10.2.2 Laboratory Findings, Vital Signs, ECGs

Clinical laboratory parameters consisting of standard hematology and clinical chemistry were measured in four Phase 2 studies of 103 patients. These studies were conducted under NDA 20-192 for the original cream formulation. Two studies were conducted in patients with tinea pedis and two studies of patients with tinea cruris or corporis. According to the sponsor, no clinically relevant laboratory abnormalities were noted.

Two reported cases were retrieved from the FDA SRS database. A single case report listing a decreased in glucose tolerance for terbinafine cream was retrieved. One case of increased gamma glutamyltransferase was reported with combined use of terbinafine cream and oral terbinafine.

10.2.3 Special Studies

Dermal irritation and sensitization studies were not conducted in support of the this NDA requesting Rx to OTC switch of terbinafine. However, adequate topical safety studies were performed in the original application NDA 20-192. No significant potential for irritation, sensitization or phototoxicity was found. ✓

10.2.4 Drug-Demographic Interactions

There were no relevant pharmacokinetic or pharmacodynamic findings reported.

10.2.5 Drug-Disease Interactions

There were no relevant pharmacokinetic or pharmacodynamic findings reported.

10.2.6 Drug-Drug Interactions

No potential interaction studies with terbinafine hydrochloride cream and other drugs have systematically been performed. Except for the following two cases recorded in the FDA SRS database, there have been no reported interactions with other topical creams.

FDA SRS database search:
One case report of a full body rash developing with concomitant use of topical Lamisil cream and Bactroban.

One case of urinary retention reported in a male with concomitant use of topical Lamisil cream and Noroxin. Relief of the symptom with use of Macrodantin was noted.

10.2.7 Withdrawal Phenomena/Abuse Potential

No reports of cases of abuse of topical or systemic terbinafine have been reported. Central nervous system effects appear to be absent and the topical route of administration would make

abuse potential extremely low. With use of oral terbinafine 250 mg for 12 and 24 weeks and with an estimated 3.5 million patient exposures world wide, there is no known potential for producing withdrawal effects. There have been no adverse event reports that are suggestive of withdrawal effects.

10.2.8 Human Reproduction Data

The approved prescription drug product is labeled as Pregnancy Category B, and carries the following statement "There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly indicated during pregnancy". There is no new data presented with this application that further advances our understanding of the effects of terbinafine cream during pregancy and lactation. Therefore, it would appear necessary to provide pregnant and lactating patients (who may desire to purchase this medication without a prescription) with the recommendation to consult a health professional before use.

11 Labeling

The following comments are offered regarding the OTC carton labeling:

12 Conclusions

Terbinafine HCl cream, 1% appears safe and effective for use without a prescription for the treatment of tinea pedis, tinea cruris and tinea corporis. A review of pediatric patients presented in this NDA, although few in number, indicates that terbinafine HCl cream, 1% appears to well tolerated in the 12 to 17 year old age group. There does not appear to any significant adverse reaction signal in adult patients which would adversely affect the 12 to 17 year old age group. The prescription drug product is currently approved for use in the 12 to 17 year old age group.

13 Recommendations

1) The use of terbinafine HCl cream, 1% in the treatment of tinea pedis should be approved for sale without prescription in patients ≥ 12 years of age. Application should be twice daily for one week in the treatment of tinea pedis (interdigital) "athlete's foot between the toes". Application should be twice daily for two weeks in the treatment of tinea pedis (moccasin) "athlete's foot on the bottom and sides of the foot".

2) The use of terbinafine HCl cream, 1% in the treatment of tinea cruris/corporis should be approved for sale without prescription. Application should be once daily for one week in patients ≥ 12 years of age.

/S/ 2/1/99

/Brenda E. Vaughan, M.D.
Medical Officer, Dermatology

cc: Orig NDA 20-980
HFD-540
HFD-540/DIV DIR/Wilkin
HFD-540/DERM TL/Walker /S/ 2/1/99
HFD-540/MO/Vaughan
HFD-540/CHEM TL/DeCamp
HFD-540/CHEM/Vidra
HFD-540/PH TOX TL/Jacobs /S/ 2/2/99
HFD-540/PHARM/Mainigi
HFD-160/MICRO TL/Cooney
HFD-160/MICRO/Hussong
HFD-520/MICRO TL/Sheldon
HFD-520/MICRO/Altaie
HFD-725/BIOSTAT TL/Srinivasan
HFD-725/BIOSTAT/Thomson
HFD-880/BIOPHARM TL/Bashaw
HFD-560/DIV DIR/Bowen
HFD-560/DEP DIR/Katz
HFD-560/MO/Chin
HFD-560/MO/Aurecchia
HFD-560/Lipnicki
HFD-560/Freeman
HFD-560/Chang
HFD-560/Cothran
HFD-560/SPM/Cook
HFD-560/PM/Walther
HFD-560/PM/Wright
HFD-540/SPM/Kozma-Fornaro
HFD-540/PROJ MGR/Cross

