CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-749

PHARMACOLOGY REVIEW(S)

FEB 1 8 1997

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

NDA 20-749 (Original Submission 10-18-1996)
Drug: LAMISIL^R (terbinafine hydrochloride) Solution, 1%

Sponsor: Sandoz Pharmaceuticals Corporation
59 Route 10
East Hanover, N.J. 07936-1080
Stephenie Barba (201-503-7548)

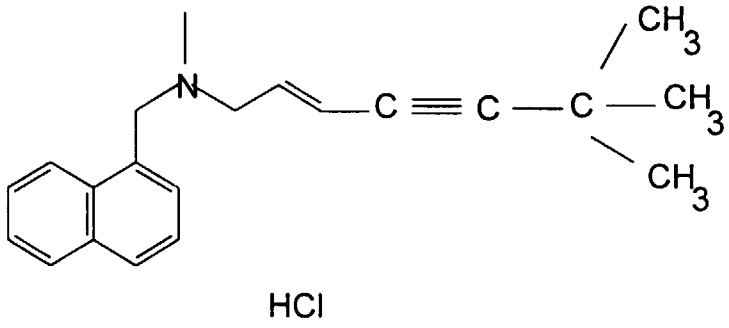
Number of Volumes: Four (4)
Date CDER Received: 10-18-1996
Date Assigned: 10-23-1996
Date Review Started: 01-06-1997
Date Review Completed: 02-05-1997

Dosage and Route of Administration: Topical, solution
Category: Antifungal
Indication: Treatment of tinea cruris, tinea corporis, and pityriasis versicolor

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:



Code Name: SF 86-327

COMPOSITION:

Names of ingredients	Function	Formula (g)
Terbinafine hydrochloride	Active compound	0.010
Cetomacrogol 1000*	Surfactant	
Propylene glycol	Solvent	
Ethanol (96%)	Solvent,preservative	
Purified water	Solvent	

* Equivalent to

Related Submissions: All submitted by Sandoz Pharmaceutical Corporation.

INDs

NDAs
20-192; Lamisil cream 1% (approved, 12-30-1992)
20-539; Lamisil tablets (approved, 05-10-1996)

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 as well as with the proposed 1% solution formulations. A large number of these studies were reviewed under several INDs and NDAs; the rest are reviewed here.

Index of Studies:

1. Therapeutic efficacy against dermatophytosis in guinea pigs.
2. Acute oral toxicity in mice and rats.
3. Primary skin irritation in rabbits.
4. Accumulated skin irritancy in rabbits.
5. Accumulated skin irritancy of deteriorated drug in rabbits.
6. Dermal sensitization in guinea pigs.
7. Primary ocular irritation in rabbits
8. Phototoxicity in guinea pigs.
9. Photosensitization in guinea pigs (I).
10 Photosensitization in guinea pigs (II).

GLP Compliance: Except for study #1, all other study reports included signed GLP statements.

Testing Facilities: The studies reviewed in this report were conducted at the following foreign facilities:

Sandoz Pharma. Basel, Switzerland (#2)

1. Therapeutic Efficacy of Topically Applied Formulations of Terbinafine Against Experimental Dermatophytosis in Guinea Pigs (103-560; June-July,1994)

Study objectives / Design: The efficacy of 1% topical terbinafine solution and two 1% terbinafine cream formulations (imported and domestically produced) in treating experimental dermatophytosis induced by *Trichophyton mentagrophytes* infection in male guinea pigs (300-354 g) was evaluated.

Two preshaved sites of the lumbar region on the back of each animal received 0.05 mL of the inoculum containing $5x10^5$ cells of *T.* Mentagrophytes. After one week, animals were divided into 7 groups of 5 animals each. After postinfection day 5, for two weeks, infected sites received daily applications of the test solution, its vehicle, or two cream preparations, and their vehicles at a dose level of 200 mg / site. A group of infected, but untreated

animals served as controls.

Observations / Evaluations: All infected sites were visually examined for dermal reactions and the therapeutic efficacy was determined for the individual groups based on the intensity of lesions and skin cultures. Infected skin tissue samples from the sacrificed animals were cultured three days after the last fungal application. A skin piece with detectable growth of *T. Mentagrophytes* was considered positive. Based on the average lesion scores, the therapeutic efficacy was statistically evaluated at several time points during the treatment.

Results / Conclusions: When compared with the untreated and vehicle control groups, the intensity of lesions decreased significantly in all the drug treated groups. However, no statistically significant differences in improvement were observed between the drug groups. In all treated animals, the lesions healed rapidly and disappeared completely after 10 days of treatment. At the end of the treatment period, no positive cultures were obtained from any drug treated pieces of skin samples.

2. SF-86-327 (1% Liquid Solution And Its Placebo): An Acute Oral Toxicity Study in Mice and Rats (Limit Test) (203-436; February-March 1989).

Study Objective / Design / Observations: The systemic toxicity of 1% alcoholic solution of terbinafine hydrochloride was determined after single oral doses of 250 mg/kg in 6 week old mice and 200mg/kg in WIST rats of both sexes (8M+8F). Control groups received equal volume of alcohol. During the 14 days observation period, animals were examined daily for morbidity, mortality, and clinical signs of toxicity. Body weights were determined daily. At study termination, all animals were subjected to necropsy examination. Only in the drug treated groups were major organs examined histopathologically.

Results / Conclusions: No deaths occurred during the study. A slight loss (3.5%) in body weight was recorded on the day of dosing. Clinical signs observed in all animals, such as flaccidity, drowsiness, prone position, disturbed equilibrium, and forced breathing were attributed to severe ethanol intoxication. No macro- or microscopic changes were observed in any drug treated animal.

