8.1.4.4.3 Safety Outcomes

Adverse Events Reported:

In the Lamisil treatment group 22/131 (17%) patients reported 22 adverse events. Four of these were judged as probable or of certain relationship to therapy.

Adverse events coded as severe were:

- erythema/swelling of the skin (resulted in withdrawal from the study during the first week of treatment)
- eye irritation

Adverse events coded as mild to moderate:

- painful stinging and cracks
- increased itch
- swelling of the skin.

In the Canesten treatment group there were 15/125 (12%) patients reporting 21 adverse events. One patient in the Canesten treatment group, patient 274 (Center 35), withdrew during Week-1 of the study who developed cellulitis of the right foot. The relationship to the drug was judged improbable by the investigator.

The Adverse Event Table is verbatim from the sponsor's submission (Table 20, Vol. 16, pgs. 16 056 and 16 057):

Table 16.

(TABLE 20)
Adverse Events (All Patients)

Treatment	Centre	Patient	Week	Event	Severity of Event	Relation to Drug	Duration of Event	Outcome
Lamisil®	1	3	3	Alveolar Abscess	Moderate	Improbable	Continuous	Other (Refered to G.P.)
	1	307	3	Pulled muscle in neck	Moderate	Improbable	-	Tolerated
	4	32	2	Pain and itching at target	Moderate	Uncertain	5 Days	Tolerated with Treatment
	4	378	1	Angina	Mild	Excluded	10 Mins	Disappeared Spontaneously
	4	380	1	Painful stinging and cracks	Mild	Probable	120 Hours	Tolerated
	4	405	4	Pain and cracks between toes	Moderate	Uncertain	3 Days	Tolerated
	4	408	4	Infected Foot	Moderate	Excluded	5 Days	Tolerated with Treatment
	8	60	2	Cold Feet	Mild	Uncertain	7 days	Disappeared Spontaneously
	8	61	1	Increased Itch	Mild	Probable	5 Days	Disappeared Spontaneously
	8	62	4	Neurological migraine	Severe	Improbable	10 Days	Tolereated with Treatment
	12	91	1	Nausea	Moderate	Uncertain	Continuous	Disappeared Spontaneously
	13	98	1	Irritation of eyes	Severe	Probable	2 Hours	Tolerated
	18	138	3	Cold	Mild	Excluded	Continuing	Tolerated with Treatment
	26	202	1	Itching as site	Moderate	Uncertain	1 Hour	Disappeared Spontaneously
	30	237	3	Acne/form	Mild	Improbable	Continuing	Tolerated
	33	257	1	Increased pruritis	Mild	Uncertain	Intermittant	Tolerated
	34	266	4	Coryza	Moderate	Excluded	10 Days	Disappeared Spontaneously

Table 16. (TABLE 20)(CONTINUED)

Treatment	Centre	Patient	Week	Event	Severity of Event	Relation to Drug	Duration of Event	Outcome
Lamisil®	34	385	6	Diarrhoea	Moderate	Excluded	3 Days	Disappeared Spontaneously
	37	292	2	Diarrhoea	Mild	Improbable	36 Hours	Tolerated with Treatment
	39	318	1	Erythema/Swelling of skin	Severe	Certain	48 Hours	Drug Stopped
	39	345	1	Acute Coryza	Mild	Improbable	2 Days	Disappeared Spontaneously
	39	404	3	Intense Irritability on application of cream	Moderate	Uncertain	7 Days	Disappeared Spontaneously

8.1.4.5 Conclusions Regarding Efficacy and Safety

This study was not evaluated for efficacy. The use of the vehicle (placebo) in this study during Weeks 2 -4, introduces a confounding variable in the sponsor's efficacy claim of superiority over comparator. The sponsor acknowledged on page 16 031 the following: "Although cure rates with only one week of Lamisil® were impressive it must be noted that the vehicle cream (placebo cream) applied for three weeks following the application of the active substance may have contributed to these results. The application of the base may have helped maintained the levels of the active substance in the stratum corneum by acting as a chemical occlusive dressing."