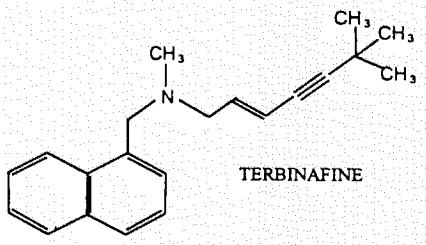
FEB 23 1999

NDA NO.: 20-980
PRODUCT: Terbinafine HCL 1% cream
SPONSOR: Novartis Pharmaceuticals
SUBM. DATE: March 27, 1998
REVIEWER Steven Aurecchia, MD

REVIEW OF NDA SUBMISSION

BACKGROUND:

This NDA supports the switch of terbinafine HCL 1% cream from prescription to non-prescription (OTC) marketing status for the topical treatment of tinea pedis (athlete's foot), tinea cruris (jock itch) and tinea corporis (ringworm). Terbinafine is a member of the allylamine group of antifungal compounds. It exerts its effect by inhibition of squalene epoxidase, an essential enzyme in sterol biosynthesis in fungi.



TERBINAFINE

Terbinafine was approved as a prescription product in December 1992 for the treatment of tinea pedis,[1] tinea cruris and tinea corporis due to *Epidermophyton floccosum, Trichophyton mentagrophytes*, or *Trichophyton rubrum*. A Supplemental Application was approved in January 1997 for the treatment of plantar tinea pedis (moccasin type) due to *Trichophyton mentagrophytes* or *Trichophyton rubrum*. The proposed OTC formulation will be identical to the currently approved 1% prescription cream.

Other currently approved new drugs indicated for the treatment of tinea pedis, tinea cruris and tinea corporis include butenafine 1%; ciclopirox olamine 1%; clotrimazole 1% (OTC); econazole nitrate 1%; ketoconazole 2%; miconazole nitrate 2%; naftifine 1%; oxiconazone nitrate; and sulconzaole nitrate 1%.

Monographed topical antifungal active ingredients for the OTC treatment of tinea pedis and/or tinea cruris and/or tinea corporis include clioquinol 3 percent, haloprogin 1%, miconazole nitrate 2%, povidone-iodine 10%, and tolnaftate 1%. Undecylenic acid, calcium undecylenate, copper undecylenate, and zinc undecylenate may also be used individually or in any ratio that provides a total undecylenate concentration of 10% to 25%.[2]

PHARMACOKINETIC AND METABOLISM:

These data were initially submitted with NDA 20-192 and have been incorporated by reference into this NDA.

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[1] Initial clinical studies were conducted primarily in patients with interdigital disease.
[2] 21 CFR Parts 310 and 333.

Percutaneous absorption of 1% terbinafine cream is low. At 24 hours after a single application of radiolabeled terbinafine under gauze (marketed formulation), greater than 95% of the applied dose is recovered in the gauze dressing and from the skin surface. The remainder of the dose, approximately 4%, is recovered in excreta, primarily the urine. Over an 11-day collection period, only low amounts of drug and/or metabolites appear in the excreta.

Following multiple applications of terbinafine cream, systemic absorption is low and highly variable. In a study of 16 healthy subjects, eight with normal skin and eight with skin artificially compromised by stripping, single and multiple applications (average 0.1 mg/cm^2 bid for 5 days) were made to various sites. In this study, the maximum measured plasma concentration of terbinafine was 11.4 ng/mL, and the maximum measured plasma concentration of the de-methylated metabolite was 11.0 ng/mL. In many patients, there were no detectable plasma levels of either parent compound or metabolite. Urinary excretion accounted for up to 9% of the topically applied dose; the majority excreted less than 4%. No measurement of fecal drug content was performed. In another study of 10 patients with tinea cruris, once daily application of 1% terbinafine cream for 7 days produced plasma concentrations of terbinafine of 0-11 ng/mL on day 7. Plasma concentrations of the metabolites of terbinafine ranged from [ ] ng/mL. In contrast, peak plasma concentrations of terbinafine of 1 µg/mL are measurable at 2 hours following oral administration of a single 250 mg dose. No effect of gender on blood levels of terbinafine was detected in clinical trials of the oral dosage form.

Approximately 75% of cutaneously absorbed terbinafine is eliminated in the urine. Based on studies with orally administered drug, terbinafine is extensively metabolized prior to renal excretion.

