CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-749

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Terbinafine HCl 1% Topical Solution
Lamisil® 1% Spray
NDA 20-749
Reviewer: E.D. Bashaw, Pharm.D.
APW

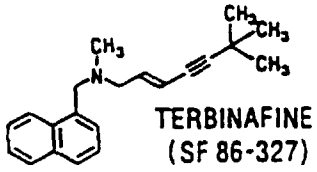
Sandoz Pharmaceutical
East Hanover, NJ 07936

Submission Date:
Oct. 18, 1996

Review of an NDA

I. Background

Terbinafine is a broad spectrum antifungal agent belonging to the allylamine family. It exerts its antifungal activity through inhibition of fungal biosynthesis of ergosterol at the point of squalene epoxidation. Cell death follows the disruption of cell membranes and the interruption of cell wall synthesis. Currently terbinafine is available on the U.S. market as an oral 250mg tablet (NDA 20-539) and as a 1% topical cream (NDA 20-192). This NDA is for a new topical formulation of terbinafine as a topical spray.



Chemically, terbinafine is 1-Naphthalenemethanamine, *N*-(6,6-dimethyl-2-hepten-4-ynyl) -*N*-methyl-,(*E*). It is highly lipid soluble and hydrophobic. It is the high degree of lipophilicity that is thought to account for its preferential uptake into the skin but not into plasma.

Terbinafine 1% spray will be indicated for the topical treatment of the following infections: pityriasis versicolor, tinea pedis (athlete's foot), tinea cruris (jock itch), or tinea corporis (ringworm). These indications are the same as for the previously approved terbinafine 1% cream. The 250mg terbinafine tablets are indicated only for the treatment of onychomycosis of the fingernail and toenail caused by dermatophytes.

In support of this new delivery system for terbinafine the applicant has included the results of three in vivo bioavailability studies. These studies evaluate the systemic absorption of terbinafine topical spray in volunteers with normal skin and in subjects with tinea cruris. In addition the sponsor has provided an evaluation of the dermatopharmacokinetics of terbinafine from the spray and the marketed cream.

II. Recommendation

This NDA is more of a supplement than a full NDA. The majority of the "classical" pharmacokinetic studies were done with the oral tablet formulation of terbinafine. Given that the exposure to terbinafine from the tablet is almost 1000x that available topically, this NDA concerns itself not with terbinafine pharmacokinetics per se, but with the comparability of the

spray dosage form to the marketed cream. Evaluation of the results of the in vivo pharmacokinetic trials submitted with this NDA indicate that the systemic absorption of terbinafine is uncalculatable being that plasma levels are either below or just at the limit of detection in all samples for parent and metabolite. Data from the 1% cream NDA indicate that it has a bioavailability of approximately 3.5%. The systemic bioavailability of the 1% spray is either equal to or lower than this. As to the dermal penetration, a comparative study of the dermatopharmacokinetics of both the spray and cream dosage forms indicates that the spray penetrates the stratum corneum as well as the cream. As the stratum corneum is the site of the infectious process this suggest and is borne out by clinical trials that the 1% spray should be at least as efficacious as the 1% cream. From a biopharmaceutics standpoint the sponsor has adequately investigated the in vivo pharmacokinetics of the 1% terbinafine spray dosage form.

INDEX

Appendix I-Studies

III. PK Studies Overview

As noted above, the sponsor has submitted the results of three in vivo pharmacokinetic studies. These studies evaluate the absorption of terbinafine from a 1% solution in both normal and fungally infected skin. In the development of this NDA the applicant evaluated two different delivery systems for this product, a spray and a dropper dosage form. The two studies (101 and 103) that dealt with systemic absorption used the dropper dosage form of the product. In study 307 the local absorption of terbinafine from both delivery systems was evaluated. Given that terbinafine is highly lipid soluble, that both delivery systems used the same formulation of the product, and that degree of local absorption was similar this should have no impact on the approvability of the 1% spray dosage form.

Formulation

The formulation detailed below is identical to that used in clinical trials protion of this NDA and in both the dropper and spray versions of the 1% solution. No other "investigational" formulations were utilized. This formulation is identical to the to-be-marketed dosage form.

Ingredient*	Amount	Function
Terbinafine HCl	0.01g	active ingredient
Cetomacrogol 1000**	g	surfactant
Propylene Glycol	g	solvent
Ethanol (96%)	g	solvent, preservative
Water (purified)		solvent
Total	1	

IV. Analytical Methods

Accuracy

The accuracy of the study was based on back calculation of the standard concentrations used to construct the daily standard curves for both parent and metabolite. Over the range of concentrations tested ıg/ml) the assay demonstrated acceptable accuracy.

Terbinafine		Metabolite	
Target(ng/ml)	Observed (CV%)	Target(ng/ml)	Observed (CV%)
0	-0.02	0	-0.07
1378.98	1349.89(0.8%)	1444.77	1413.05(3.7%)
478.8	492.2(7.3%)	501.68	523.6(6.8%)
26.84	27.76(5.5%)	28.1	28.51(7.2%)

Reproducibility

Likewise for reproducibility, a series of standard concentrations were interspersed randomly throughout the mass of plasma samples to be run. Duplicate samples were included at both at the start of and at the end of the daily sample run for both parent and metabolite. Reproduced below are the results of the analysis of these quality control samples:

Terbinafine		Metabolite	
Target(ng/ml)	Observed (CV%)	Target(ng/ml)	Observed (CV%)
830.06	827.98(1%)	861.08	863.59(1%)
207.54	218.73(6.1%)	215.27	226.56(7.3%)
20.71	20.36(5.8%)	21.56	20.76(5.4%)
8.27	7.91(9.9%)	8.57	7.69(7.9%)

Examination of this data suggests that the assay was reproducible from an intra-day standpoint.

Sensitivity

The limit of quantification was defined by the applicant as the lowest concentration on the standard curve or quality control sample for which the accuracy or bias estimate and the precision were below 20%. For this study that value was set at 8ng/ml for both parent and metabolite as this was the lowest quality control sample that was utilized in this study.

Analytical Summary

The analytical methods utilized by the sponsor were adequately validated and well reported. While this synopsis dealt with the results of trial SFF-101-E-00, a similarly detailed analytical validation report was submitted for each study in the NDA. At the bottom of each of the study summary sheets in Appendix I is summary information on the assay performance in the individual trials.

V. Summary of In Vivo Pharmacokinetic Trials

SFF-101-E-00 Bioavailability in Normal Skin

This study was an investigation of the dermal absorption of terbinafine solution following application to normal skin on their inner thigh. A total of 11 normal subjects (3M/8F) were enrolled and completed all phases of the trial. Upon enrollment into the trial a rectangular area of 150cm^2 was marked off on each subjects inner thigh with an indelible marker. Each subject was instructed to apply 3ml of 1% terbinafine solution to this area once daily in the morning for seven days. During this period of time three 8ml blood samples were collected at baseline (prior to dosing on day 1), immediately before the last dose and two hours following the last dose. Attached in Appendix I (page 2) is study summary sheet that contains detailed information on the subject demographics and study prodcedures.

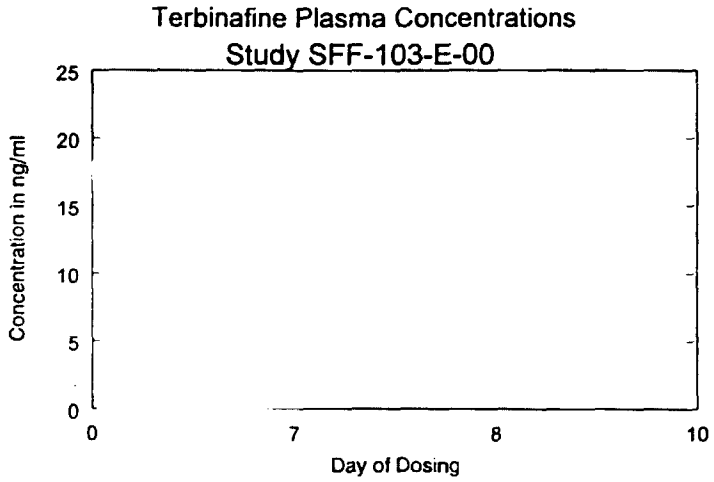
At the conclusion of this trial the 33 plasma samples were analyzed for both parent and metabolite according to the previously described analytical method. No plasma levels were above the limit of quantification (8ng/ml) for either parent or metabolite.

The results of this study suggest that terbinafine is poorly absorbed into the systemic circulation following application to intact normal skin.

SFF-103-E-00 Bioavailabilitiy in Subjects with Tinea Cruris

Unlike the previous study, this study was done in subjects suffering from tinea cruris. A total of 10 subjects (all male) were enrolled in the trial and all subjects completed all phases of the trial. Upon enrollment each subject was instructed to apply sufficient 1% solution to cover all of the affected lesions and a 1 inch border of normal skin once daily in the morning. Each subject was given six bottles of drug such that they would use one bottle for one dose only. In doing so the applicant was able to calculate the individual doses administered to each subject. On average the affected area treated in this study was 59cm^2 (range cm^2). This resulted in an average daily dose of 13.2mg of terbinafine. During this trial 8ml blood samples were collected at baseline (prior to dosing on day 1), immediately before the last dose and two hours following the last dose. Attached in Appendix I (page3-5) are the study summary sheet and supportive data describing the results of this trial.