3. Primary Skin Irritation Study of Lamisil^{R} Solution in Rabbits (203-573; July 1994).

Study Design / Observations: The skin irritation potential of 1% alcoholic solution of Lamisil was evaluated in male NZW rabbits (10 weeks old; 1.8-2.4 kg) following topical applications of 0.5 mL material on two (abraded, intact) preshaved sites on the back of each animal. Another abraded and one intact site received placebo solution. Animals were exposed to test

solution for 6 or 24 hours under occlusion, and dermal reactions (Draize scores) were graded at 7, 24, 48, or 72 hours after the treatment. Body weights were determined prior to study initiation and at termination.

Results / Conclusion: After 24 hour exposure, very slight erythema was observed in all rabbits. The mean primary irritation indices for Lamisil solution and placebo were 0.2 and 0.3, respectively. No difference in inflammation was observed between the abraded and the nonabraded sites. Under the study conditions, Lamisil 1% solution was well tolerated.

4. Accumulated Cutaneous Irritancy Study of Lamisil[R] Solution Using Rabbits for 28 Days (203-578; July-October, 1994).

Study Design / Procedures: Twelve 10 weeks old male NZW rabbits (2.30-2.86 kg) were used in this study. Of the four preshaved sites (2.5x2.5 cm/site), one site was left as untreated control, one site was treated with placebo solution, and the remaining two sites received daily applications of Lamisil 1% solution for 28 consecutive days. The test sites were either covered with impermeable oiled paper and bandaged or left uncovered. After 22 hours of exposure each day, dermal reactions were graded by the Draize (edema) and Marzulli/Maibach (erythema, eschar formation) methods. Only some selected animals were allowed to recover for 14 days. A number of sites with dermal lesions were photographed prior to treatment on days 1, 7, 41, 21 and 28, and on recovery days 7 and 14. Hematoxylin- and eosin-stained skin samples from selective sites were subjected to light microscopic examination.

Results / Conclusions: The nontreated skin remained lesion free throughout the study period with a irritation score of 0/10. No significant differences in dermal reactions were observed in sites treated with drug or placebo solutions. On the drug treated occluded sites, very slight to moderate erythema (maximum score 3/10) and edema (maximum score 2/10) were observed with a mean irritation score of 1.5. Identical maximum scores for erythema and edema obtained for occluded placebo sites gave a mean irritation score of 1.67. Open drug and placebo treated sites provided the mean irritation scores of 2.0 and 1.83, respectively. These scores remained consistent throughout the treatment period, indicating a lack of any cumulative irritation effect due to drug or placebo solutions. No inflammation was observed in any animal at the end of the recovery period.

Histopathologic examination revealed very slight to mild cell infiltration of the dermis, thickening and growth of the epidermis, and parakeratosis. No micro lesions were observed at the end of the recovery period.

5. Accumulated Cutaneous Irritancy Study of Deteriorated Lamisil[R] 1% Solution Using Rabbits for 28 Days (203-579; April-June 1995).

Study Design / Procedures: Six 10 weeks old male NZW rabbits (2.1-2.4 kg) were used in this study. Of the three preshaved sites (2.5x2.5 cm/site), one site was left as untreated control, the other two sites received daily applications of 0.1 mL of Lamisil 1% solution or deteriorated Lamisil 1% solution for 28 consecutive days. Deteriorated solution was produced by storing the freshly made preparation for two months in a room set at 50 °C with 75% relative humidity. During this period, the pH of this solution was lowered from original 3.7 to 3.2. Test sites were not covered. After 22 hours of exposure, dermal reactions were graded as in study # 4 above. The skin samples from the test sites stained with hematoxylin and eosin were examined by light microscopy.

Results / Conclusions: The untreated control sites exhibited no inflammation. No significant differences in dermal lesions were observed on sites treated with either of the test solutions. On the drug treated sites, very slight to mild erythema and edema (maximum score of 2 for both lesions) were observed. The mean irritation scores for Lamisil and deteriorated solutions were 1.5 and 1.67, respectively. These scores essentially remained unchanged during the study period, indicating a lack of any cumulative irritation effect. Histopathologic examination revealed very slight to mild cell infiltration of the dermis and thickening and growth of the epidermis.

6. Dermal Sensitization Study in Guinea Pigs (203-580; August, 1996).

Study Design / Materials / Procedures: The skin sensitization potential of Lamisil 1, 2, and 3% (W/W) solutions in female Hartley guinea pigs (5 weeks old, 322 to 396g) was evaluated by the maximization test method. The assay values for three solutions were 97.4, 94.9. and 97.2% of the nominal amount, respectively.

Skin Irritancy Test: Five animals received intradermal injections of 0.1 mL of the test solution on a pair of preshaved sites on the dorsum. The test sites were observed for 2 days for any sign of inflammation.

Primary Sensitization: Groups of animals (10/group) received 0.1 mL intradermal injections of Freund's Complete Adjuvant (FCA)-water emulsion (v/v 1:1), test solution, and test solution-FCA water emulsion on three pairs of preshaved sites (~4x6cm^2) on the suprascapular region of the back. The positive control group received 0.1 mL intradermal injections of FCA emulsion, 0.1% dinitrochlorobenzene (DNCB) solution in olive oil, and emulsion of 0.2% DNCB in FCA with an equal volume of water.

Secondary Sensitization: The same preshaved injection sites received applications of 10% sodium lauryl sulfate solution. The next day, 0.2 mL of Lamisil test solutions or 0.1% DNCB solution were applied onto the sites. The sites were occluded for 48 hours.