Protein binding of terbinafine in human plasma is high (99.6%) with low individual variation and no apparent concentration dependency.

Reviewer's Comments:

- Low systemic bioavailability is a favorable attribute for a candidate topical prescription-to-OTC switch product.
- To the extent that small amounts of terbinafine may reach the plasma compartment, saturated binding suggests a low potential for interaction with other protein bound drugs.

MARKETING EXPERIENCE:

Terbinafine HCL 1% cream is presently marketed worldwide by prescription in 82 countries. It is available OTC in Australia, Denmark, Korea, New Zealand, South Africa and Switzerland with the assistance/intervention of a pharmacist and directly to the consumer in Sweden. It has not been withdrawn from marketing in any country. The U.S. is the largest market for terbinafine, with sales of approximately/ [ ] tubes since its launch in 1993. Approximately [ ] tubes have been sold worldwide.

TERBINAFINE SAFETY:

Safety data is presented from several sources: nine double blind clinical trials, the Novartis safety database, the FDA spontaneous reporting system, and the American Association of

Poison Control Centers (AAPCC).[3] Clinical trials with patient enrollment for tinea pedis and for tinea corporis and tinea cruris are listed in Table I. Studies 2-1 and 2-2 and Studies 3-1 and 3-2 were presented in the original NDA for terbinafine cream 1% (NDA 20-192). The remaining trials are new investigations submitted with this NDA. Of 996 patients studied, 739 were for tinea pedis and 257 for tinea cruris/corporis.

TABLE I – Description of Clinical Trials

CLINICAL TRIALS FOR TINEA PEDIS			
Study No.	**N**	**Dosing Regimen**	**Control/Comparison Drug**
2-1	77	bid for 1 week	vehicle
2-2	110	bid for 1 week	vehicle
2508-01	218	bid for 1 week or bid for 4 weeks	clotrimazole bid for 1 week or bid for 4 weeks
SF0029	78	qd for 1,3,5 or 7 days	none
SF0040	256	bid for 1 week	clotrimazole bid for 4 weeks

CLINICAL TRIALS FOR TINEA CORPORIS AND TINEA CRURIS			
Study No.	**N**	**Dosing Regimen**	**Control/Comparison Drug**
3-1	86	qd for 1 week	vehicle
3-2	74	qd for 1 week	vehicle
SF2003	76	qd for 1 week	vehicle
SF2030	21	qd for 1,3,5 or 7 days	none

Table II shows the number of patients exposed to each treatment and demographics for the efficacy evaluable patients:

TABLE II – Patient Exposure and Demographics

CLINICAL TRIALS FOR TINEA PEDIS			
Study No.	**Exposure (total/terb./control)**	**Age Range**	**%M/F**
2-1	77/38/39	14-74	85/15
2-2	110/56/54	9-74	75/25
2508-01	218/109/109	7-83	76/24
SF0029	78/78/0	18-80	74/26
SF0040	256/131/125	12-81	74/26
all studies	739/412/327	7-81	77/23

CLINICAL TRIALS FOR TINEA CORPORIS/CRURIS			
Study No.	**Exposure (total/terb./control)**	**Age Range**	**%M/F**
3-1	86/42/44	5-89	78/22
3-2	74/36/38	5-76	57/43
SF2003	76/39/37	19-66	71/29
SF2030	21/21/0	22-67	73/27
all studies	257/138/119	5-89	70/30

[3] The sponsor's review of the literature identified no relevant reports.

Table III shows the total numbers of adverse events and discontinuations due to adverse events for these trials:

TABLE III – Adverse Events and Patient Discontinuations Due to Adverse Events

	Placebo Cont. Trials		Active Control Trials		No Control	Total Terbinafine
	Terb.	Vehicle	Terb.	Vehicle	Terb.	
TOTALS: Patients/AE's/Pts with AE's	211/13/8	212/11/9	240/85/54	234/60/39	93/13/11	550/111/173
Percent of Pts with AE's[1]	3.8%	4.2%	22.5%	16.7%	11.1%	13.3%
Adverse Event Rate[2]	0.06	0.05	0.35	0.26	0.13	0.20
Withdrawals due to AE's	1	1	1	2	0	2

[1] Patients with AE's/Total Number of Patients
[2] Total AE's/Total Number of Patients

Most of the adverse events reported were related to the skin and included irritation (rash, skin cracking, erythema, skin irritation, local irritation and vesicles), burning (pain, burning, stinging, tenderness and tingling), dryness and pruritis/itching (see below). Of the five patients who discontinued, two were from Study SF0040: one in the clotrimazole cohort who developed cellulitis of his right foot and another in the terbinafine group who developed severe erythema and swelling. One patient in Study 3-2 treated with vehicle developed an immediate pruritis and subsequent vesicular rash at the application site; another was considered a withdrawal because he died of asthma 18 days after treatment with terbinafine. A fifth subject from Study 2508-02 in the clotrimazole group was discontinued due to exacerbation of tinea pedis. Complaint rates for skin and appendages and all body systems are shown below in Table IV. This rate is the total number of complaints reported by the patient population. Some patients reported more than one complaint.