After 8 days of dosing most of the observed plasma concentrations were either at or below the limit of detection of parent drug and the plasma (see below).



The results of this study gives us some idea of the steady-state plasma levels associated with this formulation of terbinafine. To put these levels in perspective, a single dose of the 250mg oral tablet of terbinafine in NDA 20-539 gave peak plasma levels of 1,796ng/ml (Study SFP-101). In a study with the 1% cream formulation (NDA 20-192) patients suffering from P. versicolor had peak plasma levels of 6ng/ml. While the levels seen here are somehat higher than those observed with the 1% cream, it should be noted that in the 1% cream study no attempt was made to determine the individual dose administered. In addition the data from this study is somewhat limited in that the day 7 data represents a trough level and the day 8 data as two hours after application. At best this study indicates that the systemic absorption of the 1% solution is approximately the same as that following the 1% topical cream and that both topical dosage forms produce steady-state plasma levels that are greatly inferior to those from the oral dosage form.

SFF-307-E-00 Dermatopharmacokinetics of 1% Cream and 1% Spray

Because of the low systemic plasma levels produced by either the cream or spray dosage forms the applicant undertook an evaulation of the uptake of terbinafine into the stratum corneum. The study was done using a rathter complicated study design consisting of six parallel treatment arms (see below):

Trt. Arm	Dosage Form	Dose	Duration
A-1	Dropper	0.5gm	1 day
A-2	Dropper	0.5gm	7 days
B-1	Spray	0.5gm	1 day
B-2	Spray	0.5gm	7 days
C-1	Cream	0.5gm	1 day
C-2	Cream	0.5gm	7 days

Each treatment arm consisted of 3 males and 3 females for a total of 36 subjects. Two subjects dropped out of the trial and were replaced. Attached in Appendix I (pages 6-15) is the Study Summary Sheet and supporting demographic and in vivo data from this trial.

The dermatopharmcokinetics of this product were obtained via a skin stripping technique. This technique was done following application of the various treatments to a proscribed area on the back of ~190cm^2. The material was allowed to dry (15min for spray and dropper, 30min for the cream) prior to stripping. Skin stripping was accomplished by applying ul of adhesive to a glass microscope slide. The slide plus adhesive side was then applied to the skin surface and allowed to set for 20-30 sec. On removal of the slide from the skin surface, a layer of stratum corneum 3-4 cell layers thick adhered to the slide. This procedure was repeated five times at each study site to fully remove the stratum corneum. This removal procedure was conducted at time zero, and 4, 8, 12, 24, 48, 72, 96 and 168hrs at a different site for each sample time. In order to standardize the procedure, all samples were obtained by the same person. Once obtained the slides were labeled and frozen at -20C until ready for analysis. Attached as pages 7-13 are the individual study treatment results, reproduced below is a summary table of results for Total extracted drug (skin levels 1-5):

Trt. Arm	Dosage Form	Duration	AUC0-t	Cmax	Half-life
A-1	Dropper	1 day	7627 (12%)	687 (8%)	15.63 (16%)
A-2	Dropper	7 days	10437 (14%)	848 (9%)	24.79 (18%)
Ratio Day 7/Day 1			1.37	1.23	1.59
B-1	Spray	1 day	7721 (9%)	692 (8%)	14.19 (12%)
B-2	Spray	7 days	9054 (23%)	780 (17%)	19.92 (38%)
Ratio Day 7/Day 1			1.17	1.13	1.41
C-1	Cream	1 day	8469 (16%)	780 (16%)	20.05(49%)
C-2	Cream	7 days	9650 (25%)	805 (15%)	17.6 (29%)
Ratio Day 7/Day 1			1.14	1.03	0.88

Although a bioequivalency determination was not done on this data, it is clear from examination of the raw data and plots that the spray and cream dosage forms are very similar in their penetration of dermal tissues. The dropper dosage form (not being pursued at this time) does seem to deliver more drug to the tissues than the spray or cream dosage forms. While no clear explanation is readily available for this difference it should be noted that the spray and dropper dosage forms use the same formulation of terbinafine solution (thereby ruling out formulation effects). In addition, as the dropper dosage form was used in studies SFF-101 and -103, the systemic exposure seen in those studies would be to the extreme side of those produced by the spray dosage form.

VI. Conclusions

As noted earlier in this review, this NDA is in reality a line extension of the Lamisil® product line. Terbinafine is currently avialable as an oral tablet and as a 1% cream. The solution dosage form is intended to provide consumers and practitioners another route of administration for patient convenience. From a pharmacokinetic standpoint, terbinafine is poorly absorbed into the systemic circulation. The applicant has postulated in their NDA that the high lipid solubility of terbinafine has the net result of localizing it in the dermal tissues, rather than being taken up into the systemic circulation. From a pharmacokinetic standpoint the applicant has demonstrated that systemic absorption is increased in diseased skin, and that the resulting plasma levels are markedly inferior to the oral product. In relation to the topical cream, terbinafine solution as a spray appears to taken up to the same extent as the cream in all layers of the stratum corneum. While a bioequivalency determination was not done (nor would it be appropriate) the steady-state bioavailability in the stratum corneum for the 1% spray was 94% (based on day 7 AUC values). Given that more detailed pharmacokinetics have been done with the approved oral tablet and given that the plasma and stratum corneum levels of the product are similar to the approved cream, no additional pharmacokinetic information is required for approval.

9/18/97

E. Dennis Bashaw, Pharm.D.
Senior Pharmacokineticist (HFD-550)
Division of Pharmaceutical Evaluation-III

Secondary Review, John Lazor, Pharm.D. 9/22/97

CC: NDA 20-749 (ORIG),
HFD-540/DIV File
HFD-540/CSO/Cross
HFD-880(Bashaw)
HFD-880(Lazor)
CDR. ATTN: B. Murphy
HFD-344(Viswanathan)

Appendix I-Studies

NDA/IND# 20-749 Suppl/Amend.# Orig. Submission Date: 10/18/96 Volume: 1.7

Study Type: Bioavailability Study # SFF-101-E-00

Study Title: Plasma Concentrations of Terbinafine Following 1% Topical Solution for 7 Days

Clinical Investigator

Site

Analytical Investigator

Site

Single Dose: ___ Multiple Dose: Y Washout Period: N

Cross-Over ___ Parallel ___ Other Design: Single Treatment

Fasted N/A Food Study N FDA High Fat Breakfast ___

If fasted, how long (hrs.)? ___

Subject Breakdown

Normal XX Patients ___ Young XX Elderly ___ Renal ___ Hepatic ___

	Subject Type	Males		Group	All	N=	11	M=	3	F= 8
Weight	Mean 76.5	Range	kg.	Group		N=		M=		F=
Age	Mean 35	Range	yrs.	Group		N=		M=		F=
	Subject Type	Females		Group		N=		M=		F=
Weight	Mean 55.7	Range	kg	Group		N=		M=		F=
Age	Mean 30.6	Range	yrs.	Group		N=		M=		F=

Treatment Group	Dose	Dosage Form	Strength	Lot#	Lot Size
All Subjects	3ml	Topical Solution	1%	Y608-0492	

Sampling Times

Plasma 8ml, at baseline (before first application), immediately before and 2 hrs after last application

Urine N/A

Feces N/A

Assay Method:

Assay Sensitivity 8ng/ml limit of quantification

Assay Accuracy Target|Obs.|%CV;830|827|1%;207.5|218.7|6.1%;20.7|20.4|5.8%;8.3|7.9|9.9%

Labeling Claims From Study: Following seven days of topical application of 3ml of 1% topical solution to normal skin on the inner thigh, no detectable levels of terbinafine or its primary metabolite were detected in plasma.