Challenge: Two weeks later, 1.5 cm diameter sites on animals were challenged with 0.1 mL applications of provocative antigens. The sites were occluded for 24 hours. Forty animals in the negative control group were similarly treated with three Lamisil test solutions, or 0.1% DNCB solution.

Determinations / Observations: On a daily basis, animals were examined for mortality, morbidity and other clinical signs of toxicity. Body weights were determined at regular intervals throughout the study. Test sites were graded for erythema and edema at 24 and 48 hours, after removal of occlusive patches of provocative antigens. Group mean scores for test animals were compared with the negative control values. At study termination, all animals were sacrificed.

Results / Conclusions: The mean ~~irritation~~ reaction scores for three test solutions were as follows:

Lamisil Solution (%)	Mean Irritation Scores	
	24 Hrs.	48 Hrs.
1	0.1	0.1
2	0.2	0.2
3	0.3	0.4

These scores were not statistically significant when compared with the negative and positive control values, indicating that topical applications of Lamisil were nonsensitizing and well tolerated in the maximization test in the guinea pigs.

7. Eye Irritation Study in the Male Rabbits on Lamisil® (SF 86-327) Topical Solution 1% (203-575; March-April, 1995).

Study Design / Procedures: Six male Japanese albino rabbits (13 weeks old, 2.5-2.8 kg) received 0.1 mL of Lamisil 1% solution into the conjunctiva of the right eye. The left eye remained as untreated control. Four hours postapplication, one group of treated eyes were washed with saline for 30 seconds. At 1, 24, 48, and 72 hours postdose, eyes were examined for corneal opacity and redness and swelling of the iris and conjunctiva, and corneal damage was evaluated. Eyes were also stained with 2% sodium fluorescein and examined by light microscopy at 24 and 72 hours postdose. Ocular lesions were graded according to Draize.

Results / Conclusions: At 1 hour postdose, all treated animals exhibited some ocular discharge. Mean irritation scores at 1, 24, 48, and 72 hours were 6.00, 2.67, 2.00 and 0.00, respectively. In the irrigated eyes, the scores were 4.00, 2.67, 1.3, and 0.00, respectively. Redness in the conjunctiva was observed in 3/6 rabbits up to 24 hours postapplication. No treatment related lesions were observed in the cornea or iris. The fluorescein stained-corneas did not exhibit any lesions. Up to 48 hours, edema of the nictating membrane was observed in all treated eyes washed or unwashed. It was concluded that Lamisil 1% solution was slightly irritant to the rabbit eye, but the irritation was reduced after irrigation.

8. Phototoxicity Study of SF Solution in Guinea Pigs (203-576; December 1989).

Study Design / Procedures (Morikawa et. al. 1974[1]): Groups of 6-weeks old female Hartley guinea pigs (345-492g; 6 animals/group) received dermal applications of 0.1 mL Lamisil 1, 2, or 3% solution or 0.1 g of positive control (10% anthracene in white vaseline) on two preshaved sites (2x2cm / site) per animal. The negative control group was treated with white vaseline only. Following 30 minutes of exposure, the test substance was wiped off and one-half of the sites were covered with aluminum foil; the rest of the sites were subjected to 45 minutes of UV radiation from a distance of 15 cm at 300-430 nm yielding a cumulative radiant energy of $1.2x10^8$ ergs/cm^2. Rays <320 were blocked by inserting a 3 mm thick glass sheet between the light source (Dermaray irradiator with 10 FL-20s BLB UV lamps) and the application sites.

Dermal lesions were graded (Draize) using a scale of 0 to 4 at 24, 48, and 72 hours after irradiation. Body weights were determined daily, and animals were also observed regularly for mortality and clinical signs of toxicity.

Results / Conclusions: In positive control group, erythema (2-3/4) and edema (1/4) were observed in 100 or 33% animals, respectively, at 24 or 48 hours after irradiation. Two nonirradiated positive control animals also exhibited erythema (1/4) at 24 and 48 hours, respectively.

Erythema (1/4) was observed in a few treated sites in the irradiated as well as nonirradiated animals. No edema was observed in any Lamisil treated animals. Erythema 1/4) was also observed in a few animals of the negative control group.

The study author concluded that Lamisil solution up to a strength of 3% did not induce phototoxicity in guinea pigs.

[1]Morikawa, F. Et al., (1974): Techniques for evaluation of phototoxicity and photoallergy in laboratory animals. In: Sunlight and man (Fitzpatrick T.B. et al., eds): 529-557; University of Tokyo Press.

9. Skin Photosensitization Study of SF Solution in Guinea Pigs (203-577; October-November 1989).

Study Design / Procedures: In the induction phase, 6-weeks old female Hartley guinea pigs (372-475g; 12/group) were treated intradermally with 0.1 mL water emulsion of Freunds Complete Adjuvant. Twenty-four hours later, two preshaved skin sites (1.5x1.5cm/site) per animal were treated with 1, 2, or 3% Lamisil solution, vehicle, or 0.1 mL of positive control TCSA (3, 3', 4', 5-tetrachlorosalicylanilide, 2% w/v in ethanol) for 30 minutes. The application sites were subjected to daily UV-irradiation (320-400 nm) at a cumulative radiant energy of $1x10^8$ ergs/cm^2 for five days. Rays <320 nm were blocked by a 3 mm thick glass shield placed between the Dermaray irradiator and the exposure sites. Twenty-one days later, two preshaved application sites / animal were challenged with 0.02 mL of 1, 2, 3% Lamisil solution, vehicle, or positive control for 30 minutes. One site was covered with the aluminium foil, while the other site was UV-irradiated as before.