TABLE IV – Complaint Rates in Clinical Trials

	TERB/VEH[1]	VEH	TERB/CLO[2]	CLO	TERB[3]	TERB/ALL[4]	TOTAL[5]
Total AE's for Skin	3	3	19	27	5	27	57
Tot. Pts. with Skin AE's	2	2	12	15	5	19	36
Total AE's for All Body Systems	13	11	85	60	13	111	182
Total Patients	211	212	240	234	99	550	996
Pts with Skin AE's/Total Patients	0.95%	0.94%	5.0%	6.4%	5.1%	3.5%	3.6%
Total Skin AE's/Total Patients	0.014	0.014	0.079	0.115	0.051	0.049	0.057
Total Skin AE's/Total Patients	0.062	0.052	0.354	0.256	0.131	0.202	0.183

[1] AE's in terbinafine-treated patients in vehicle controlled trials
[2] AE's in terbinafine-treated patients in active (clotrimazole)-controlled trials
[3] AE's in uncontrolled trials
[4] Total terbinafine AE's for all trials
[5] All treatments

For the marketing period from October 1990 through December 1997, Novartis received eight spontaneous reports of serious adverse events involving topical terbinafine. Three of these are described below in cases retrieved from the FDA Spontaneous Reporting System (SRS) database (cases #1452080, #1819948, and #2042273). Summaries of the remaining five cases are as follows:

- A 60-year-old man was treated with Lamisil cream for athlete's foot. After one day, he was hospitalized with exanthematous pustulosis. The patient recovered fully in about three weeks. The reporter deemed the event probably related to Lamisil.
- On three occasions, a 36 year old woman with an apparent history of myasthenia gravis experienced neck weakness, dyspnea at rest and proximal arm weakness four days after using topical Lamisil for a nail fungus. The patient was hospitalized and her symptoms improved after plasmapheresis.
- A 41-year-old woman was treated with topical Lamisil followed by Lamisil tablets for onychomycosis during the first two weeks of pregnancy. She subsequently had a miscarriage. Concomitant medication included dydrogesterone (sic). She also had a history of reversal of laparoscopic sterilization and miscarriage. The physician deemed the event not related to Lamisil treatment.
- A 42-year-old male was treated for nail onychomycosis with Lamisil tablets for two weeks with intermittent application of Lamisil cream. On subsequent re-treatment with Lamisil tablets, he developed angioedema and maculopapular exanthema of the face and forearms. He was treated emergently with Fenistil and steroids with resolution of the angioedema.
- A female patient (age unspecified) treated for tinea corporis with lamisil cream twice a day and oral Lamisil twice daily for 14 days developed a contact dermatitis which was attributed to the cream.

In the FDA SRS database overall, there are 982 adverse event case reports for lamisil/terbinafine hydrochloride (domestic and foreign, all routes of administration, including unspecified)[4]. The vast majority (911) were received from the manufacturer. Of the 134 with a serious outcome, three occurred in conjunction with use of terbinafine cream. In four additional reports, the route of administration was not specified. Summaries of these seven cases follow:

#1452080: This 92-year-old female was treated initially with Canesten®, Daktacort® and Conotrane® creams for a fungal skin infection. The rash continued to spread and Lamisil® cream and oral fluconazole were added on January 17th and January 20th, respectively. Concomitant medications included amoxicillin (duration not given) and ibuprofen for several years and aspirin. On January 24th she was admitted to the hospital, where toxic epidermal necrolysis was diagnosed. All medications were discontinued that day. She died on January 30th.

#1819948: A patient (age, sex not given) was using Lamisil® cream for two to three weeks and developed erosion of the skin over the metatarsal area of the right foot. This was complicated by an ascending bacterial cellulitis (culture positive for group A Strep, Staph and Pseudomonas). Treatment with cephalosporin was initiated with no response after 10 days. The patient was hospitalized for further treatment. The treating podiatrist felt that the skin erosion was associated with the cellulitis and not the Lamisil® cream.