There were 7 patients listed in the 10 - 19 year age range; however, data listings including this demographic data were not submitted. Patient outcome in this age group is unknown.

8.1.5.1 Reviewer's Trial #5 (Tinea Pedis (interdigital type) Sponsor's Protocol # SF0029

Study dates were between June 5, 1990 and November 15, 1991. This study was conducted in the United Kingdom.

Title: "A Double-Blind, Randomized, Parallel Group Study to Investigate the Safety and Efficacy of Lamisil ® (terbinafine) Cream Applied Once for One Day, Three Days, Five Days, or Seven Days in Patients with Tinea Pedis"

8.1.5.1 Objective/Rationale:

To investigate determine the minimum duration of therapy of Lamisil® (terbinafine) 1% Cream in the treatment of interdigital tinea pedis.

8.1.5.2 Design

This was an uncontrolled, multicenter, double-blind, randomized, parallel-group study in the treatment of tinea pedis. This study was submitted by the sponsor in support of safety.

Study Plan

Inclusion criteria restricted entry to patients over 18 years of age. No rationale for this age restriction was provided. Patients were randomly assigned to one of four treatment schedules for terbinafine cream 1% : one day, three days, five days or seven days. Each patient was be given seven tubes, one for each day of the week to be applied once daily in the evening. The material for each treatment group were as follows:

	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

(A: Active P: Placebo)

Follow-up evaluations were scheduled at 2 weeks (14 days), 1 month (28 days), and 3 months (84 days).

8.1.5.4.1 Populations enrolled/analyzed

A total of 78 patients were recruited. The mean age ranged from 34 in the seven day group to 37 in the five day group. The majority of patients were male and Caucasian. The inclusion/ exclusion criteria were similar to the previous studies except enrollment was limited to 18 years or older. Additionally, 11 of the 65 evaluable patients had a diagnosis of plantar type tinea pedis. The majority of the patients were infected with T. rubrum.

8.1.5.4.3 Safety outcomes

According to the sponsor, 10 adverse events were discovered as entries under the concomitant medication listings for this study and Study SF0030. Study SF0030 was not listed in this NDA review and it could not be determined by this reviewer whether this was a typographical error. There were similarly numbered studies (SF2003 listing no adverse events or SF2030 listing 3 terbinafine treated patients listed with adverse events). According to the sponsor, the concomitant medication listing was scanned for signs or symptoms not present on the first day of the study. The sponsor did not list the adverse events even though the study was specifically identified (pg.10 007) as only discussed in the Integrated Summary of Safety specifically in support of safety. It was implied that the 10 adverse events were not felt to be serious or related to the study treatment. None of the adverse events had a recorded severity.

The following listing may not have captured all AEs occurring during the course of the trial. Dates of study entry for the patients were not provided. One adverse event, pruritus on back, was listed under the adverse event heading.

Probable adverse events (as extracted by this reviewer from the concomitant medication listings) follow. The adverse events, excluding tinea pedis, are those AEs which appeared to be present on week one.

Adverse Events (those preceded by an asterisk may have been study drug related):

sunburn
*rash on foot
*heel lesion
tonsillitis
vaginal thrush
asthma
*fissures-toes
rhinitis
hypertension (reported in two patients)
ingrowing toenail
UTI

8.1.5.5 Conclusion Regarding Efficacy Data and Safety

Study SF 0029 is uncontrolled and was submitted by the sponsor in support of safety (pg. 10 007, Vol 10). Statistical validation for this study was not performed. The design of this study does not support efficacy claims.

In the Integrated Summary of Safety (pg. 10 013) 10 adverse events were discovered as entries under the concomitant medication listings for Study SF0030 and Study SF0029. An amended list

of adverse events was not provided. It was implied that the 10 adverse events were not felt to be related to the study treatment; however, this assumption may not be accurate. None of the adverse events had a recorded severity.