Dermal reactions were graded at a scale of 0 to 4 (Draize) at 24 and 48 hours after provocative irradiation. Animals were monitored daily for signs of toxicity, and their body weights were determined weekly.

Results / Conclusions: As expected, TCSA produced well-defined erythema in 67-75% of the animals, thus validating the assay. Non-irradiated sites in the positive control group exhibited very slight erythema. It was related to well known primary irritation or skin sensitization properties of TCSA.

Very slight erythema (score of 1 / 4) was observed at irradiated as well non-irradiated test sites treated with 1 (irradiated: 3/12 animals at 24 hours, 7/12 at 48 hours; non-irradiated: 2/12 at 24 and 48 hours) and 2% (irradiated: 1/12 at 24 and 5/12 at 48 hours; non-irradiated: 1/12 at 48 hours) Lamisil solutions.

With 3% Lamisil solution, slight erythema was noted in 5/12 and well-defined erythema in 1/12 animals at the irradiated sites at 24 hours. At 48 hours, 6 irradiated sites indicated score of 1, while well-defined (score of 2) erythema was observed in only one animal. At the non-irradiated sites, well defined erythema was observed in 2/12 animals at both examination points. It must be mentioned that the grade 2 reactions were observed in the irradiated and non-irradiated sites of the same animals. Very slight edema was observed at the irradiated site in 2 animals and in one animal at the non-irradiated sites at 48 hours. According to the study author, the erythema observed with Lamisil solutions might possibly be due to skin sensitization. Since no erythema was observed in these animals after re-irradiation, it was inferred that Lamisil solutions did not exhibit photosensitizing potential.

10. Skin Photosensitization Study of SF Solutions in Guinea Pigs (203-574; February-June 1990).

Study Design / Materials / procedures

Animals: Four-weeks old female Hartley guinea pigs, 296-373 g

Test Solutions

Sensitization Phase: 3% Lamisil solution; 2% TCSA (w/v) in acetone (positive control); distilled water (negative control).

Challenge Phase: 1, 2 and 3% Lamisil solutions; respective vehicles; 1% TCSA

Light Source: Six Toshiba FL-40S BLB UV lamps (300-400 nm; maximum wave length, 360 nm) arranged in parallel.

In the sensitization phase, preshaved dorsal sites (2x4 cm) in 20 animals in each group received applications of 0.2 mL of 3% Lamisil solution, or distilled water. Five animals received applications of 0.2 mL of TCSA. After 30 minutes, the sites were exposed to UV radiation at an energy level of $3x10^8$ ergs/cm^2 through 3 mm thick glass filter. The whole procedure was repeated three times on alternate days.

Twenty-four days later, the preshaved sites (2x2 cm) in the same animals were challenged for 30 minutes with 0.05 mL of respective Lamisil solutions, vehicle, or TCSA. One-half of the test sites were covered with aluminium foil, while the other half were exposed to UV radiation of 4.33 to 4.45 mW/cm^2 yielding a cumulative radiant energy of $9x10^7$ ergs/cm^2.

Dermal reactions (erythema, edema) were graded according to Draize at 24 and 48 hours post-irradiation. Animals were monitored daily for clinical signs of toxicity. Body weights were determined during the induction phase and on days 7, 14, 21, and 30.

Results / Conclusions: When compared to the vehicle control, no dermal reactions were observed on irradiated or non-irradiated sites in the animals treated with Lamisil solutions. TCSA group exhibited erythema (maximum score 4) and edema (maximum score 2) at irradiated sites at 24 and 48 hours. A few non-irradiated sites indicated grade 1 erythema at both examination points. Under the study conditions, Lamisil 1, 2, or 3% solutions did not produce any photosensitivity.

Labeling

The current draft for labeling was approved for Lamisil® Tablets, NDA 20-539. No additional studies to support the current formulation were required, requested, or conducted. However, it is recommended that the genotoxicity portion (paragraph #3) under Carcinogenesis, Mutagenesis, Impairment of Fertility should be modified as follows to include the names of the tests conducted.

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 have been approved for marketing. 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 1% solution for the topical treatment of athletes foot, (tinea pedis), jock itch (tinea cruris), ring worms (tinea corporis), and pityriasis versicolor. In addition, a number of additional studies were conducted to evaluate the efficacy, primary dermal and ocular irritations, phototoxicity, and photosensitivity potentials of Lamisil 1% solution.

In a therapeutic efficacy study where guinea pigs infected with *T. Mentagrophytes* were treated with 1% Lamisil solution, a 100% mycological cure rate was achieved. Clinically this solution will be used at a maximum level of twice a day for one week (treatment of Pityriasis versicolor). In animal studies, this drug has been tested for much longer duration at much higher dose levels. In primary irritation studies in rabbits, the drug was well tolerated. The topical applications of 1, 2, and 3% Lamisil solutions were nonsensitizing in guinea pig maximization tests. The same solutions did not induce any phototoxicity or photosensitivity in guinea pigs. However, it must be mentioned that all the phototoxicity and photosensitivity studies were deficient. Though the UV absorption spectra for terbinafine indicates that the compound only absorbs in the UVB range, yet due to some

unexplained reason, animals were only exposed to the UVA spectrum. In fact in all cases, the UVB portion of the spectra was methodically filtered out. At the same time it must also be mentioned that in a human study, none of the 31 healthy volunteers exposed to combined UVA and UVB irradiation, exhibited contact photoallergy or dermal sensitization.

In a rabbit ocular toxicity study, Lamisil 1% solution was observed to be a mild, but reversible irritant.

On the whole, taking into account a safe and sound toxicity profile that has emerged from the extensive testing in multiple animals 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% solution for its short-term clinical use.