#1797655: This 62-year-old male was treated with ketoconazole cream bid and terbinafine cream bid for a suspected fungal infection on the face and the interdigital areas of both hands. The patient applied the creams mainly to the face and the forearms. He developed a severe rash after the second application, which prompted an ER visit and hospitalization. Concomitant medications included warfarin and Maxzide®. He was treated with steroids and diphenhydramine. As the patient had also handled straw from a flowerbed, the rash was judged

[4] Internal report generated 11/25/98. It covers the period 1993 through 1997. All terbinafine reports were included in the query to capture those with an unspecified route of administration.

a possible contact dermatitis, but a reaction to the topical antifungals could not be excluded. There was no rechallenge with either topical antifungal.

#1562324: This 46 year old male entered into a study of Lamisil cream for one week versus clotrimazole cream for four weeks in patients with tinea pedis. Concomitant medication included Prozac. He had a prior history of chronic fatigue syndrome, lumbar disc rupture and spinal fusion. Four weeks after the last test drug administration he developed a back injury and was hospitalized. The outcome was not reported and the code was not broken. The investigator considered this event unrelated to study drug.

#2037337: A 68-year-old woman began treatment with Lamisil in July 1992. After three weeks of treatment (dose, frequency and route of administration unspecified), she developed tinnitus. In December 1992 she complained of deafness and stopped Lamisil. The deafness persisted and audiometric tests done in July 1995 showed a perceptive hearing loss. The event was judged by the ENT specialist as likely coincidental and age-related.

#2042273: A female patient (age unspecified) experienced some type of cardiac decompensation after using Lamisil (frequency and route of administration unspecified) concomitantly with penicillin. The patient was hospitalized. No further details were provided. This may be an erroneous report, since the report date antedated the US approval of Lamisil. Alternatively, the patient may have purchased the product in another country.

#198568: A 53-year-old woman was treated with Lamisil for a fungal nail infection. She was in good general health apart from mild hypertension and knee problems. No concomitant medications were specified. After about three months of treatment, she presented with urticaria and severe itching, a high fever and arthritic pain. Lamisil was discontinued. Antihistamines and subsequently prednisolone tablets were started. Her condition worsened and she was hospitalized. Her hospital course was lengthy and complicated by adult respiratory distress syndrome, probable sepsis, coma and acute renal failure. After a lengthy hospitalization she recovered and had no active medical problems at the time of discharge.

A query of the FDA Adverse Event Reporting System (AERS)[5] for topical Lamisil returned 41 case reports involving 91 clinical adverse events (a single report may contain more than one event). With respect to organ systems, the distribution of events is shown in Table V:

TABLE V – Adverse Event Count by System and Organ Class

System/Organ Class	Count	System/Organ Class	Count
Skin/Subcutaneous Tissue Disorders	34	Nervous System Disorders	5
General/Administration Site Conditions	21	Metabolism/Nutrition Disorders	3
Surgical/Medical Procedures	8	Hepato-Biliary Disorders	2
Cardiac Disorders	7	Infections/Infestations	5
Immune System Disorders	5	Blood/Lymphatic System Disorders	1

The majority of reports were in the Skin and Subcutaneous Tissue Disorders and the General Disorders and Administration Site Conditions categories. In the former, non-specified dermatitis (16) and contact dermatitis (4) were the most frequent primary adverse event terms. In the

[5] Internal report generated 12/10/98. It includes case reports in the SRS database and captures most of 1998.

latter category, primary adverse event terms comprised non-specified site reactions (8), non-specified pain (5), non-specified edema (3), drug ineffective (3), and condition aggravated (2).

There are 148 cases of exposure to terbinafine cream in the American Association of Poison Control Centers (AAPCC) database.[6] Over 80% of these exposures were in young children. Ninety-nine percent were accidental, with ingestion the principal route of exposure. The level of toxicity was low. No cases involved major toxic effects or death. Occurrence of symptoms relative to route of exposure is shown in Table VI.

TABLE VI – Exposures to Terbinafine Cream: AAPCC Database

	N (% of Total Patients)					
	Ingestion	Dermal	Ocular	Other	Multiple	Total
Symptoms						148
none	113 (76.4)	9 (6.1)	1 (0.7)	4 (2.7)	8 (5.4)	135 (91.2)
related symptoms	2 (1.4)	1 (0.7)	7 (4.7)	1 (0.7)	2 (1.4)	13 (8.8)

Reviewer's Comments:

- The time and extent to which Lamisil® 1% cream has been marketed as a prescription product appears sufficient to support an OTC switch.
- In the primary trials of the safety and efficacy of Lamisil® cream, discontinuations due to adverse events were rare. The adverse event profile reflected primarily cutaneous problems, which were also infrequent. No new signals have appeared in the course of post-marketing surveillance attributable to either labeled use or misuse of the prescription product. True allergy to terbinafine has not been reported. Of course, post-marketing surveillance has significant limitations related to the nature of the reporting system. Reporting is voluntary and may be variable and incomplete; the population at risk is poorly defined; and our ability to infer causality or quantitate risk is quite limited.
- Drug-drug interactions do not appear to be a problem with Lamisil® 1% cream, but this issue has not been adequately studied.