NDA/IND# 20-749 Suppl/Amend.# Orig. Submission Date: 10/18/96 Volume: 1.7

Study Type: Bioavailability Study # SFF-103-E-00

Study Title: Plasma Concentrations of Terbinafine Following 1% Topical Solution for 7 Days in Tinea Cruris

Clinical Investigator

Site

Analytical Investigator

Site

Single Dose: ___ Multiple Dose: Y Washout Period: N

Cross-Over ___ Parallel ___ Other Design: Single Treatment

Fasted n/a Food Study ___ FDA High Fat Breakfast ___

If fasted, how long (hrs.)? ___

Subject Breakdown

Normal XX Patients ___ Young XX Elderly XX Renal ___ Hepatic ___

	Subject Type	Males		Group	All	N=	10	M=	10	F=
Weight	Mean 76.3	Range kg		Group		N=		M=		F=
Age	Mean 37.9	Range yrs.		Group		N=		M=		F=
	Subject Type			Group		N=		M=		F=
Weight	Mean	Range		Group		N=		M=		F=
Age	Mean	Range		Group		N=		M=		F=

Treatment Group	Dose	Dosage Form	Strength	Lot#	Lot Size
All Subjects	Varies	Topical Solution	1%	Y608-0492	

Sampling Times

Plasma 8ml, at baseline (before first application), immediately before and 2 hrs after last application

Urine N/A

Feces N/A

Assay Method:

Assay Sensitivity (Limit of Quantification) Parent 4.8ng/ml, Metabolite 5.1ng/ml

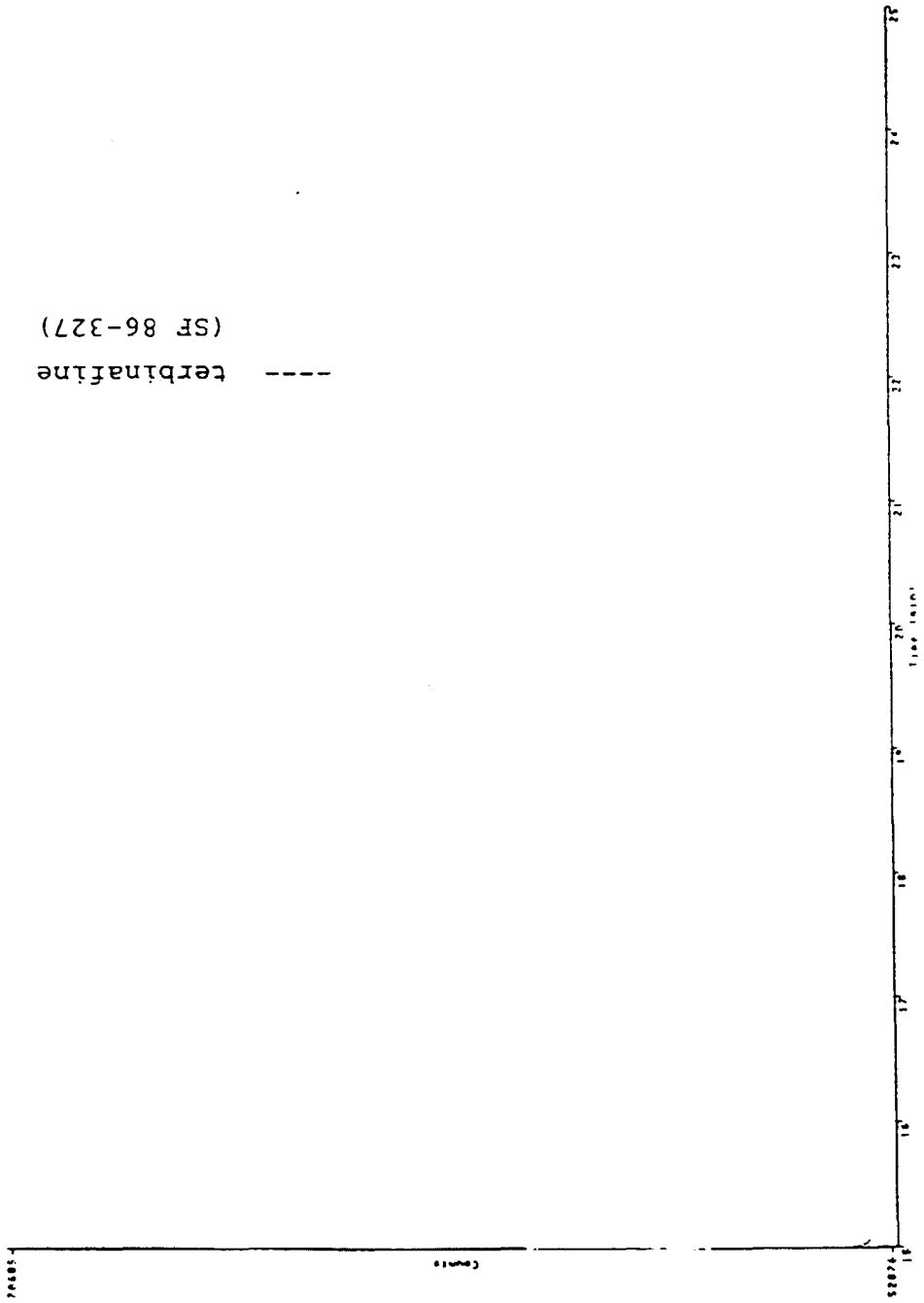
Assay Accuracy Target|Obs.|%CV;111.9|102.5|3.8%;27.3|26.5|1.3%;3.24|3.51|11.6%;1.4|1.14|47.8%

Labeling Claims From Study: A total of 10 subjects were enrolled in this study. They were infected with T. rubrum (6), T. mentagrophytes (2) and E. floccosum (2). Following seven days of once daily administration to the affected areas a clinical cure (negative signs, symptoms, and culture) was observed in all 10 patients. Plasma levels for terbinafine and metabolite were at the limit of detection.

CHROM 1

Typical chromatograms for the determination of terbinafine (SF 86-327) and metabolite 86-621 in human plasma

A Subject day 0 (patient's blank)
B Subject day 7
C Calibration standard (C-00), blank



Individual plasma concentrations of terbinafine (SF 86-327)
Project: SDZ 86-327 Study: SFF 103

Time [day]->	0.0	7.0	8.0
Subjects			
V			

* concentration below limit of quantification ng/mL)

Individual plasma concentrations of metabolite 86-621
Project: SDZ 86-327 Study: SFF 103

Time [days]->	0.0	7.0	8.0
Subjects			
V			

* concentration below limit of quantification ng/mL)

NDA/IND# 20-749 Suppl/Amend.# Orig. Submission Date: 10/18/97 Volume: 1.8

Study Type: Bioavilability Study # SFF-307-E-00

Study Title: Bioavailability Comparison of Terbinafine From Two Topical Delivery Devices and Cream.

Clinical Investigator _____ Analytical Investigator _____

Site _____ Site _____

_____ _____

_____ _____

Single Dose: ___ Multiple Dose: Y Washout Period: N _____

Cross-Over ___ Parallel Y Other Design: _____

Fasted n/a Food Study ___ FDA High Fat Breakfast ___

If fasted, how long (hrs.)? ___

Subject Breakdown

Normal XX Patients ___ Young XX Elderly ___ Renal ___ Hepatic ___

See Attachment for detailed breakdown of subject demographics

Treatment Group	Dose	Dosage Form	Strength	Lot#	Lot Size
Cream	0.5gm	Cream	1%	Y6130594	
Spray	~0.5gm*	Solution Spray	1%	Z0250992	
Dropper	~0.5gm*	Solution Dropper	1%	Y6140594	

*dose equal to 0.5ml=0.4845gm using a density of 0.969gm/ml (dosed as 20-22 drops or 5-6sprays)

Note: This study was designed as a six group study in 36 patients. Each group consisted to six subjects (3M/3F). The groups were further divided by dosage form, with two groups (12 subjects) each receiving one of the three treatments. Within the three treatments one group received a single application to two areas on the back (each measuring 3x5in.) while the other group received a single daily dose for seven days.

Skin Sampling Times

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

Day 3&5 prior to dosing on days 3 and 5

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

Assay Method: _____

Assay Sensitivity (Limit of Quantification) 7.3ng/ssb

Assay Accuracy Target|Obs.|%CV;3000|3503| 8.8%; 2500|2534|2.9%; 2000|1925|8.4%; 1000|1121.5|6.9%; 250|256.9|9.4%; 12.5|12.55|6.1%;

Labeling Claims From Study Stratum Corneum concentrations increased from day 1 to day 7. The increase was similar among the treatment groups and no significant differences were noted between the treatments.

Table 2.1
Summary of Baseline Demographics
(Population: Randomised Subjects)

		Treatment Group					
		Lamisil Solution Dropper		Lamisil Solution Spray		Lamisil Cream	
		One Day (N=6)	Seven Days (N=6)	One Day (N=7)	Seven Days (N=7)	One Day (N=6)	Seven Days (N=6)
Age (years)	N	6	6	7	7	6	6
	Mean	32.3	34.8	31.0	31.6	35.2	32.7
	Median	27.0	35.0	28.0	23.0	37.0	32.5
	s.d.	16.18	12.32	9.76	12.46	5.38	8.14
	Minimum	19	22	22	20	28	24
	Maximum	59	48	46	48	41	42
Sex	Male	3 (50.0%)	3 (50.0%)	3 (42.9%)	3 (42.9%)	3 (50.0%)	3 (50.0%)
	Female	3 (50.0%)	3 (50.0%)	4 (57.1%)	4 (57.1%)	3 (50.0%)	3 (50.0%)
Race	Caucasian	6 (100.0%)	6 (100.0%)	6 (85.7%)	7 (100.0%)	6 (100.0%)	6 (100.0%)
	Black	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Height (cm)	N	6	6	7	7	6	6
	Mean	170.7	171.0	166.6	174.1	172.8	169.5
	Median	171.5	170.0	155.0	175.0	175.5	175.0
	s.d.	9.48	14.03	15.25	12.56	7.11	15.18
	Minimum	155	157	155	158	160	149
	Maximum	183	190	190	193	178	183
Weight (kg)	N	6	6	7	7	6	6
	Mean	68.67	68.83	74.50	69.36	66.00	63.33
	Median	71.50	72.50	69.00	66.00	64.00	66.00
	s.d.	11.255	15.303	9.206	12.944	6.197	11.112
	Minimum	49.0	48.0	64.0	49.0	58.0	49.0
	Maximum	79.0	85.0	85.0	83.5	76.0	76.0