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

2/18/97

Kumar D. Mainigi, Ph.D., M.P.H., D.A.B.T
Toxicologist

CC: Original NDA 20-749
HFD-82
HFD-540
MO/Toombs
Pharm/Mainigi
Chem/Vidra
CSO/Cross
Pharm/Jacobs
Biopharm/Bashaw
Micro/Sweeny, HFD-160
Micro/Altaie, HFD-520

Concurrence:
A.Jacobs,TL, HFD-540 2/14/97
J.Wilkin, Dir, HFD-540 2/28/97

OCT 16 1997

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Division of Dermatologic & Dental Drug Products, HFD-540

NDA 20-749 (Addendum to the original review dated 02-05-1997)
Drug: LAMISIL^R (terbinafine hydrochloride) Solution, 1%
Sponsor: Sandoz Pharmaceuticals Corporation
59 Route 10
East Hanover, N.J. 07936-1080
Stephenie Barba (201-503-7548)
Comment: The purpose of this addendum is to document recommended changes to the Pharmocology/Toxicology section of the label. The changes in the draft are high lighted by shading.

Number of Volumes: Four (4) Red
Date CDER Received: 10-18-1996
Date Assigned: 10-23-1996
Date Review Started: 01-06-1997
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Indication: Treatment of tinea cruris, tinea corporis, and pityriasis versicolor

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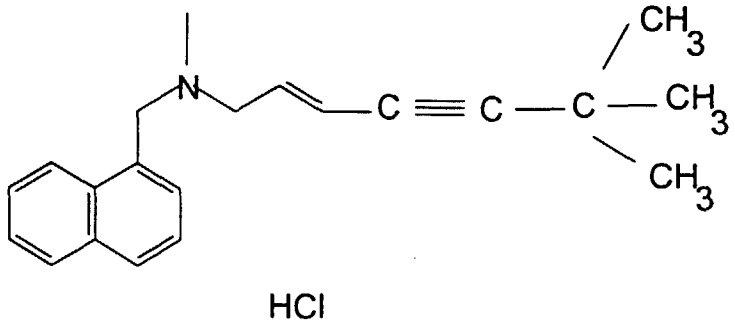
Chemical Structure:



Code Name: SF 86-327

COMPOSITION:

Names of ingredients	Function	Formula (g)
Terbinafine hydrochloride		0.010
Cetomacrogol 1000*		
Propylene glycol		
Ethanol (96%)		
Purified water		

* Equivalent to

Related Submissions: All submitted by Sandoz Pharmaceutical Corporation.

INDs

NDAs
20-192; Lamisil cream 1% (approved, 12-30-1992)
20-539; Lamisil tablets (approved, 05-10-1996)

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 as well as with the proposed 1% solution formulations. A large number of these studies were reviewed under several INDs and NDAs; the rest are reviewed here.

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Sandoz Pharma. Basel, Switzerland (#2)

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Study objectives / Design: The efficacy of 1% topical terbinafine solution and two 1% terbinafine cream formulations (imported and domestically produced) in treating experimental dermatophytosis induced by *Trichophyton mentagrophytes* infection in male guinea pigs (300-354 g) was evaluated.

Two preshaved sites of the lumbar region on the back of each animal received 0.05 mL of the inoculum containing $5x10^5$ cells of *T.* Mentagrophytes. After one week, animals were divided into 7 groups of 5 animals each. After postinfection day 5, for two weeks, infected sites received daily applications of the test solution, its vehicle, or two cream preparations, and their vehicles at a dose level of 200 mg / site. A group of infected, but untreated

animals served as controls.

Observations / Evaluations: All infected sites were visually examined for dermal reactions and the therapeutic efficacy was determined for the individual groups based on the intensity of lesions and skin cultures. Infected skin tissue samples from the sacrificed animals were cultured three days after the last fungal application. A skin piece with detectable growth of *T. Mentagrophytes* was considered positive. Based on the average lesion scores, the therapeutic efficacy was statistically evaluated at several time points during the treatment.

Results / Conclusions: When compared with the untreated and vehicle control groups, the intensity of lesions decreased significantly in all the drug treated groups. However, no statistically significant differences in improvement were observed between the drug groups. In all treated animals, the lesions healed rapidly and disappeared completely after 10 days of treatment. At the end of the treatment period, no positive cultures were obtained from any drug treated pieces of skin samples.

2. SF-86-327 (1% Liquid Solution And Its Placebo): An Acute Oral Toxicity Study in Mice and Rats (Limit Test) (203-436; February-March 1989).

Study Objective / Design / Observations: The systemic toxicity of 1% alcoholic solution of terbinafine hydrochloride was determined after single oral doses of 250 mg/kg in 6 week old mice and 200mg/kg in WIST rats of both sexes (8M+8F). Control groups received equal volume of alcohol. During the 14 days observation period, animals were examined daily for morbidity, mortality, and clinical signs of toxicity. Body weights were determined daily. At study termination, all animals were subjected to necropsy examination. Only in the drug treated groups were major organs examined histopathologically.

Results / Conclusions: No deaths occurred during the study. A slight loss (3.5%) in body weight was recorded on the day of dosing. Clinical signs observed in all animals, such as flaccidity, drowsiness, prone position, disturbed equilibrium, and forced breathing were attributed to severe ethanol intoxication. No macro- or microscopic changes were observed in any drug treated animal.