NEW CLINICAL INVESTIGATIONS:

Five new clinical trials are presented in support of the efficacy of Lamisil® 1% cream for the one-week treatment of interdigital tinea pedis and tinea corporis/cruris (2508-01, SF 0040, SF 0029, SF2003, and SF2030). The efficacy variables in each of these trials are defined below. With the exception of delayed exclusions,[7] all patients with at least one assessment post-baseline were included in the efficacy analyses (clinically evaluable) for each visit at which they contributed an outcome.

1) Conversion to negative mycology: conversion of target lesions from positive to negative mycology, i.e., from both positive microscopy and positive culture at the beginning of the study to both negative microscopy and negative culture.

[6] Report from PEGUS Research commissioned by the sponsor. It covers the period from 1993 through 1996.

[7] If the baseline culture proved to be negative for dermatophyte or showed evidence of a concomitant yeast or bacterial infection, the patient was excluded and dropped.

2) Reduction/change in mean sum of signs and symptoms scores: the various signs and symptoms of the target lesion were graded on a scale of 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe).

3) Mycological cure: negative microscopy and culture with minimal signs and symptoms (i.e., total score of ≤2 for the target lesion).

4) Complete cure: conversion to negative microscopy and culture with no residual signs and symptoms.

5) Effective therapy: both complete cure and mycological cure.
Brief summaries of these five new trials follow. Data and data analyses presented are those of the sponsor.[8]

> Study 2508-01: A double-blind, parallel, multicenter trial comparing the efficacy and safety of 1% terbinafine cream with 1% clotrimazole cream in the treatment of tinea pedis (interdigital type) athlete's foot.

This study was designed to 1) compare one and four-week courses of topical therapy with two different antifungal agents; and 2) examine the relapse rates for both treatments over a twelve-week period. Specifically, the study compared the efficacy and safety of:

1) 1% terbinafine cream BID for one week with 1% terbinafine cream BID for four weeks
2) 1% terbinafine cream BID for one week with 1% clotrimazole cream BID for one week
3) 1% terbinafine cream BID for one week with 1% clotrimazole BID for four weeks
4) 1% clotrimazole cream BID for one week with 1% clotrimazole BID for four weeks

Patients receiving a one-week treatment course were evaluated at end of treatment, Day 8, and at follow-up visits Days 15 and 29, and Weeks 6,9 and 12. Those receiving a four-week treatment course were evaluated during treatment at Days 8 and 15, at Day 29 (end of treatment) and at follow-up visits at Weeks 6, 9 and 12 (Attachment 1). The lengthy follow-up period was designed to assess the duration of maintenance of clearing of the target lesions.

A total of 218 patients were enrolled in the study. There were 25 patients with either an entry criteria violation or no follow-up visit. Efficacy analyses were thus based on data from 193 evaluable patients. No statistical differences were evident between treatment groups with respect to mean age, gender, race (Caucasian versus non-Caucasian), or overall disease severity. Patients in the terbinafine one-week group tended to have longer disease duration; however, there were no statistically significant group differences with respect to duration of disease. Eighty-two percent of all patients had a baseline organism identification of *T. rubrum* and a comparison of the proportion of patients in each treatment group with this organism yielded no statistically significant results. The groups were also statistically comparable with respect to compliance (i.e., missed applications).

Mycological responses at endpoint and Week 12 are shown below in Table VII. A comparison between the one-week and four-week courses of terbinafine yielded a statistically significant difference favoring the one-week treatment course. Similar results were seen for the comparison between the one and four-week courses of clotrimazole (Fishers Exact Test, two-tailed).

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[8] Please refer to the primary clinical and statistical reviews of this NDA for technical comments.

TABLE VII – Study 2508-01: Mycological Responses

Treatment	Week 12	Endpoint
T1	29/34 (85%)	38/47 (81%)
T4	36/42 (86%)	39/46 (85%)
C1	13/37 (35%)	15/50 (30%)
C4	30/41 (73%)	34/50 (68%)
Comparisons	**p-value at Wk 12**	**p-value at Endpoint**
T1 vs. C1	<0.001	<0.001
C1 vs. C4	0.001	<0.001

T1 = terbinafine one-week regimen; C1 = clotrimazole one-week regimen.
T4 = terbinafine four-week regimen; C4 = clotrimazole four-week regimen.
Numerator = number of patients with negative prep. KOH and negative culture.
Denominator = numerator plus number of patients with either a positive KOH prep. or positive culture.

