Study Design
This was a multicenter, double-blind, randomized, parallel group study conducted in the United Kingdom. All patients were given seven tubes; however, active treatment was once daily for one day, three days, five days or seven days only. Vehicle was used for the remaining trial days, except for the 7-day treatment group. There was no vehicle arm in this study.

8.2.4.4 Results
Twenty-one patients were recruited to the study. Fourteen patients were evaluable. The majority of patients had *T. rubrum* infection.

8.2.4.4.2 Efficacy Endpoint Outcome
This study did not contain a vehicle arm and statistical analysis was not performed by the FDA. This study has minimal regulatory utility in support of efficacy.

8.2.4.4.3 Safety Outcomes
There were no reports of adverse events.

8.2.4.5 Conclusions Regarding Efficacy and Safety Data
This study was reviewed primarily in support of safety. Of the 14 evaluable patients, it is unclear how many had a diagnosis of tinea cruris. The sample size is inadequate and the study design does not support efficacy of terbinafine 1% cream in the treatment of tinea cruris. According to the sponsor, in the small numbers of patients studied there were no differences in efficacy in terms of mycological cure and percentage of patients effectively treated between the four groups was demonstrated in the small numbers of patients studied.

9 Overview of Efficacy
The sponsor's claims of efficacy were supported in treatment of interdigital type tinea pedis by Studies 2-1 and 2-1, moccasin type tinea pedis by Studies 2509-01 and 2509-02, and tinea cruris/ corporis by Studies 3-1 and 3-2.

Tinea Pedis

Definitions: Results are presented as complete cure (negative KOH and culture with no residual signs or symptoms) and mycological cure (KOH and culture negative with residual signs less than or equal to 2 plus a maximum score of 1=mild for each of erythema, fissuring, maceration, desquamation and pruritus).

Tinea Pedis (Interdigital) Study 2-1:
Patients were treated for one week then evaluated at EOT, 2,4, and 6 weeks. As expected, there is no clinical/statistical difference in treatment outcomes between the vehicle and terbinafine arms at EOT (1 week). During the following weeks (2,4, and 6) there are no subjects in the vehicle

arm who ever achieve complete cure. Meanwhile, in the terbinafine arm the complete cure rate shows initial statistical significance(p=0.035) from the vehicle at 2 weeks with 12% cured, and maintains statistical significance as the cure rate rises to 21% at week 4 and 23% at week 6. The subjects achieving mycologic cure (still minimal residual signs) also separate statistically (p=0.004) from the vehicle at the end of week 2, with a 28% mycologic cure rate in the terbinafine group which increases to 54% at week 4 and 65% at week 6. The vehicle group has a 6% mycologic cure rate by week 6.

Following one week of treatment, terbinafine demonstrates efficacy over the vehicle in both clinical cure and mycologic cure by week two. Terbinafine demonstrates successful treatment in a majority of patients by week 5, but the highest rate of complete clinical cure achieved is in 21% of subjects at week 6.

Tinea Pedis (Interdigital) Study 2-2:
Study 2-2 demonstrates a similar pattern to study 2-1, although superiority over vehicle in complete cure (p=0.006) and mycologic cure (p=0.002) is not demonstrated until slightly later at week 4. The complete cure rate rises from 23% at week 4 to 37% at week 6, with a parallel rise in the mycologic cure rate from 47% at week 4 to 66% at week 6. Interestingly, the vehicle group in this study has a 15 percent mycologic cure rate by week 6.

Following one week of treatment, the terbinafine demonstrates successful treatment in a majority of patients by week 6, but the highest rate of complete clinical cure achieved is in 38% of subjects at week 6.

Tinea Pedis (Interdigital) Study 2508-01(Tables 10 and 11 in statistical review):
This study provides a head to head demonstration of the outcomes of treatment with terbinafine for one week versus 4 weeks. At no point (including an extended follow-up out to 12 weeks) is there a demonstration of statistical significance between the outcomes of the one week treatment arm versus the four week treatment arm for either of the endpoints (complete cure and mycologic cure.) This study suggests that clinically there is no apparent difference in patient results between a one week and a four week course of terbinafine in the treatment of the interdigital variant of tinea pedis. The results of this study support labeling for a shorter time course than currently approved. This study is useful in contributing information to support the labeling of the OTC product, but is not particularly useful in providing information concerning the efficacy of terbinafine in comparison with other active agents. The statistical review elucidates the mathematical rationale for this conclusion. In addition, the clinical design of this study could have been enhanced by the inclusion of a blinded placebo arm.