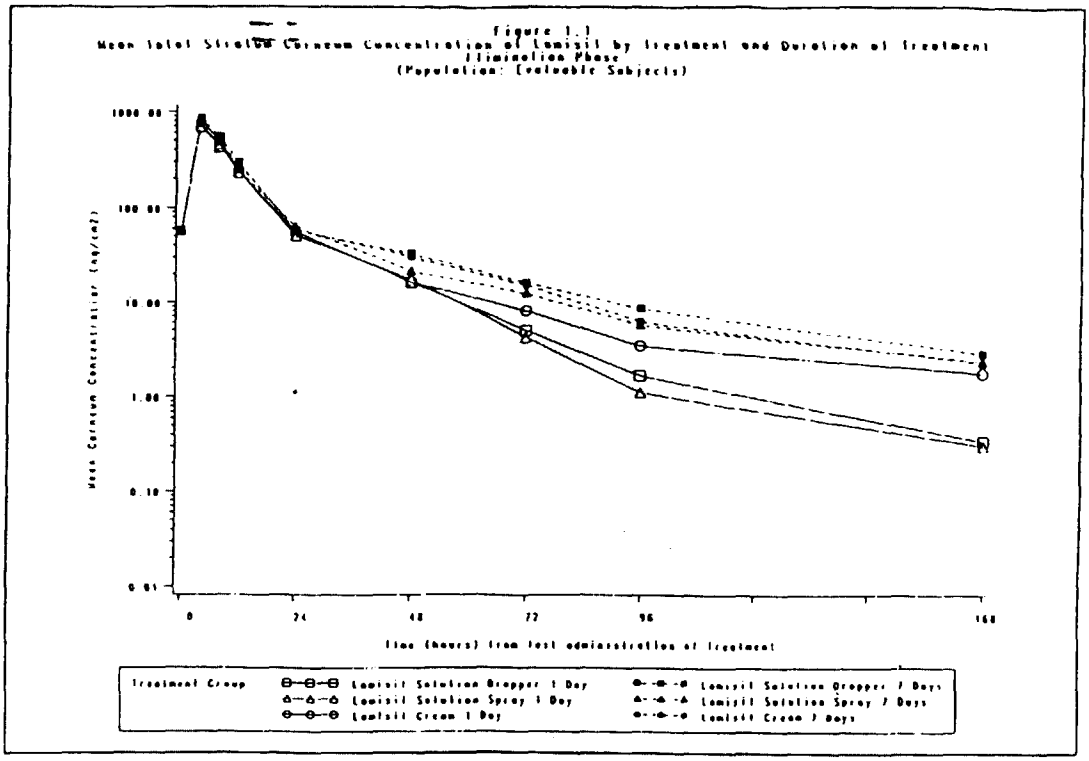


Table 3.1.1.1
Summary of Total Stratum Corneum Concentrations (ng/cm2)
(One Day Treatment Duration)
(Population: Evaluable Subjects)

		Time (hrs)								
		0	4	8	12	24	48	72	96	168
Lamisil Solution Dropper (N=6)	N	6	6	6	6	6	6	6	6	6
	Mean	0.000	686.992	422.060	226.300	54.950	14.012	1.603	0.365	0.000
	Median	0.000	682.475	443.585	245.325	56.965	12.265	0.000	0.000	0.000
	s.d.	0.0000	52.0667	77.5962	50.1691	12.7161	8.2398	2.5570	0.8941	0.0000
	Minimum									
	Maximum									
Lamisil Solution spray (N=6)	N	6	6	6	6	6	6	6	6	6
	Mean	0.000	692.088	448.490	227.637	50.132	15.280	2.888	0.000	0.000
	Median	0.000	671.085	420.090	233.140	55.600	11.290	2.145	0.000	0.000
	s.d.	0.0000	56.4852	60.9523	54.1746	13.8376	10.8284	3.3242	0.0000	0.0000
	Minimum									
	Maximum									
Lamisil Cream (N=6)	N	6	6	6	6	6	6	6	6	6
	Mean	0.000	780.045	503.603	227.573	54.510	14.455	5.177	0.947	0.460
	Median	0.000	754.535	477.515	226.940	54.735	16.375	5.550	0.000	0.000
	s.d.	0.0000	127.4180	85.3947	46.1381	12.2229	6.9668	4.8903	1.5087	1.1268
	Minimum									
	Maximum									

Summary of Total Stratum Corneum Concentrations (ng/cm2)
(Seven Days Treatment Duration)
(Population: Evaluable Subjects)

		Time (hrs)											
		-144	-96	-48	0	4	8	12	24	48	72	96	168
Lamisil Solution Dropper (N=6)	N	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	0.000	40.898	49.513	58.212	848.307	539.298	290.345	56.257	31.913	14.485	6.427	0.363
	Median	0.000	39.740	49.785	55.870	827.050	534.460	312.815	57.060	35.640	17.050	7.375	0.000
	s.d.	0.0000	8.6917	6.6707	10.1169	79.6556	74.5125	54.6062	10.6570	10.6626	7.3175	3.9558	0.8900
	Minimum												
	Maximum												
Lamisil Solution spray (N=6)	N	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	0.000	46.505	52.030	55.538	780.873	470.157	240.232	62.422	20.642	9.652	3.473	0.000
	Median	0.000	45.480	50.625	55.565	812.675	469.435	243.315	57.960	21.210	10.150	2.375	0.000
	s.d.	0.0000	5.9307	4.4594	5.5209	131.5753	75.4231	69.3444	25.2454	9.2879	7.2773	3.6975	0.0000
	Minimum												
	Maximum												
Lamisil Cream (N=6)	N	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	0.000	45.488	51.687	54.092	805.417	475.848	272.782	58.193	29.627	13.068	3.383	0.000
	Median	0.000	43.300	51.920	51.250	806.450	454.190	261.030	54.740	31.810	14.210	2.345	0.000
	s.d.	0.0000	6.3645	8.7016	8.8731	118.6961	127.4865	98.7252	16.1283	9.1213	8.1350	3.8674	0.0000
	Minimum												
	Maximum												

Note:

1) 0 hrs corresponds to the time of the skin sample taken immediately prior to the last application of study medication.

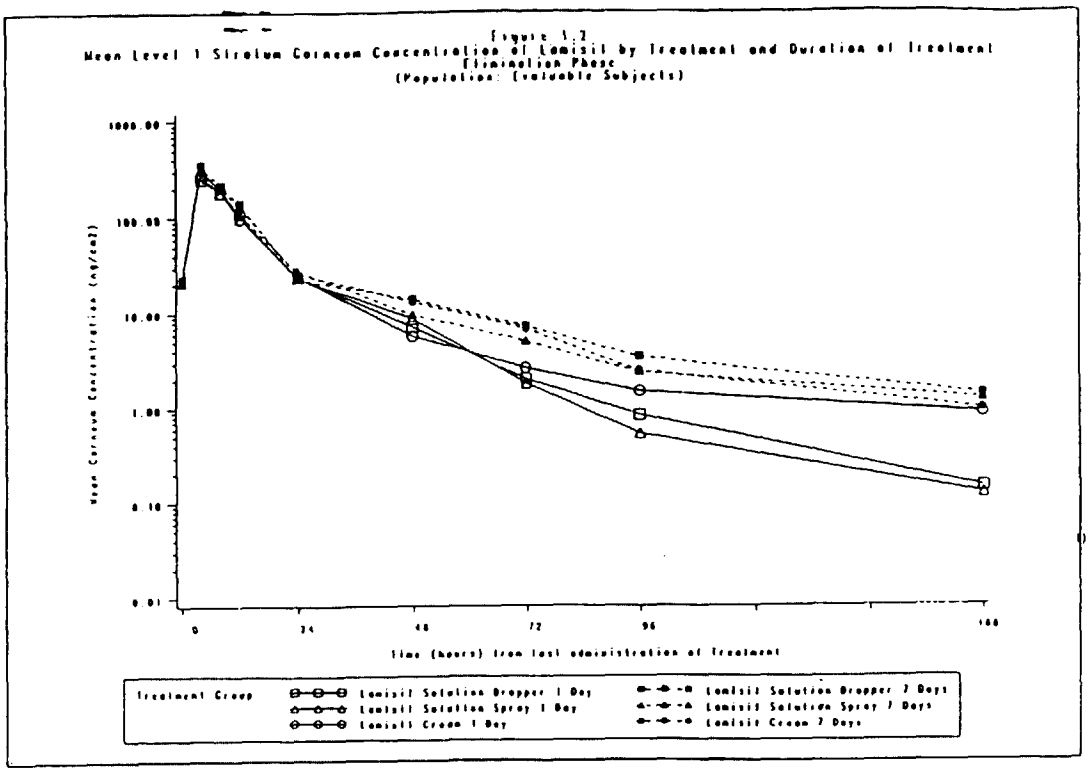


Table 3.2.1.1
Summary of Level 1 Stratum Corneum Concentrations (ng/cm2)
(One Day Treatment Duration)
(Population: Evaluable Subjects)