For signs and symptoms at the end of 12 weeks, the one-week terbinafine regimen was significantly more effective than the one-week clotrimazole regimen in reducing the overall score ($p = 0.001$) and the individual scores for desquamation ($p = 0.005$), fissuring ($p = 0.019$) and pruritus ($p = 0.054$).

Mycologically cured patients, as defined above, were considered as possible relapses (i.e., relapses or reinfections) if they subsequently had one or more positive cultures. Using Fisher's Exact Test and comparing the proportion of cured patients who relapsed, statistically significant differences favoring T1 were found for the comparisons with both C1 and with C4. A maximum possible relapse rate was also estimated assuming all mycologically negative patients whose last mycological evaluation prior to the week 12 endpoint would have converted to positive culture on or before this timepoint. Under these conditions statistical significance was achieved favoring T1 for the comparison with C1 and favoring C1 for the comparison of C1 with C4. State differently, 9.3% of cured patients (8.5% of all treated patients) who received the one-week terbinafine regimen and 11.4% of cured patients (10.9 of all treated patients) who received the four-week clotrimazole regimen experienced relapse.

Effective therapy was defined in the protocol as negative mycology with total score of signs and symptoms ≤ 2, and the scores for erythema, maceration, scaling, pruritus and fissures each <2. The results are summarized in Table VIII. At the end of the 12-week study period and at study endpoint (end of treatment), T1 was statistically superior to C1 ($p = 0.004$ and $p < 0.001$, respectively). C1 was also statistically superior to C4, but only at endpoint ($p = 0.020$).

——— next page ———

TABLE VIII – Study 2508-01: Effective Therapy

Treatment	Week 12	Endpoint
T1	22/34 (65%)	27/47 (57%)
T4	27/42 (64%)	27/46 (59%)
C1	11/37 (30%)	11/50 (22%)
C4	20/41 (49%)	23/50 (46%)
Comparisons	**p-value at Wk 12**	**p-value at Endpoint**
T1 vs. C1	0.004	<0.001
C1 vs. C4	N.S.	<0.020

T1 = terbinafine one-week regimen; C1 = clotrimazole one-week regimen.
T4 = terbinafine four-week regimen; C4 = clotrimazole four-week regimen.
Numerator = number of patients with negative prep. KOH and negative culture.
Denominator = numerator plus number of patients with either a positive KOH prep. or positive culture.

With regard to safety, adverse events were tabulated by body system and event. No statistical testing was done due to the small size of the treatment groups. Cutaneous adverse events are summarized in Table IX.

TABLE IX - Study 2508-01: Cutaneous Adverse Events

Event	Terbinafine		Clotrimazole	
	1 week	4 weeks	1 week	4 weeks
burning	0 (0%)	1 (2%)	3 (6%)	0 (0%)
Itching	0 (0%)	2 (4%)	2 (4%)	1 (2%)
pruritus	0 (0%)	1 (2%)	0 (0%)	0 (0%)

Study SF0040: A double-blind, randomized, parallel group study to compare Lamisil® (terbinafine) 1% cream given for one week with Canesten® (clotrimazole) 1% cream given for four weeks in tinea pedis (athlete's foot type).

This trial was designed to compare the safety and efficacy of Lamisil® cream applied twice daily for one week with Canesten® 1% cream applied twice daily for four weeks in the treatment of tinea pedis. Procedures and study visits are summarized on the attached flowchart (Attachment 2).

Of the 256 patients who entered the study, 211 were evaluable and included in the efficacy analysis. The treatment groups were well balanced with respect to age, sex, and race (the majority of patients were male and Caucasian). *T. rubrum* was recovered at baseline from the majority of patients (68/107 in the Lamisil® group and 79/104 in the Canesten® group). Patient compliance was also good for the duration of the trial. The median was 42 days for both treatment groups.

The numbers and percentages of patients mycologically cured (negative microscopy and culture) at each visit are shown in Table X. Results at weeks 4 and 6 show a statistically

significant difference between the two treatment groups favoring Lamisil®. There was no evidence of relapse following cessation of treatment in either cohort.

TABLE X - Study SF0040: Mycological Cure

Week	Lamisil®	Canesten®	% Difference	95% C.I.
1	42/107 (39.3%)	40/104 (38.5%)	0.8%	(-12.4, 14%)
2	75/107 (70.1%)	56/104 (53.8%)	16.3%	(3.4%, 29.2%)
3	90/107 (84.1%)	74/104 (71.2%)	12.9%	(1.9%, 23.9%)
4	100/107 (93.5%)	76/104 (73.1%)	20.4%	(10.7%, 30.1%) p = 0.0001
6	104/107 (97.2%)	87/104 (83.7%)	13.5%	(5.8%, 21.2%) p = 0.001

With respect to clinical signs and symptoms, the median change in total sign and symptom scores from baseline to week 6 showed no statistical difference between the two treatment groups (p = 0.72).