Tinea Pedis (Interdigital) Study SF0040
This study compared the efficacy of one week of terbinafine compared to four week of clotrimazole therapy in the treatment of interdigital tinea pedis. There are limits to the utility of

this study, as the one week treatment arm actually had a 3 week vehicle phase for blinding against the 4 week treatment. Results are not presented for "complete cure". At the EOT (1 week), 19% of terbinafine treated patients demonstrated effective treatment, 50% at end of 2 weeks, 78% at end of three weeks, 90% at end of 4 weeks and 90% at the end of 6 weeks. Conversion rates to KOH negativity consistently increase over time. This study is supportive of the efficacy of terbinafine used for one week in the treatment of interdigital tinea pedis.

Tinea Pedis (Moccasin)

As the sponsor is not requesting a change in the treatment directions for use without a prescription, the currently approved prescription instructions of twice daily treatment for 2 weeks do not require additional demonstration.

Tinea Pedis Efficacy Conclusion

The sponsor has adequately demonstrated the efficacy of treatment with terbinafine twice daily for one week (tinea pedis/interdigital type) and twice daily for two weeks (tinea pedis/ moccasin plantar type). The clinical effect may not be apparent for 2-6 weeks following the end of treatment. The majority of patients do not achieve clinical cure at any timepoint. A majority of patients do achieve successful treatment by week 4.

Tinea Corporis/Cruris

Evidence of efficacy is apparent at a substantially earlier timepoint in the tinea corporis/cruris study than in the tinea pedis trials.

Study 3-1

Study 3-1 (SF2002) demonstrates that at the EOT(week 1) and continuing through week 4 there is a statistically and clinically significant difference between the terbinafine and vehicle arms for both complete cure AND mycologic cure. At EOT 15% of terbinafine treated patients are completely cured, increasing to 40% at week 2 and 74% at week 4. Similarly, at EOT 32% of terbinafine patients are successfully treated (mycologic cure), increasing to 75% at week 2 and 88% at week 6.

Study 3-2

These results are confirmed in Study 3-2 (SF2004), in which there is again demonstration of statistical and clinically significant differences between the terbinafine and vehicle arms for both complete cure and mycologic cure starting at week 2 for complete cure and week 1 for mycologic cure. At EOT(week 1), 3% of terbinafine treated patients are completely cured, increasing to 54% at week 2 and 77% at week 4. Similarly, at EOT, 41% of terbinafine patients are successfully treated (mycologic cure), increasing to 77% at week 2 and 90% at week 6.

Study SF2003/SF 86-327
This new study did not demonstrate statistical significance between the active and vehicle arms at any timepoint for the outcomes complete cure or conversion to KOH negativity. The only statistically significant outcome (p=0.01) was the comparison of "effective therapy" between the active (12/14=86%) and vehicle (6/17=35%) at week 4.

Sponsor's Metaanalysis: Integrated Summary of Efficacy
The sponsor has presented a metaanalysis in the integrated summary of efficacy at week 4 for the tinea corporis/tinea cruris Studies 3-1, 3-2, and SF2003. Combining these three studies brings the total sample size to 80 patients. At week 4, there is a significant difference ($p<0.001$) between placebo and terbinafine treatment in all three outcomes of complete cure (66%), effective treatment (84%), and conversion to KOH negativity(90%).

Tinea Corporis/Cruris Efficacy Conclusion
The sponsor has adequately demonstrated the efficacy of terbinafine once daily treatment for the indications tinea corporis and tinea cruris. In contrast to the pedal infections, a majority of patients(approximately 50%) do achieve complete clinical cure at week 2, and a total of approximately 75% patients demonstrate successful treatment at week 2.

Overall Conclusion
Efficacy at the proposed dose and duration has been demonstrated for terbinafine HCl cream, 1% in the treatment of :

- between the toes (interdigital) tinea pedis for twice daily applications for one week
- side/bottoms of feet (moccasin) tinea pedis for twice daily applications for 2 weeks
- tinea cruris/corporis with once daily applications for 1 week.