3. Primary Skin Irritation Study of Lamisil^{R} Solution in Rabbits (203-573; July 1994).

Study Design / Observations: The skin irritation potential of 1% alcoholic solution of Lamisil was evaluated in male NZW rabbits (10 weeks old; 1.8-2.4 kg) following topical applications of 0.5 mL material on two (abraded, intact) preshaved sites on the back of each animal. Another abraded and one intact site received placebo solution. Animals were exposed to test

solution for 6 or 24 hours under occlusion, and dermal reactions (Draize scores) were graded at 7, 24, 48, or 72 hours after the treatment. Body weights were determined prior to study initiation and at termination.

Results / Conclusion: After 24 hour exposure, very slight erythema was observed in all rabbits. The mean primary irritation indices for Lamisil solution and placebo were 0.2 and 0.3, respectively. No difference in inflammation was observed between the abraded and the nonabraded sites. Under the study conditions, Lamisil 1% solution was well tolerated.

4. Accumulated Cutaneous Irritancy Study of Lamisil[R] Solution Using Rabbits for 28 Days (203-578; July-October, 1994).

Study Design / Procedures: Twelve 10 weeks old male NZW rabbits (2.30-2.86 kg) were used in this study. Of the four preshaved sites (2.5x2.5 cm/site), one site was left as untreated control, one site was treated with placebo solution, and the remaining two sites received daily applications of Lamisil 1% solution for 28 consecutive days. The test sites were either covered with impermeable oiled paper and bandaged or left uncovered. After 22 hours of exposure each day, dermal reactions were graded by the Draize (edema) and Marzulli/Maibach (erythema, eschär formation) methods. Only some selected animals were allowed to recover for 14 days. A number of sites with dermal lesions were photographed prior to treatment on days 1, 7, 41, 21 and 28, and on recovery days 7 and 14. Hematoxylin- and eosin-stained skin samples from selective sites were subjected to light microscopic examination.

Results / Conclusions: The nontreated skin remained lesion free throughout the study period with a irritation score of 0/10. No significant differences in dermal reactions were observed in sites treated with drug or placebo solutions. On the drug treated occluded sites, very slight to moderate erythema (maximum score 3/10) and edema (maximum score 2/10) were observed with a mean irritation score of 1.5. Identical maximum scores for erythema and edema obtained for occluded placebo sites gave a mean irritation score of 1.67. Open drug and placebo treated sites provided the mean irritation scores of 2.0 and 1.83, respectively. These scores remained consistent throughout the treatment period, indicating a lack of any cumulative irritation effect due to drug or placebo solutions. No inflammation was observed in any animal at the end of the recovery period.

Histopathologic examination revealed very slight to mild cell infiltration of the dermis, thickening and growth of the epidermis, and parakeratosis. No micro lesions were observed at the end of the recovery period.

5. Accumulated Cutaneous Irritancy Study of Deteriorated Lamisil[R] 1% Solution Using Rabbits for 28 Days (203-579; April-June 1995).

Study Design / Procedures: Six 10 weeks old male NZW rabbits (2.1-2.4 kg) were used in this study. Of the three preshaved sites (2.5x2.5 cm/site), one site was left as untreated control, the other two sites received daily applications of 0.1 mL of Lamisil 1% solution or deteriorated Lamisil 1% solution for 28 consecutive days. Deteriorated solution was produced by storing the freshly made preparation for two months in a room set at 50 °C with 75% relative humidity. During this period, the pH of this solution was lowered from original 3.7 to 3.2. Test sites were not covered. After 22 hours of exposure, dermal reactions were graded as in study # 4 above. The skin samples from the test sites stained with hematoxylin and eosin were examined by light microscopy.

Results / Conclusions: The untreated control sites exhibited no inflammation. No significant differences in dermal lesions were observed on sites treated with either of the test solutions. On the drug treated sites, very slight to mild erythema and edema (maximum score of 2 for both lesions) were observed. The mean irritation scores for Lamisil and deteriorated solutions were 1.5 and 1.67, respectively. These scores essentially remained unchanged during the study period, indicating a lack of any cumulative irritation effect. Histopathologic examination revealed very slight to mild cell infiltration of the dermis and thickening and growth of the epidermis.

6. Dermal Sensitization Study in Guinea Pigs (203-580; August, 1996).

Study Design / Materials / Procedures: The skin sensitization potential of Lamisil 1, 2, and 3% (W/W) solutions in female Hartley guinea pigs (5 weeks old, 322 to 396g) was evaluated by the maximization test method. The assay values for three solutions were 97.4, 94.9, and 97.2% of the nominal amount, respectively.

Skin Irritancy Test: Five animals received intradermal injections of 0.1 mL of the test solution on a pair of preshaved sites on the dorsum. The test sites were observed for 2 days for any sign of inflammation.

Primary Sensitization: Groups of animals (10/group) received 0.1 mL intradermal injections of Freund's Complete Adjuvant (FCA)-water emulsion (v/v 1:1), test solution, and test solution-FCA water emulsion on three pairs of preshaved sites (~4x6cm^2) on the suprascapular region of the back. The positive control group received 0.1 mL intradermal injections of FCA emulsion, 0.1% dinitrochlorobenzene (DNCB) solution in olive oil, and emulsion of 0.2% DNCB in FCA with an equal volume of water.

Secondary Sensitization: The same preshaved injection sites received applications of 10% sodium lauryl sulfate solution. The next day, 0.2 mL of Lamisil test solutions or 0.1% DNCB solution were applied onto the sites. The sites were occluded for 48 hours.

Challenge: Two weeks later, 1.5 cm diameter sites on animals were challenged with 0.1 mL applications of provocative antigens. The sites were occluded for 24 hours. Forty animals in the negative control group were similarly treated with three Lamisil test solutions, or 0.1% DNCB solution.