		Time (hrs)								
		0	4	8	12	24	48	72	96	168
Lamisil Solution Dropper (N=6)	N	6	6	6	6	6	6	6	6	6
	Mean	0.000	265.038	178.625	98.602	23.405	7.065	1.215	0.365	0.000
	Median	0.000	264.905	182.750	103.180	21.590	6.155	0.000	0.000	0.000
	s.d.	0.0000	19.6167	30.0130	16.9842	7.0189	3.9265	1.8867	0.8941	0.0000
	Minimum									
	Maximum									
Lamisil Solution spray (N=6)	N	6	6	6	6	6	6	6	6	6
	Mean	0.000	246.528	181.348	97.925	23.133	8.630	1.475	0.000	0.000
	Median	0.000	247.100	176.275	94.610	22.890	6.670	1.140	0.000	0.000
	s.d.	0.0000	26.6103	22.0546	26.5886	3.2469	5.6062	1.6611	0.0000	0.0000
	Minimum									
	Maximum									
Lamisil Cream (N=6)	N	6	6	6	6	6	6	6	6	6
	Mean	0.000	286.320	198.417	95.145	23.523	5.643	2.425	0.947	0.460
	Median	0.000	289.685	198.800	93.935	23.455	5.850	3.115	0.000	0.000
	s.d.	0.0000	57.9081	24.4260	24.4087	6.0134	1.7618	1.9866	1.5087	1.1268
	Minimum									
	Maximum									

Summary of Level 1 Stratum Corneum Concentrations (ng/cm2)
(Seven Days Treatment Duration)
(Population: Evaluable Subjects)

		Time (hrs)											
		-144	-96	-48	0	4	8	12	24	48	72	96	168
Lamisil Solution Dropper (N=6)	N	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	0.000	16.948	19.535	22.857	348.890	213.542	137.528	22.272	13.775	6.897	3.397	0.363
	Median	0.000	17.320	19.685	22.760	341.895	215.125	148.205	22.570	14.180	7.680	3.715	0.000
	s.d.	0.0000	2.4624	0.8728	1.7382	41.1784	34.6005	37.8048	3.1712	5.5470	4.1621	2.1585	0.8900
	Minimum												
	Maximum												
Lamisil Solution spray	N	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	0.000	18.398	20.847	21.063	315.593	192.927	103.757	27.340	9.470	4.720	1.965	0.000
	Median	0.000	17.180	20.575	20.775	309.890	196.925	106.475	23.010	8.365	5.270	2.375	0.000
	s.d.	0.0000	3.6946	2.0364	1.3982	22.4414	25.5055	32.3279	15.1067	3.8749	2.9383	1.6247	0.0000
	Minimum												
	Maximum												
Lamisil Cream (N=6)	N	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	0.000	18.852	20.163	21.810	310.150	207.283	124.272	25.640	12.938	6.630	2.205	0.000
	Median	0.000	18.735	19.540	21.705	313.220	202.720	135.665	22.530	15.100	6.225	2.345	0.000
	s.d.	0.0000	1.7973	1.8002	1.0606	56.3364	51.0101	42.2166	11.1825	4.8759	3.8178	2.0399	0.0000
	Minimum												
	Maximum												

Note:

1) 0 hrs corresponds to the time of the skin sample taken immediately prior to the last application of study medication

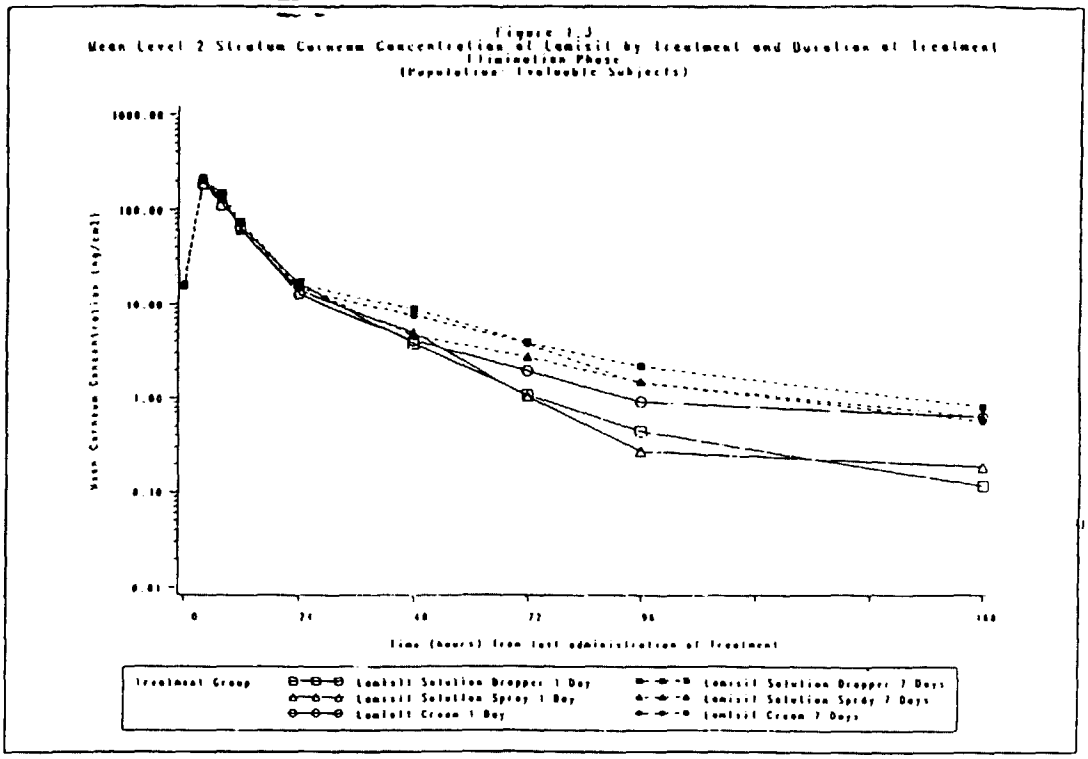


Table 3.3.1.1
Summary of Level 2 Stratum Corneum Concentrations (ng/cm2)
(One Day Treatment Duration)
(Population: Evaluable Subjects)

		Time (hrs)								
		0	4	8	12	24	48	72	96	168
Lamisil Solution Dropper (N=6)	N	6	6	6	6	6	6	6	6	6
	Mean	0.000	187.323	110.935	65.867	16.240	3.435	0.000	0.000	0.000
	Median	0.000	184.525	119.350	75.165	17.590	3.535	0.000	0.000	0.000
	s.d.	0.0000	16.9742	24.2342	18.1926	4.7945	2.0762	0.0000	0.0000	0.0000
	Minimum									
	Maximum									
Lamisil Solution spray (N=6)	N	6	6	6	6	6	6	6	6	6
	Mean	0.000	188.890	129.602	60.690	13.808	4.343	0.688	0.000	0.000
	Median	0.000	190.855	135.900	60.490	14.775	3.800	0.000	0.000	0.000
	s.d.	0.0000	20.8744	24.5888	23.2467	3.3100	4.9067	1.0664	0.0000	0.0000
	Minimum									
	Maximum									
Lamisil Cream (N=6)	N	6	6	6	6	6	6	6	6	6
	Mean	0.000	206.722	143.408	60.887	12.557	3.642	1.530	0.000	0.000
	Median	0.000	200.240	146.130	58.065	12.360	4.275	1.305	0.000	0.000
	s.d.	0.0000	20.1696	16.5421	11.8495	2.3602	2.1297	1.6949	0.0000	0.0000
	Minimum									
	Maximum									

Summary of Level 2 Stratum Corneum Concentrations (ng/cm2)
(Seven Days Treatment Duration)
(Population: Evaluable Subjects)

		Time (hrs)										
		-144	-96	-48	0	4	8	12	24	48	72	96	168
Lamisil Solution Dropper (N=6)	N	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	0.000	11.722	13.983	15.630	216.160	148.650	73.188	16.075	8.663	3.673	1.860	0.000
	Median	0.000	12.790	13.750	14.965	227.125	139.870	73.845	16.475	8.970	4.385	2.480	0.000
	s.d.	0.0000	3.1517	1.3779	3.5010	42.9952	30.9634	17.8358	2.4187	3.0733	1.8808	1.4673	0.0000
	Minimum												
	Maximum												
Lamisil Solution spray (N=6)	N	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	0.000	12.267	14.542	15.725	213.812	125.692	58.787	16.060	4.473	2.205	0.797	0.000
	Median	0.000	11.280	13.495	15.710	213.915	129.475	61.470	16.120	4.420	2.625	0.000	0.000
	s.d.	0.0000	2.0357	3.1535	3.3068	35.0494	16.3349	14.1590	4.7055	1.6532	1.9024	1.2562	0.0000
	Minimum												
	Maximum												
Lamisil Cream (N=6)	N	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	0.000	13.555	15.718	15.043	209.238	128.042	71.060	14.378	7.390	3.485	0.423	0.000
	Median	0.000	13.505	15.115	15.125	210.500	125.535	60.600	15.080	6.855	3.515	0.000	0.000
	s.d.	0.0000	1.8692	2.2511	2.1826	33.5082	30.8028	33.6062	2.1101	3.1143	2.2046	1.0370	0.0000
	Minimum												
	Maximum												

Note:

1) 0 hrs corresponds to the time of the skin sample taken immediately prior to the last application of study medication.