The sponsor was not diligent in providing adverse events in an easily reviewable format for this study or correcting the error "...no adverse events were reported in the study." statement contained in the conclusion of the study synopsis (pg. 20 013, vol. 20). Since, according to the sponsor, this study was submitted in support of safety a correction should accompany the study report.

8.1.6 Reviewer's Trial #6 Tinea Pedis (moccasin type) Studies # 2509-01 and # 2509-02

Study #	Title
2509-01	**"A Double-Blind, Randomized, Parallel-Group, Vehicle Controlled Multicenter Study in Patients with Tinea Pedis of the Moccasin Type"**
2509-02	**"A Double-Blind, Randomized, Parallel-Group, Vehicle Controlled Multicenter Study in Patients with Tinea Pedis of the Moccasin Type"**

The following is referenced from approved NDA 20-192/1S. According to the Medical Officer's review dated December 13, 1993, Study 2509-01 and Study 2509-02 provided adequate demonstration of the effectiveness of Lamisil cream in the treatment of tinea pedis of the moccasin type. Both studies demonstrated a superiority of Lamisil cream over the vehicle at endpoint with the exception for the effect of fissuring. The majority of the patients were infected with tinea rubrum in both studies.

8.1.6.4.3 Safety outcomes

There were no adverse events reported in the active group. Mild burning of the bottom of the feet in one vehicle patient was reported. Safety and efficacy in pediatric patients below the age of 12 years was not established.

8.1.6.5 Conclusions Regarding Efficacy and Safety Data

Terbinafine HCl cream, 1% was approved as safe and effective under NDA 20-192/1S for treatment of moccasin type tinea pedis and supports the sponsor's current application. The sponsor is requesting an OTC switch for the moccasin type tinea pedis indication at the same duration and frequency of application as the approved product; therefore, re-analysis of the efficacy data is not needed.

No adverse events were reported. Safety and efficacy in pediatric patients below the age of 12 years was not established.

Indication #2 **Tinea Corporis/Cruris**

Introduction

Studies 3-1 and 3-2 were reviewed in support of the efficacy and safety of once daily application of terbinafine cream for one week. The remaining studies were reviewed primarily for safety of use in an OTC setting without the intervention of a learned intermediary.

Pivotal studies (3-1 and 3-2) were not independent studies. Dr Zaias was a principal investigator in each study. In the original review, rather than disqualifying both studies, data were analyzed by excluding Dr. Zaias from one of the studies. According to the original NDA 20192 medical reviewer comments (pg. 125), supplemental analysis by the FDA statistician performed concluded that there was "...a clear superiority for active over vehicle ($p = 0.05$ or less) at all time points whether Dr. Zaias is included in the data or not for mycology conversion and effective therapy." Supplemental analysis of tinea cruris confirmed that terbinafine is more effective than vehicle when used once daily for one week in tinea cruris.

Studies SF2003 and SF2030 were not considered as pivotal studies and were not analyzed for efficacy although efficacy data were submitted by the sponsor. These studies were reviewed primarily for safety.

8.2 Indication # 2 Tinea corporis/cruris

The following inclusion/exclusion criteria were common for the tinea corporis/cruris studies; however, the following differences were noted:

1) Entry criteria for pivotal studies (3-1 and 3-2) was limited to a diagnosis of tinea cruris.
2) Studies SF 2030 and SF 2003 entry criteria allowed entry with a diagnosis of tinea corporis or cruris.

Inclusion criteria:

1. Sex: male or female. Non-pregnant female patients of childbearing age may only be included if reliable contraceptive measures are maintained

throughout the study.

2. Age: A patient of 18 years or older may be treated.
3. Legal status: able to give, or have parent or guardian give, informed consent to participate in the trial.
4. Indication: Tinea cruris, suspected clinically and provisionally confirmed by detection of hyphae in a KOH wet mount.