Determinations / Observations: On a daily basis, animals were examined for mortality, morbidity and other clinical signs of toxicity. Body weights were determined at regular intervals throughout the study. Test sites were graded for erythema and edema at 24 and 48 hours, after removal of occlusive patches of provocative antigens. Group mean scores for test animals were compared with the negative control values. At study termination, all animals were sacrificed.

Results / Conclusions: The mean irritation scores for three test solutions were as follows:

Lamisil Solution (%)	Mean Irritation Scores	
	24 Hrs.	48 Hrs.
1	0.1	0.1
2	0.2	0.2
3	0.3	0.4

These scores were not statistically significant when compared with the negative and positive control values, indicating that topical applications of Lamisil were nonsensitizing and well tolerated in the maximization test in the guinea pigs.

7. Eye Irritation Study in the Male Rabbits on Lamisil[R] (SF 86-327) Topical Solution 1% (203-575; March-April, 1995).

Study Design / Procedures: Six male Japanese albino rabbits (, 13 weeks old, 2.5-2.8 kg) received 0.1 mL of Lamisil 1% solution into the conjunctiva of the right eye. The left eye remained as untreated control. Four hours postapplication, one group of treated eyes were washed with saline for 30 seconds. At 1, 24, 48, and 72 hours postdose, eyes were examined for corneal opacity and redness and swelling of the iris and conjunctiva, and corneal damage was evaluated. Eyes were also stained with 2% sodium fluorescein and examined by light microscopy at 24 and 72 hours postdose. Ocular lesions were graded according to Draize.

Results / Conclusions: At 1 hour postdose, all treated animals exhibited some ocular discharge. Mean irritation scores at 1, 24, 48, and 72 hours were 6.00, 2.67, 2.00 and 0.00, respectively. In the irrigated eyes, the scores were 4.00, 2.67, 1.3, and 0.00, respectively. Redness in the conjunctiva was observed in 3/6 rabbits up to 24 hours postapplication. No treatment related lesions were observed in the cornea or iris. The fluorescein stained-corneas did not exhibit any lesions. Up to 48 hours, edema of the nictating membrane was observed in all treated eyes washed or unwashed. It was concluded that Lamisil 1% solution was slightly irritant to the rabbit eye, but the irritation was reduced after irrigation.

8. Phototoxicity Study of SF Solution in Guinea Pigs (203-576; December 1989).

Study Design / Procedures (Morikawa et. al. 1974[1]): Groups of 6-weeks old female Hartley guinea pigs (345-492g; 6 animals/group) received dermal applications of 0.1 mL Lamisil 1, 2, or 3% solution or 0.1 g of positive control (10% anthracene in white vaseline) on two preshaved sites (2x2cm / site) per animal. The negative control group was treated with white vaseline only. Following 30 minutes of exposure, the test substance was wiped off and one-half of the sites were covered with aluminum foil; the rest of the sites were subjected to 45 minutes of UV radiation from a distance of 15 cm at 300-430 nm yielding a cumulative radiant energy of $1.2x10^6$ ergs/cm^2. Rays <320 were blocked by inserting a 3 mm thick glass sheet between the light source (Dermaray irradiator with 10 FL-20s BLB UV lamps) and the application sites.

Dermal lesions were graded (Draize) using a scale of 0 to 4 at 24, 48, and 72 hours after irradiation. Body weights were determined daily, and animals were also observed regularly for mortality and clinical signs of toxicity.

Results / Conclusions: In positive control group, erythema (2-3/4) and edema (1/4) were observed in 100 or 33% animals, respectively, at 24 or 48 hours after irradiation. Two nonirradiated positive control animals also exhibited erythema (1/4) at 24 and 48 hours, respectively.

Erythema (1/4) was observed in a few treated sites in the irradiated as well as nonirradiated animals. No edema was observed in any Lamisil treated animals. Erythema 1/4) was also observed in a few animals of the negative control group.

The study author concluded that Lamisil solution up to a strength of 3% did not induce phototoxicity in guinea pigs.

[1]Morikawa, F. Et al., (1974): Techniques for evaluation of phototoxicity and photoallergy in laboratory animals. In: Sunlight and man (Fitzpatrick T.B. et al., eds): 529-557; University of Tokyo Press.

9. Skin Photosensitization Study of SF Solution in Guinea Pigs (203-577; October-November 1989).

Study Design / Procedures: In the induction phase, 6-weeks old female Hartley guinea pigs (372-475g; 12/group) were treated intradermally with 0.1 mL water emulsion of Freunds Complete Adjuvant. Twenty-four hours later, two preshaved skin sites (1.5x1.5cm/site) per animal were treated with 1, 2, or 3% Lamisil solution, vehicle, or 0.1 mL of positive control TCSA (3, 3', 4', 5-tetrachlorosalicylanilide, 2% w/v in ethanol) for 30 minutes. The application sites were subjected to daily UV-irradiation (320-400 nm) at a cumulative radiant energy of $1x10^8$ ergs/cm^2 for five days. Rays <320 nm were blocked by a 3 mm thick glass shield placed between the Dermaray irradiator and the exposure sites. Twenty-one days later, two preshaved application sites / animal were challenged with 0.02 mL of 1, 2, 3% Lamisil solution, vehicle, or positive control for 30 minutes. One site was covered with the aluminium foil, while the other site was UV-irradiated as before.

Dermal reactions were graded at a scale of 0 to 4 (Draize) at 24 and 48 hours after provocative irradiation. Animals were monitored daily for signs of toxicity, and their body weights were determined weekly.

Results / Conclusions: As expected, TCSA produced well-defined erythema in 67-75% of the animals, thus validating the assay. Non-irradiated sites in the positive control group exhibited very slight erythema. It was related to well known primary irritation or skin sensitization properties of TCSA.