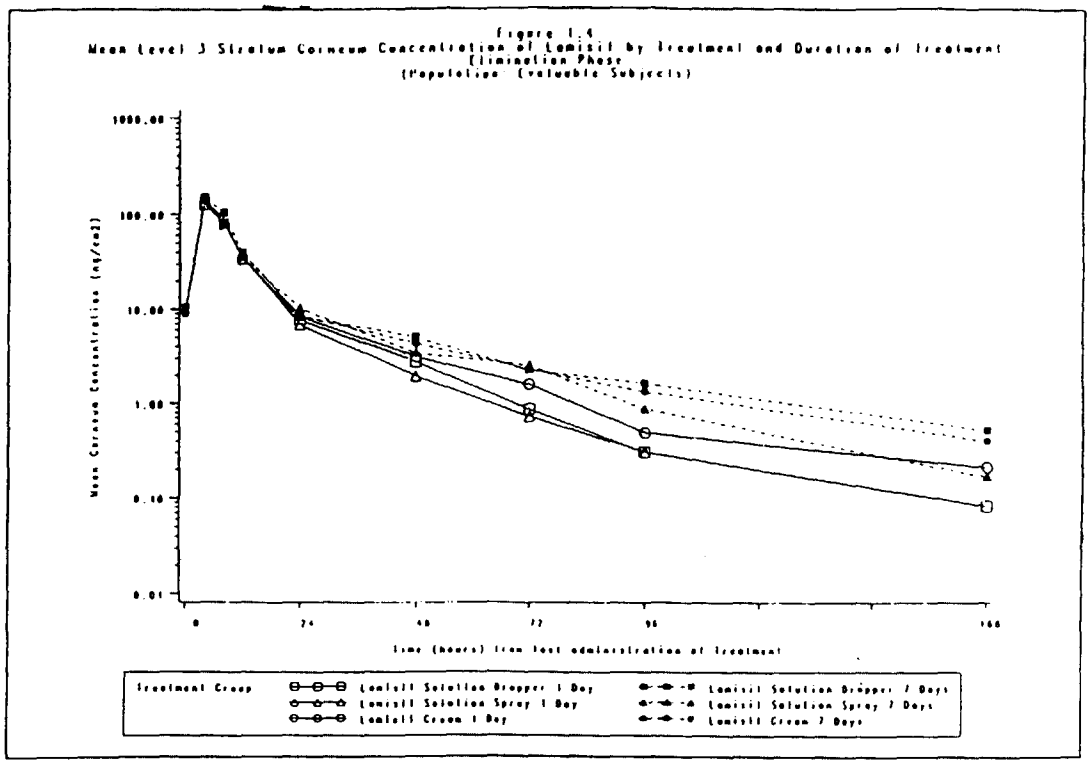


Table 3.4.1.1
Summary of Level 3 Stratum Corneum Concentrations (ng/cm2)
(One Day Treatment Duration)
(Population: Evaluable Subjects)

		Time (hrs)								
		0	4	8	12	24	48	72	96	168
Lamisil Solution Dropper (N=6)	N	6	6	6	6	6	6	6	6	6
	Mean	0.000	125.133	76.933	33.150	7.778	2.312	0.388	0.000	0.000
	Median	0.000	117.735	80.940	37.645	6.280	2.845	0.000	0.000	0.000
	s.d.	0.0000	18.5198	20.1639	11.7545	3.7392	1.8776	0.9512	0.0000	0.0000
	Minimum									
	Maximum									
Lamisil Solution spray (N=6)	N	6	6	6	6	6	6	6	6	6
	Mean	0.000	132.403	80.202	34.182	6.928	1.478	0.390	0.000	0.000
	Median	0.000	133.495	78.345	32.800	7.040	1.160	0.000	0.000	0.000
	s.d.	0.0000	15.9515	10.3257	5.2313	3.9087	1.7107	0.9553	0.0000	0.0000
	Minimum									
	Maximum									
Lamisil Cream (N=6)	N	6	6	6	6	6	6	6	6	6
	Mean	0.000	143.462	86.447	33.765	8.448	2.515	1.222	0.000	0.000
	Median	0.000	140.285	84.865	34.145	7.940	3.395	1.130	0.000	0.000
	s.d.	0.0000	21.7680	18.6283	7.2696	2.2505	2.0000	1.3431	0.0000	0.0000
	Minimum									
	Maximum									

Summary of Level 3 Stratum Corneum Concentrations (ng/cm2)
(Seven Days Treatment Duration)
(Population: Evaluable Subjects)

		Time (hrs)											
		-144	-96	-48	0	4	8	12	24	48	72	96	168
Lamisil Solution Dropper (N=6)	N	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	0.000	5.990	8.942	10.477	147.625	103.328	39.037	8.597	4.958	2.247	1.170	0.000
	Median	0.000	5.380	8.285	9.540	149.890	99.500	36.725	8.415	5.575	2.440	1.000	0.000
	s.d.	0.0000	1.5427	2.8557	3.7382	18.6028	23.4868	11.3411	3.2741	1.3194	1.2074	1.3150	0.0000
	Minimum												
	Maximum												
Lamisil Solution spray	N	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	0.000	7.540	8.975	10.020	140.697	80.382	34.758	10.425	3.253	1.965	0.363	0.000
	Median	0.000	7.590	9.360	9.595	147.775	86.520	37.600	10.830	3.925	1.705	0.000	0.000
	s.d.	0.0000	1.3604	1.0585	1.7259	31.4352	18.1986	14.9046	4.2721	1.6974	2.1766	0.8900	0.0000
	Minimum												
	Maximum												
Lamisil Cream (N=6)	N	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	0.000	6.357	8.480	8.838	146.957	79.103	38.702	8.678	4.290	1.533	0.755	0.000
	Median	0.000	5.910	8.605	7.555	151.515	77.665	32.080	7.905	3.925	1.310	0.000	0.000
	s.d.	0.0000	2.0629	3.0562	2.4470	25.0898	23.8717	15.6522	2.4404	1.6273	1.7393	1.1709	0.0000
	Minimum												
	Maximum												

Note:

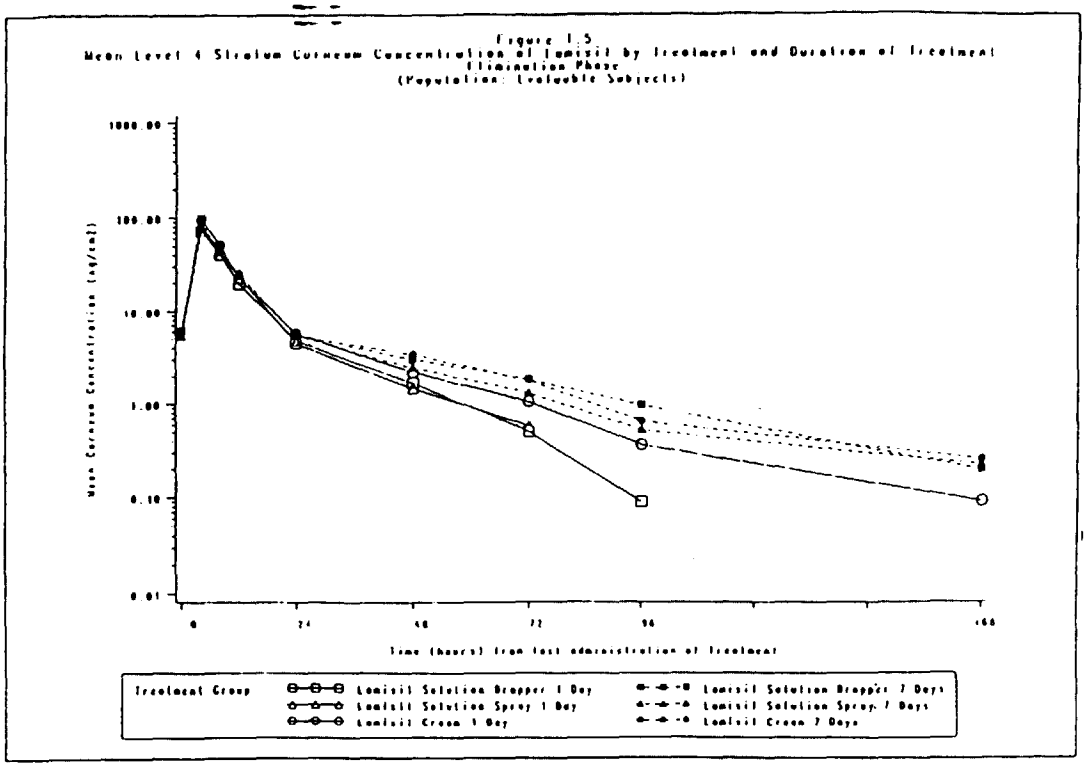


Table 3.5.1.1
Summary of Level 4 Stratum Corneum Concentrations (ng/cm2)
(One Day Treatment Duration)
(Population: Evaluable Subjects)