Exclusion criteria

1. Pregnant or breast-feeding women.
2. Radiation therapy, systemic therapy with cytostatic or immunosuppressive drugs, or therapy with antibacterial, antifungal, antiviral or anthelminthic drugs, either currently or during the two weeks preceding initiation of drug trial.
3. Inability to give reliable answers to questions on history, subjective symptoms and tolerance.
4. Anticipated unwillingness or inability on the part of the patient to comply with the requirements of the study.
5. Inability to culture a dermatophyte, or culture of pathogens other than a dermatophyte from the lesion (delayed exclusion)

Efficacy Endpoints were similar to those of the tinea pedis studies previously listed with differences noted in the studies.

8.2.1 Reviewer's Trial #1 Tinea corporis/cruris Study # 3-1 (SF2002)

(Note: The original clinical review of NDA 20-192, stamped 09/25/92, consisted of 208 pages. Some summaries, tables, and comments from efficacy results of studies 3-1 and 3-2 that follow were extracted from that review.)

Study dates: May 1988 to April 1989.

Title: "Double-Blind, Multicenter, Clinical Therapeutic Trial of the Efficacy and Safety of Topical Terbinafine 1% Cream Applied Once Daily Compared to Vehicle During One Week in Patients with Tinea Corporis/Cruris"

8.2.1.1.1 Objective/Rationale

Evaluation of safety and efficacy of topical 1% cream SF 86-327, 1% terbinafine HCl cream, compared to vehicle placebo in the treatment of tinea cruris.

8.2.1.2 Design

This was a double-blind, randomized, parallel-group, multicenter study.

Study Plan

Patients with a diagnosis of tinea corporis, tinea cruris, or both, confirmed by positive KOH and culture, applied 1% terbinafine HCl cream once daily for one week. Follow-up evaluations were scheduled at EOT, weeks 2, and 4.

8.2.4 Results

8.2.1.4.1 Populations enrolled/analyzed

Table 17. Disposition

Pt. Population	Terbinafine	Vehicle	Total
Entered	40	43	83
Delayed excel.	2	1	3
Dropouts	4	5	9
Evaluable cases	34	37	71

Table 18. Demographics

Pt. Population	Terbinafine	Vehicle	Total
male/female	27/9	31/7	58/16
age (mean) yrs.	38.9	35.6	37.2

Thirty-five patients had lesions located in the inguinal region. The age range was 5 to 89 years. There were 5 pediatric patients exposed to active drug. The ages of the pediatric patients were as follows: one 5 year old, one 7 year old, two 14 year old, and one 17 years of age.

Racial Distribution

Thirty-three (45%) enrolled evaluable patients were Caucasian, with 11 (15%) Black, 16 (22%) Hispanic, and 14 (19%) listed as Mestizo.

Infecting organisms

The infecting organisms were T. rubrum (62%), T. mentagrophytes (22%), E. floccosum (11%), M. canis (3%), M. gypsem (1%), and T. violaceum (1%).

8.1.1.4.2 Efficacy endpoint outcomes

Efficacy endpoints were as follows:

1) Mycological Cure defined as KOH, culture negative, and signs <=2 plus a maximum score of "1=mild" for each of erythema, desquamation, and pruritus.
2) Complete Cure defined as KOH and culture negative with no residual signs and symptoms.

For Mycological Cure at the end of one week treatment, statistical review concluded that statistical significance over vehicle occurred at Week-1 ($p \leq 0.006$), Week-2 ($p \leq 0.001$), Week-4 ($p \leq 0.001$), and LOCF.

Statistical significance was demonstrated for terbinafine over vehicle. Statistical significance

was demonstrated for Complete Cure at the end of one week treatment ($p \leq 0.034$) , Week-2 ($p \leq 0.036$), Week- 4 ($p \leq 0.006$) and at Week-6 ($p \leq 0.006$).

8.1.1.4.3 Safety outcomes

All patients were included in the safety analysis. There were no discontinuations due to therapy. Three adverse events were reported. One patient reported two episodes of moderate episodes of sinusitis. One placebo patient reported a mild headache. No AEs were thought to be drug related.