Very slight erythema (score of 1 / 4) was observed at irradiated as well non-irradiated test sites treated with 1 (irradiated: 3/12 animals at 24 hours, 7/12 at 48 hours; non-irradiated: 2/12 at 24 and 48 hours) and 2% (irradiated: 1/12 at 24 and 5/12 at 48 hours; non-irradiated: 1/12 at 48 hours) Lamisil solutions.

With 3% Lamisil solution, slight erythema was noted in 5/12 and well-defined erythema in 1/12 animals at the irradiated sites at 24 hours. At 48 hours, 6 irradiated sites indicated score of 1, while well-defined (score of 2) erythema was observed in only one animal. At the non-irradiated sites, well defined erythema was observed in 2/12 animals at both examination points. It must be mentioned that the grade 2 reactions were observed in the irradiated and non-irradiated sites of the same animals. Very slight edema was observed at the irradiated site in 2 animals and in one animal at the non-irradiated sites at 48 hours. According to the study author, the erythema observed with Lamisil solutions might possibly be due to skin sensitization. Since no erythema was observed in these animals after re-irradiation, it was inferred that Lamisil solutions did not exhibit photosensitizing potential.

10. Skin Photosensitization Study of SF Solutions in Guinea Pigs (203-574; February-June 1990).

Study Design / Materials / procedures

Animals: Four-weeks old female Hartley guinea pigs, 296-373 g

Test Solutions

Sensitization Phase: 3% Lamisil solution; 2% TCSA (w/v) in acetone (positive control); distilled water (negative control).

Challenge Phase: 1, 2 and 3% Lamisil solutions; respective vehicles; 1% TCSA

Light Source: Six Toshiba FL-40S BLB UV lamps (300-400 nm; maximum wave length, 360 nm) arranged in parallel.

In the sensitization phase, preshaved dorsal sites (2x4 cm) in 20 animals in each group received applications of 0.2 mL of 3% Lamisil solution, or distilled water. Five animals received applications of 0.2 mL of TCSA. After 30 minutes, the sites were exposed to UV radiation at an energy level of $3x10^8$ ergs/cm^2 through 3 mm thick glass filter. The whole procedure was repeated three times on alternate days.

Twenty-four days later, the preshaved sites (2x2 cm) in the same animals were challenged for 30 minutes with 0.05 mL of respective Lamisil solutions, vehicle, or TCSA. One-half of the test sites were covered with aluminium foil, while the other half were exposed to UV radiation of 4.33 to 4.45 mW/cm^2 yielding a cumulative radiant energy of $9x10^7$ ergs/cm^2.

Dermal reactions (erythema, edema) were graded according to Draize at 24 and 48 hours post-irradiation. Animals were monitored daily for clinical signs of toxicity. Body weights were determined during the induction phase and on days 7, 14, 21, and 30.

Results / Conclusions: When compared to the vehicle control, no dermal reactions were observed on irradiated or non-irradiated sites in the animals treated with Lamisil solutions. TCSA group exhibited erythema (maximum score 4) and edema (maximum score 2) at irradiated sites at 24 and 48 hours. A few non-irradiated sites indicated grade 1 erythema at both examination points. Under the study conditions, Lamisil 1, 2, or 3% solutions did not produce any photosensitivity.

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Proposed Labeling

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 have been approved for marketing. 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 1% solution for the topical treatment of athletes foot, (tinea pedis), jock itch (tinea cruris), ring worms (tinea corporis), and pityriasis versicolor. In addition, a number of additional studies were conducted to evaluate the efficacy, primary dermal and ocular irritations, phototoxicity, and photosensitivity potentials of Lamisil 1% solution.

In a therapeutic efficacy study where guinea pigs infected with *T. Mentagrophytes* were treated with 1% Lamisil solution, a 100% mycological cure rate was achieved. Clinically this solution will be used at a maximum level of twice a day for one week (treatment of Pityriasis versicolor). In animal studies, this drug has been tested for much longer duration at much higher dose levels. In primary irritation studies in rabbits, the drug was well tolerated. The topical applications of 1, 2, and 3% Lamisil solutions were nonsensitizing in guinea pig maximization tests. The same solutions did not induce any phototoxicity or photosensitivity in guinea pigs. However, it must be mentioned that all the phototoxicity and photosensitivity studies were deficient. Though the UV absorption spectra for terbinafine indicates that the compound only absorbs in the UVB range, yet due to some unexplained reason, animals were only exposed to the UVA spectrum. In fact in all cases, the UVB portion of the spectra was methodically filtered out. At the same time it must also be mentioned that in a human study, none of the 31 healthy volunteers exposed to combined UVA and UVB irradiation, exhibited contact photoallergy or dermal sensitization. In a rabbit ocular toxicity study, Lamisil 1% solution was observed to be a mild, but reversible irritant.

On the whole, taking into account a safe and sound toxicity profile that has emerged from the extensive testing in multiple animals 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% solution for its short-term clinical use.

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

10/16/97

Kumar D. Mainigi, Ph.D., M.P.H., D.A.B.T
Toxicologist

CC: Original NDA 20-749
HFD-82
HFD-540
MO/Toombs
Pharm/Mainigi
Chem/Vidra
CSO/Cross
Pharm/Jacobs
Biopharm/Bashaw
Micro/Sweeny, HFD-160
Micro/Altaie, HFD-520

Concurrence:
A.Jacobs,TL, HFD-540 10/16/97
J.Wilkin, Dir, HFD-540 10/17/97

P.S. The labeling portion was revised after the original review was finalised.