		Time (hrs)								
		0	4	8	12	24	48	72	96	168
Lamisil Solution Dropper (N=6)	N	6	6	6	6	6	6	6	6	6
	Mean	0.000	72.020	38.897	19.020	4.480	0.818	0.000	0.000	0.000
	Median	0.000	71.505	35.785	20.385	4.325	0.000	0.000	0.000	0.000
	s.d.	0.0000	7.0182	12.0448	9.2671	3.2273	1.2678	0.0000	0.0000	0.0000
	Minimum									
	Maximum									
Lamisil Solution spray (N=6)	N	6	6	6	6	6	6	6	6	6
	Mean	0.000	80.820	39.677	22.707	3.995	0.828	0.335	0.000	0.000
	Median	0.000	78.535	45.600	17.000	4.660	0.000	0.000	0.000	0.000
	s.d.	0.0000	13.5401	21.7213	13.2376	3.4358	1.2836	0.8206	0.0000	0.0000
	Minimum									
	Maximum									
Lamisil Cream (N=6)	N	6	6	6	6	6	6	6	6	6
	Mean	0.000	94.010	50.240	21.580	5.737	1.483	0.000	0.000	0.000
	Median	0.000	90.235	44.235	20.915	5.270	1.170	0.000	0.000	0.000
	s.d.	0.0000	25.5622	21.5026	8.5400	2.0852	1.6620	0.0000	0.0000	0.0000
	Minimum									
	Maximum									

Summary of Level 4 Stratum Corneum Concentrations (ng/cm2)
(Seven Days Treatment Duration)
(Population: Evaluable Subjects)

		Time (hrs)											
		-144	-96	-48	0	4	8	12	24	48	72	96	168
Lamisil Solution Dropper (N=6)	N	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	0.000	4.498	4.613	6.140	95.312	50.092	23.953	5.550	2.770	0.985	0.000	0.000
	Median	0.000	4.570	3.900	5.785	89.270	46.805	23.935	5.225	3.065	0.000	0.000	0.000
	s.d.	0.0000	1.3187	1.6960	2.2886	19.6829	15.3961	6.6124	1.8914	1.5512	1.5309	0.0000	0.0000
	Minimum												
	Maximum												
Lamisil Solution spray (N=6)	N	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	0.000	5.022	5.053	5.347	74.037	45.472	24.928	5.452	2.122	0.762	0.000	0.000
	Median	0.000	4.885	4.915	5.345	79.195	42.780	25.295	5.495	2.600	0.000	0.000	0.000
	s.d.	0.0000	1.1245	0.9213	1.0884	17.7259	21.7525	14.1500	2.2558	1.7828	1.1800	0.0000	0.0000
	Minimum												
	Maximum												
Lamisil Cream (N=6)	N	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	0.000	4.773	5.113	5.743	89.750	41.870	21.528	5.402	3.385	0.973	0.000	0.000
	Median	0.000	4.065	4.270	4.880	86.950	37.065	20.785	5.360	3.180	0.000	0.000	0.000
	s.d.	0.0000	2.2198	2.0392	2.4757	21.8718	19.5150	8.9446	0.6946	0.7180	1.5433	0.0000	0.0000
	Minimum												
	Maximum												

Note:

1. 0 hrs corresponds to the time of the skin sample taken immediately prior to the last application of study medication.

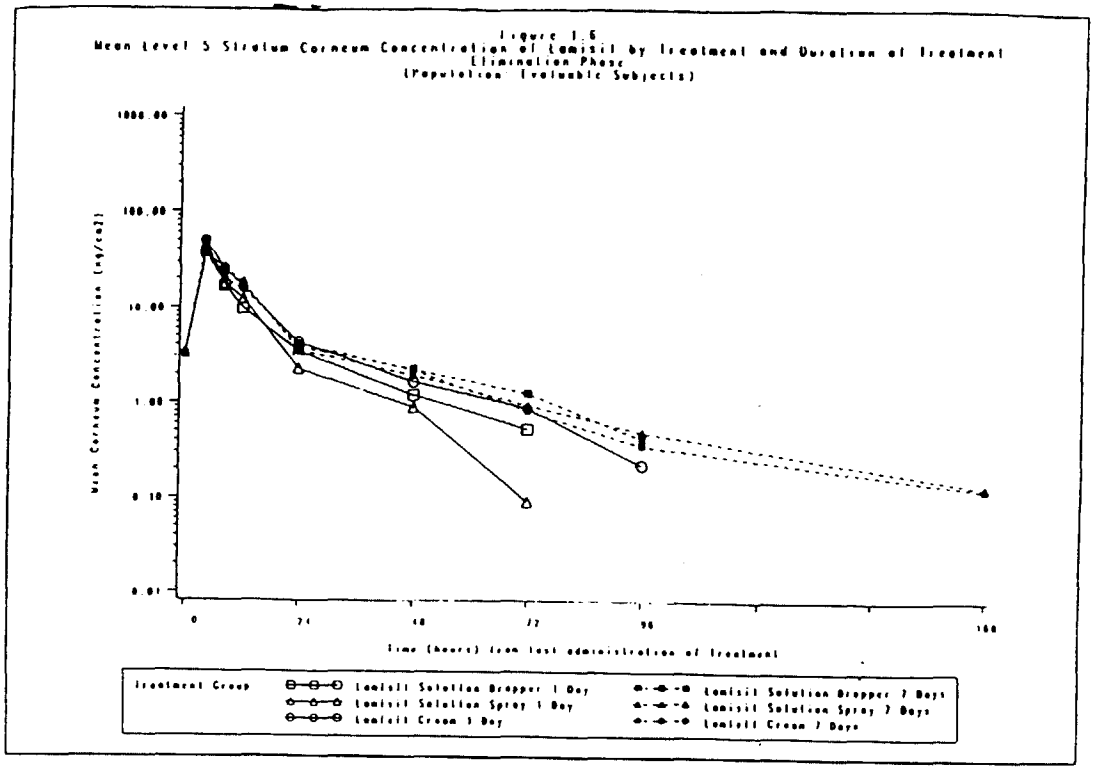


Table 3.6.1.1
Summary of Level 5 Stratum Corneum Concentrations (ng/cm2)
(One Day Treatment Duration)
(Population: Evaluable Subjects)

		Time (hrs)								
		0	4	8	12	24	48	72	96	168
Lamisil Solution Dropper (N=6)	N	6	6	6	6	6	6	6	6	6
	Mean	0.000	37.577	16.670	9.662	3.047	0.382	0.000	0.000	0.000
	Median	0.000	38.225	13.975	9.560	2.960	0.000	0.000	0.000	0.000
	s.d.	0.0000	8.6650	8.9470	5.7864	3.0421	0.9349	0.0000	0.0000	0.0000
	Minimum									
	Maximum									
Lamisil Solution spray (N=6)	N	6	6	6	6	6	6	6	6	6
	Mean	0.000	43.447	17.662	12.133	2.267	0.000	0.000	0.000	0.000
	Median	0.000	43.500	14.685	10.625	2.430	0.000	0.000	0.000	0.000
	s.d.	0.0000	14.1817	12.4316	6.1783	2.1435	0.0000	0.0000	0.0000	0.0000
	Minimum									
	Maximum									
Lamisil Cream (N=6)	N	6	6	6	6	6	6	6	6	6
	Mean	0.000	49.532	25.092	16.197	4.245	1.172	0.000	0.000	0.000
	Median	0.000	48.255	18.605	14.795	4.060	1.085	0.000	0.000	0.000
	s.d.	0.0000	13.0370	17.7675	7.3138	1.3333	1.2880	0.0000	0.0000	0.0000
	Minimum									
	Maximum									

Summary of Level 5 Stratum Corneum Concentrations (ng/cm2)
(Seven Days Treatment Duration)
(Population: Evaluable Subjects)

		Time (hrs)											
		-144	-96	-48	0	4	8	12	24	48	72	96	168
Lamisil Solution Dropper (N=6)	N	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	0.000	1.740	2.440	3.108	40.320	23.687	16.638	3.763	1.747	0.683	0.000	0.000
	Median	0.000	1.140	2.320	2.555	38.380	23.015	14.385	3.370	2.455	0.000	0.000	0.000
	s.d.	0.0000	2.0328	1.4512	1.0890	9.4172	9.1337	4.5560	1.1893	1.3681	1.0591	0.0000	0.0000
	Minimum												
	Maximum												
Lamisil Solution spray	N	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	0.000	3.278	2.613	3.383	36.735	25.685	18.002	3.145	1.323	0.000	0.348	0.000
	Median	0.000	3.060	3.005	3.275	37.100	20.795	18.370	3.525	1.170	0.000	0.000	0.000
	s.d.	0.0000	0.9819	1.3398	0.5438	17.0866	15.4779	9.1415	1.6560	1.4760	0.0000	0.8532	0.0000
	Minimum												
	Maximum												
Lamisil Cream (N=6)	N	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	0.000	1.952	2.212	2.657	49.322	19.550	15.220	4.095	1.623	0.447	0.000	0.000
	Median	0.000	2.510	2.400	2.545	47.535	15.735	13.120	4.160	2.120	0.000	0.000	0.000
	s.d.	0.0000	1.5941	2.1053	2.4449	17.9681	10.6464	7.3210	0.9598	1.3154	1.0941	0.0000	0.0000
	Minimum												
	Maximum												