8.2.2.5 Conclusions Regarding Efficacy and Safety Data

This study supports the sponsor's claim of efficacy and safety of terbinafine HCl cream, 1% at once daily application for one week in treatment of tinea corporis/cruris. Entry criterion; however, limited enrollment to patients with a diagnosis of tinea cruris. An amended protocol was not submitted to this NDA by the sponsor. The number of pediatric patients enrolled, although small, supports the use in pediatric patients 12 to 17 years of age.

8.2.2.1 Reviewer's Trial #2 (Tinea corporis/cruris) Sponsor's Study # 3-2 (SF2004)

(Study dates: August 8, 1988 to August 18, 1989)

Title: "Double-Blind, Multicenter, Clinical Therapeutic Trial of the Efficacy and Safety of Topical Terbinafine 1% Cream Applied Once Daily Compared to Vehicle During One Week in Patients with Tinea Corporis/Cruris"

The objective, study design, and procedures were the same as Study 3-1.

8.2.4 Results

8.2.2.4.1 Populations enrolled/analyzed

Table 19. Patient Disposition

Pt. Population	Terbinafine	Vehicle	Total
Entered	36	38	74
Delayed excel.	1	0	1
Dropouts	5	3	8
Evaluable cases	30	35	65

Table 20. Demographics

Pt. Population	Terbinafine	Vehicle	Total
male/female	19/11	17/18	36/29
age (mean) yrs.	31.1	39.9	35.8

The majority of patients had lesions located in the inguinal area. The age range was 5 to 76 years. There were 5 pediatric patients exposed to active drug. The age of the pediatric population were as follows: one 6 year old, one 14 year old, two 16 year old, and one patient 17 years of age.

Racial Distribution

Enrolled evaluable patients were listed as 30 (46%) listed as Mestizo, 22 (34%) Latino, 11 (17%) were Caucasian, and 2 (3%) Black .

Infecting organisms

The infecting organisms were T. rubrum (54%), T. mentagrophytes (37%), E. floccosum (3%), M. canis (2%), M. gypsem (2%), and M. audouini (3%).

8.1.1.4.2 Efficacy endpoint outcomes

Efficacy endpoints were as follows:

1) Mycological Cure defined as KOH, culture negative, and signs <=2 plus a maximum score of "1=mild" for each of erythema, desquamation, and pruritus.
2) Complete Cure defined as KOH and culture negative with no residual signs and symptoms.

For Mycological Cure at the end of one week treatment, statistical review indicated that significance over vehicle was demonstrated at Week-1, Week-2, Week-4, and LOCF with $p \leq 0.001$ for each measure.

Statistical significance of terbinafine over vehicle was demonstrated for Complete Cure at Week-2 ($p \leq 0.001$), Week- 4 ($p \leq 0.001$) and at Week-6 ($p \leq 0.001$).

8.1.1.4.3 Safety outcomes

There was one death reported in a 67 year old male enrolled in the active group. The death occurred 18 days after application of terbinafine HCl cream, 1%. Cause of death was listed as asthma and no causality to use of terbinafine is suspected.

There were two adverse events (pruritus and vesicles) reported occurring in one vehicle group patient. These were thought to be study related. There were no discontinuations reported due

to therapy. Two adverse events were reported. One patient reported two episodes of moderate episodes of sinusitis. One placebo patient reported a mild headache. No AEs were thought to be drug related.

8.2.2.5 Conclusions Regarding Efficacy and Safety Data

This study supports the sponsor's claim of efficacy and safety of terbinafine HCl cream, 1% at once daily application for one week in treatment of tinea cruris/corporis. The number of pediatric patients enrolled, although small, supports the use in pediatric patients 12 to 17 years of age.

8.2.3.1 Reviewer's Trial #3 (tinea corporis/cruris) Sponsor's Study Code # SF 2003 (Project # SF 86-327)

(Study start date: June 20, 1988 Last patient completed: December 8, 1989)

Title: "A General Practice Multicenter Double-Blind Therapeutic Trial of the Efficacy and Safety of Topical SF86-327, 1% Cream Applied Once Daily Compared to Its Vehicle During One Week in Patients with Tinea Corporis/Cruris"

8.2.3.1 Objective/Rationale

The trial was designed to compare the efficacy and tolerability of once daily application of topical terbinafine with that of placebo in the treatment of tinea corporis/cruris.