The percentage of patients treated effectively for each treatment group at each visit is summarized in Table XI. The difference between groups was statistically significant at weeks 4 and 6 and favored Lamisil®.

TABLE XI - Study SF0040: Effective Treatment

Week	Lamisil®	Canesten®	% Difference	95% C.I.
1	20/107 (18.7%)	9/104 (8.7%)	10.0%	(0.8%, 19.2%)
2	54/107 (50.5%)	24/104 (23.1%)	27.4%	(14.9%, 39.9%)
3	83/107 (77.6%)	50/104 (48.1%)	29.5%	(17.1%, 41.9%)
4	96/107 (89.7%)	61/104 (58.7%)	31.0%	(19.9%, 42.1%) p = 0.0001
6	96/107 (89.7%)	76/104 (73.1%)	16.6%	(6.3%, 26.9%) p = 0.002

Regarding adverse events, 22/131 (16.8%) in the Lamisil® group reported a total of 22 adverse events compared to 15/125 (12%) who reported a total of 21 adverse events with Canesten®. Four events in the Lamisil® group were considered probably or certainly drug-related. Two of these were severe. Symptoms included painful stinging and cracks, increased itch, irritation of the eyes and erythema/swelling of the skin. One patient discontinued Lamisil® due to erythema/swelling of the skin. In the Canesten® group, 3 adverse events of probable or certain relationship to therapy were reported. Two of these were considered severe. Signs and symptoms experienced included erythema, soreness and red rash. One patient with cellulitis of the foot, not likely Canesten®-related, discontinued treatment.

Study SF0029: A double-blind, randomized, parallel group study to investigate the safety and efficacy of Lamisil® (terbinafine) 1% cream applied once daily for one day, three days, five days, or seven days in patients with tinea pedis.

This uncontrolled trial was designed to explore the minimum duration of therapy needed for efficacy. Patients were randomized to one of four treatment sequences as shown in Table XII

(A = active; P = placebo). Procedures and the study visits are summarized on the attached flowchart (Attachment 3).

TABLE XII - Study SF0029: Treatment Sequences

	DAY						
	1	2	3	4	5	6	7
1 Day	A	P	P	P	P	P	P
3 Day	A	A	A	P	P	P	P
5 Day	A	A	A	A	A	P	P
7 Day	A	A	A	A	A	A	A

Of the 78 subjects entering the study, 65 were evaluable. Treatment groups were well matched for age, height, weight and race. The one and seven-day group having a higher number of females compare to the two other cohorts (7 and 8, respectively, versus 2 and 3 for the three-day and five-day groups). The groups were also well balanced with respect to baseline cultures, with the majority of infections caused by *Trichophyton rubrum*, as expected. Compliance was checked by collection and weighing of tubes after use. Although imprecise, Individual tube weights did not suggest overuse of lack of use of study medication.

The numbers and percentages of patients mycologically cured at each timepoint are shown in Table XIII. The p-values represent a chi-squared test of the differences between treatments.

TABLE XIII - Study SF0029: Mycological Cure

	DAY 0	DAY 8	DAY 14	DAY 28	DAY 84
1 Day	0/18	5/18 (28%)	13/18 (72%)	14/18 (78%)	17/18 (94%)
3 Day	0/18	6/18 (33%)	10/18 (56%)	15/18 (83%)	12/18 (67%)
5 Day	0/17	6/17 (35%)	10/17 (59%)	14/17 (82%)	15/17 (88%)
7 Day	0/12	6/12 (50%)	7/12 (58%)	10/12 (83%)	11/12 (92%)
p-value	---	0.66	0.74	0.97	0.09

At Day 28, no statistically significant difference in mycological cure rate was evident between treatments. The Day 84 assessment was included to explore the incidence of relapse following such short durations of treatment.

Mean total signs and symptoms scores decreased rapidly over time in all treatment groups. At day 28, the mean total score was not statistically significantly different between treatments. The same was true for the Day 84 timepoint.

Effective treatment in this study was defined as mycological cure with a total signs and symptoms score of '2' or less (provided that the '2' comprised two milds and not one moderate score). All other outcomes were classified as ineffectively treated. Results are shown in Table XIV. The differences between the treatment groups were not statistically significant at any timepoint (chi-squared test of the differences between treatments).