Note:

TABLE 1

TOTAL STRATUM CORNEUM PHARMACOKINETIC PARAMETERS						
	Lamisil® Solution Dropper		Lamisil® Solution Spray		Lamisil® Cream	
	1 Day	7 Days	1 Day	7 Days	1 Day	7 Days
No. of Subjects	6	6	6	6	6	6
AUC_{0-t} (ng•hr/cm^2)						
mean	7,628	10,437	7,722	9,054	8,470	9,650
s.d.	941	1,465	680	2,116	1,389	2,363
C_{max} (ng/cm^2)						
mean	687	848	692	781	780	805
s.d.	52	80	56	132	127	119
$t_{½}$ (hrs)	n=2#	n=5	n=3#	n=5#	n=4#	n=6
mean	15.6	24.8	14.2	19.9	20.1	17.6
s.d.	2.5	4.4	1.8	7.6	9.9	5.1

#-Missing subjects had terbinafine levels detectable at <3 timepoints during the elimination phase.
Source: Appendix 1

TABLE 2

COMPARISON OF PHARMACOKINETIC PARAMETERS - P VALUES#			
	AUC_{0-t}	C_{max}	$t_{½}$
Lamisil® Solution Dropper vs. Cream			
1 day	0.345	0.124	0.424
7 days	0.377	0.446	0.073 (*)
Lamisil® Solution Spray vs. Cream			
1 day	0.426	0.147	0.235
7 days	0.542	0.652	0.547
Lamisil® Solution Dropper vs. Spray			
1 day	0.879	0.925	0.804
7 days	0.140	0.229	0.234
1 day vs. 7 days:			
Lamisil® Solution Dropper	0.005**	0.009**	0.096 (*)
Lamisil® Solution Spray	0.194	0.148	0.225 (*)
Lamisil® Cream	0.264	0.653	0.550

The p-values correspond to Student's t-test
*** $p<0.001$, ** $0.001 \le p < 0.01$, * $0.01 \le p \le 0.05$, (*) $0.05 \le p < 0.10$
Source: Appendix 1

	Treatment Group					
	Lamisil Solution Dropper		Lamisil Solution Spray		Lamisil Cream	
	One Day (N=6)	Seven Days (N=6)	One Day (N=6)	Seven Days (N=6)	One Day (N=6)	Seven Days (N=6)
N	6	6	6	6	6	6
Mean	7627.987	10437.343	7721.817	9054.400	8469.520	9650.057
Median	7956.670	11079.080	7514.720	9404.930	8521.050	9368.390
s.d.	940.5621	1465.4694	680.4030	2115.7949	1388.6896	2363.1862
Minimum						
Maximum						

Comparison		Geometric Mean Ratio	95% Confidence Interval	p-value	
Lamisil Solution Dropper vs. Cream:	1 day	0.91	(0.73, 1.12)	0.345	
	7 days	1.10	(0.89, 1.36)	0.377	
Lamisil Solution Spray vs. Cream:	1 day	0.92	(0.74, 1.14)	0.426	
	7 days	0.94	(0.76, 1.16)	0.542	
Lamisil Solution Dropper vs. Spray:	1 day	0.98	(0.80, 1.22)	0.879	
	7 days	1.17	(0.95, 1.45)	0.140	
1 day vs. 7 days:	Lamisil Solution Dropper	0.73	(0.59, 0.91)	0.005	**
	Lamisil Solution Spray	0.87	(0.70, 1.08)	0.194	
	Lamisil Cream	0.89	(0.72, 1.10)	0.264	

Table 3.1.2.2
Summary of Total-Stratum Corneum Pharmacokinetic Parameters: Cmax (nq/cm2)
(Population: Evaluable Subjects)

	Treatment Group					
	Lamisil Solution Dropper		Lamisil Solution Spray		Lamisil Cream	
	One Day (N=6)	Seven Days (N=6)	One Day (N=6)	Seven Days (N=6)	One Day (N=6)	Seven Days (N=6)
N	6	6	6	6	6	6
Mean	686.992	848.307	692.088	780.873	780.045	805.417
Median	682.475	827.050	671.085	812.675	754.535	806.450
s.d.	52.0667	79.6556	56.4852	131.5753	127.4180	118.6961
Minimum						
Maximum						

Comparison		Geometric Mean Ratio	95% Confidence Interval	p-value	
Lamisil Solution Dropper vs. Cream:	1 day	0.89	(0.76, 1.03)	0.124	
	7 days	1.06	(0.91, 1.23)	0.446	
Lamisil Solution Spray vs. Cream:	1 day	0.89	(0.77, 1.04)	0.147	
	7 days	0.97	(0.83, 1.13)	0.652	
Lamisil Solution Dropper vs. Spray:	1 day	0.99	(0.85, 1.16)	0.925	
	7 days	1.10	(0.94, 1.28)	0.229	
1 day vs. 7 days:	Lamisil Solution Dropper	0.81	(0.70, 0.94)	0.009	**
	Lamisil Solution Spray	0.89	(0.77, 1.04)	0.148	
	Lamisil Cream	0.97	(0.83, 1.13)	0.653	

Table 3.1.2.4
Summary of Total Stratum Corneum Pharmacokinetic Parameters: t1/2 (hrs)
Population: (Evaluable Subjects)

	Treatment Group					
	Lamisil Solution Dropper		Lamisil Solution Spray		Lamisil Cream	
	One Day (N=6)	Seven Days (N=6)	One Day (N=6)	Seven Days (N=6)	One Day (N=6)	Seven Days (N=6)
N	2	5	3	5	4	6
Mean	15.63	24.79	14.19	19.92	20.05	17.60
Median	15.63	25.42	13.50	18.61	17.23	17.69
s.d.	2.538	4.423	1.756	7.620	9.876	5.051
Minimum						
Maximum						

Comparison		Mean Difference	95% Confidence Interval	p-value	
Lamisil Solution Dropper vs. Cream:	1 day	-4.43	(-15.77, 6.91)	0.424	
	7 days	7.19	(-0.74, 15.11)	0.073	(*)
Lamisil Solution Spray vs. Cream:	1 day	-5.86	(-15.86, 4.13)	0.235	
	7 days	2.32	(-5.60, 10.25)	0.547	
Lamisil Solution Dropper vs. Spray:	1 day	1.43	(-10.52, 13.38)	0.804	
	7 days	4.86	(-3.42, 13.14)	0.234	
1 day vs. 7 days:	Lamisil Solution Dropper	-9.16	(-20.11, 1.79)	0.096	(*)
	Lamisil Solution Spray	-5.73	(-15.29, 3.83)	0.225	
	Lamisil Cream	2.46	(-5.99, 10.91)	0.550	

Note :

1) The p-values correspond to Student's t-test on t1/2 using the pooled estimate of residual variance from the analysis of variance of the six treatment groups. Flags on p-values indicate the following: *** for p<0.001, ** for 0.001<=p<0.01, * for 0.01<=p<0.05 and (*) for 0.05<=p<0.10.

2) n/a = Not applicable due to insufficient data.

Biopharmaceutic Comments 10/11/96

1.) At the present time the sponsor has not provided a pk comparison between the marketed Lamisil soln and the proposed Lamisil gel. Since Lamisil gel NDA contains its own safety and efficacy data, an assessment of bioequivalence is not required. Even so the sponsor must indicate in the label that the comparability of the dosage forms has not been demonstrated.

2.) As part of the biopharm package the sponsor provided the results of a pk trial in which the absorption of drug from Lamisil gel was compared to normal volunters. We need to have some assurance that the way in which it was studied is in general compliance with the proposed label.

Subject: Topical Antifungal Evaluation Groups (Revised)

Topical Antifungal Evaluation Groups

Intent to Treat - every subject who was dispensed a study treatment (active or vehicle).

Modified Intent to Treat - every subject in the ITT group who ADDITIONALLY had a positive dermatophyte mycology.

Safety Subset - every subject in the ITT group who had a post-baseline assessment.

MITT includes both subjects with and without a post-baseline assessment.
Safety Subset includes both subjects with and without a positive dermatophyte mycology.
The post-baseline assessment that defines, in part, the Safety Subset need not be an actual visit to the clinical study site. Correspondence and telephone calls may suffice.

We are interested in whether females handle the test drug differently than males in terms of both efficacy and safety. We use meta analysis procedures to combine the trials. From this, we calculate a 95% CI on the response rates for males and females separately. If these two CI's overlap, i.e., are not statistically differentiable, we conclude there is no evidence that a difference in efficacy exists. One can alternatively calculate a 95% CI on the difference between Response Rates. If this CI includes "0", we conclude there is no evidence of a difference in efficacy. Similarly, we compare AE's and safety data. The same approach applies to age as defined in the August 2, 1994 geriatric CFR.