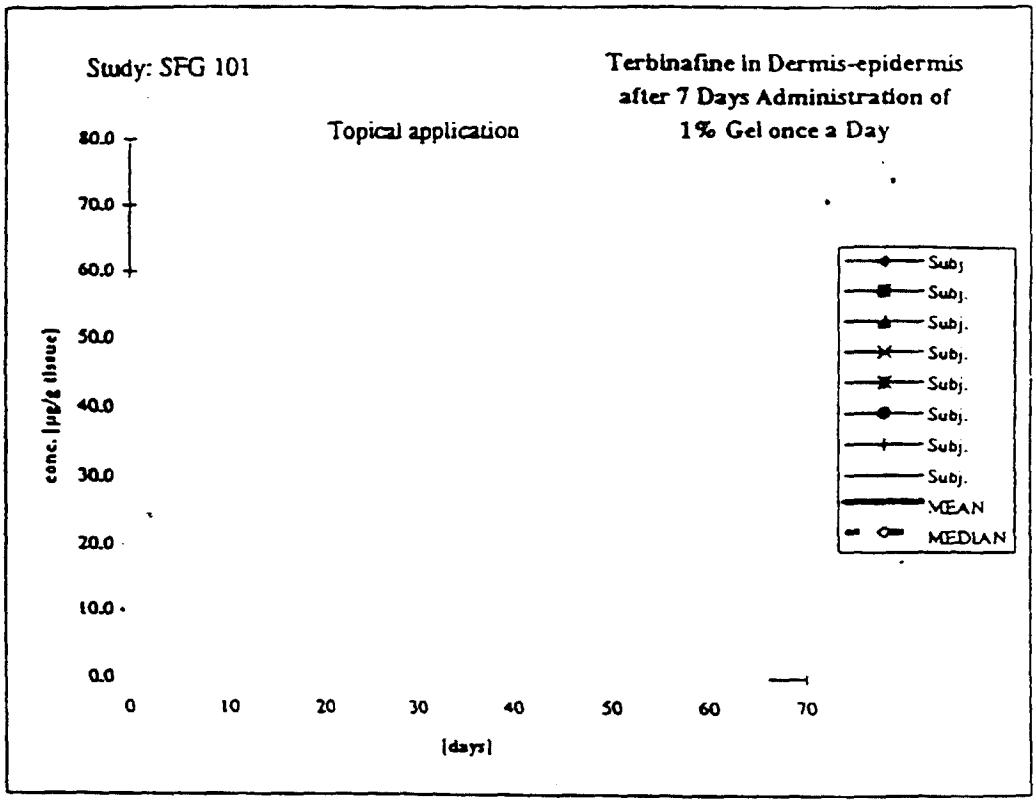
Day =>	0	8	9	13	19	31	43	55	61
Subj. No.	conc. [µg/g]								
[redacted]									

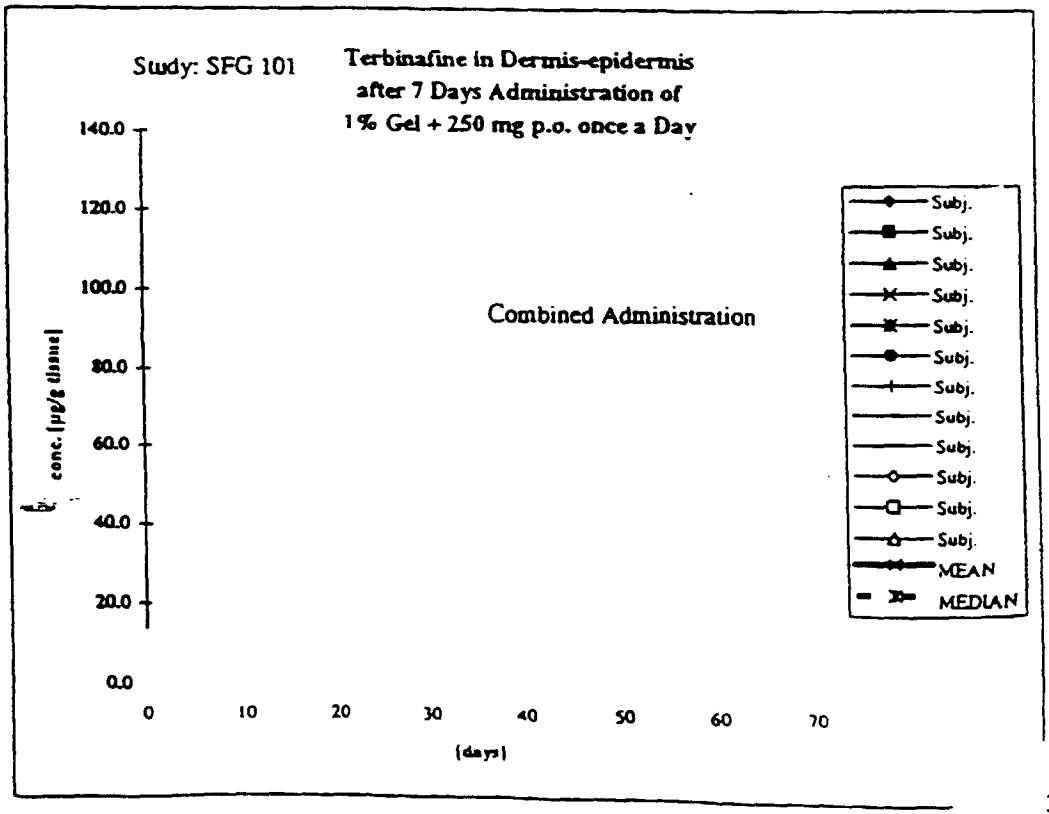
Topical:									
MEAN	9.9	17.4	17.6	2.2	1.4	9.7	5.5	6.2	7.8
StDev	18.0	24.0	24.0	5.1	2.8	21.4	9.0	20.2	20.1
CV[%]	182.1	137.5	136.0	229.4	200.7	221.7	165.1	325.6	258.7
MEDIAN	0.0	7.9	1.8	0.0	0.0	0.0	0.0	0.0	0.0

Combined:									
MEAN	1.2	42.2	14.0	1.8	22.4	11.8	11.1	1.6	1.0
StDev	2.2	25.1	17.1	4.2	43.1	20.9	17.5	5.6	2.5
CV[%]	183.4	59.5	121.9	241.3	192.4	176.6	157.5	346.3	239.4
MEDIAN	0.0	39.3	13.0	0.0	0.0	0.0	0.0	0.0	0.0

	Topical	Combined
MEAN AUC(8-61d) [µg*days/g]	336.8	559.8
MEAN Cmax [µg/g]	17.6	42.2
MEDIAN AUC(8-61d) [µg*days/g]	105.0	348.0
N	12	12

FIGURES 7 AND 8





CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-846

ADMINISTRATIVE DOCUMENTS