8.2.3.2 Design

This study was restricted to 18 years or older. No rationale for this restriction was provided. This was a multicenter, randomized, efficacy and safety study comparing once daily topical administration of terbinafine with placebo in patients with tinea corporis/cruris in general practice. Treatment was administered for one week.

Study procedure

The study compared once daily topical application of terbinafine 1% cream or vehicle in patients with tinea corporis or tinea cruris. Patients were assessed pre-treatment, at the end of one week treatment, and at two follow-up visits at Weeks 2 and 4 of the study. Treatment was once daily for one week.

8.2.3.4 Results

8.2.3.4.1 Population

Seventy-six male and female patients with tinea cruris or corporis were recruited from 18 centers into the study; however, only 31 patients were evaluable. Eighteen investigators participated in the multicenter, double-blind, vehicle controlled study conducted in the United Kingdom. Principal Investigator was Dr. J.C. Coley, Cheshire, UK. No investigator CVs were provided.

Patient disposition:

Disposition	Total No.	Terbinafine Arm	Vehicle Arm
Total Entered	76	39	37
Delayed Exclusion	30	18	12
Discontinued	15	7	8
Evaluable	31	14	17

Only 41% of the enrolled population was evaluable, however, no differences between active or control exclusions were apparent. Delayed exclusions were patients with positive microscopy that were not subsequently confirmed by mycological culture. Fifteen patients were listed as dropped from the study. Three were lost to follow-up and 12 were protocol violations.

Demographics:

Twenty-six of the 31 evaluable patients were Caucasian. Of these five non-Caucasians, the ethnic origin was listed as other (Indian, Anglo-Indian, Oriental) for three and not stated for two others.

Table 21. Demographics

Patient Population	Total	Terbinafine	Placebo
Total evaluated	31	14	17
Male/Female	22/9	9/5	13/4
Age (min/max)	19/66	19/66	19/64
Age (mean)	39	39	39

No pediatric patients were enrolled in this study.

Distribution by Center:

Centers were pooled with two groups. Center A is listed as Manchester with a total enrollment of 47 and Center B as non-Manchester with an enrollment of 29.

Table 22. Distribution By Indication Total Entered (N = 76) Evaluable (N = 31)

Diagnosis	Status	Center A			Center B		
		Active	Placebo	Total	Active	Placebo	Total
Tinea Cruris*	Evaluable	6	4	10	3	5	8
	Drop-outs	10	6	16	7	7	14
Tinea Corporis*	Evaluable	6	7	13	0	3	3
	Drop-outs	6	8	14	3	2	5

* Some patients had a diagnosis of both tinea cruris and tinea corporis.

The majority of the patients were infected with *Trichophyton rubrum.*

8.2.3.4.2 Efficacy Endpoint Outcomes

This study was not considered pivotal. It was reviewed primarily for safety.

8.2.3.4.3 Safety Outcomes

No adverse events were reported.

8.2.3.5 Conclusion Regarding Efficacy and Safety Data

Study SF2003 in support safety of terbinafine 1% cream in the treatment of tinea cruris is marginal. There were only 9 (3%) evaluable patients with a diagnosis of tinea cruris receiving active drug. The sample size of patients with a diagnosis of tinea cruris was small. No pediatric patients were enrolled.

8.2.4.3 Reviewer's Trial #4(Tinea corporis/cruris) Sponsor's Study Code # SF 2030

Study date: Between May 23, 1990 and September 23, 1991.

Title: "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 Corporis/Cruris"

Objective/Rationale

This study was submitted in support of safety. The study objective is to investigate the safety and efficacy of Lamisil 1% cream given once daily for one day, three days, five days or seven days in male or female patients, 18 years or older, with tinea corporis or tinea cruris and to determine the minimum duration of treatment.