10 Overview of Safety

Safety profiles were presented by the sponsor from each for only the nine key trials presented under this NDA. Additional safety data from other formulations (e.g., the emulsion gel) were included. The emulsion gel was listed as pending at the time of this NDA submission. There has been five years of post-marketing experience with the 1% cream formulation. Safety data were presented in support of this NDA from clinical trials and post-marketing experience. These data sources are as follows:

1) Clinical trials
- Four clinical trials submitted with the original NDA 20-192
- Two clinical trial submitted with NDA 20-192/1S.
- Five clinical trials presented in this NDA (controlled and two uncontrolled)
- Integrated Summary of Safety for the Emulsion Gel, 1% (NDA 20-846)
- Integrated Summary of Safety for the Solution, 1% (NDA 20-749)
- Integrated Summary of Tablet 250 mg (NDA 20-539)

2) Post-Marketing
- Spontaneous case reports to Novaritis for terbinafine cream, 1%

- Spontaneous case reports to the FDA for terbinafine cream, 1%
- Summary of data obtained from the American Association of Poison Control Centers database

Clinical Trials

A total of 3,550 patients participated in 50 clinical trials conducted by the Sponsor in the United States, the United Kingdom, Central America, and South America. Terbinafine was received by 2,265 (64%) of these patients, 656 (19%) received placebo, and 629 (18%) received active control.

The following was extracted from Medical Officer's Review of Safety (pg. 205). A total of 2,265 patients received topical terbinafine cream, 1% during the clinical development of the drug. This data base represents all patients (U.S. and foreign). The table includes all patients (U.S. and foreign) in the data base. The number of patients reporting adverse reactions by the dosing regimens used follows:

Table 23. Medical Officer's safety review, extracted from page 205 (NDA 20-192)/Adverse Events Occurring During Clinical Development

Regimen	Max. No. Of Exposures	Terbinafine Group		
		N	No. AER (%)	No. DC*
Up to 7 days, q.d.	7	201	4 (2.0)	1
1 week, b.i.d.	14	94	6(6.4)	0
2 weeks, q.d.	14	511	9(1.8)	1
2 weeks, b.i.d.	28	624	9(1.4)	1
3 weeks, q.d.	21	89	2(2.2)	1
3 weeks, b.i.d.	42	9	0 (0)	0
4 weeks, q.d.	28	279	17(6.1)	2
4 weeks, b.i.d.	56	434	4(0.9)	0
6 weeks, q.d.	42	24	1 (4.2)	0
		2295	52 (2.3)	6

* DC = Discontinued due to adverse event.

Adverse events associated with terbinafine by indication are listed below. The total number of patients (N) studied per indication extracted from page 206 of the Medical Officer's safety review (NDA 20-192) follows:

Table 24. Adverse Events By Indication

Indication	Terbinafine	
Adverse Events	%	(N)
T. pedis	3.85	(675)
T. corporis/cruris	2.95	(271)
Candidiasis	2.37	(211)
All "other" studies*	1.17	(1108)
All studies	2.30	(2265)

*"other" includes clinical pharmacology and uncontrolled studies

The adverse reactions reported were predominately skin related. The Table 25 provides the principal reaction by rate. The percentage rate is higher than the 2.3% of total patients reporting because some patients reported more than one reaction.

Table 25. Adverse Reactions Occuring During Clinical Development

Reaction	Terbinafine	
Skin and Appendages:		
Irritation	1.0%	(22/2264)
Burning	0.8%	(19/2265)
Pruritus	0.2%	4/2265)
Dryness	0.2%	(5/2265)
Total Reactions for Skin & Appendages	2.6%	(59/2265)
Total Reactions for All Body Systems	3.1%	(70/2265)

Reactions characterized as "severe" occurred in 15 of 70 (21%) of the terbinafine reactions. There was one report of severe seborrhea and one severe application site reaction which were probably related to terbinafine therapy. Most of the severe reactions were probably not related to therapy and were not skin related. These reactions were coded as vomiting, sweating, bone pain, etc. There were two deaths reported in the clinical trials which were not thought to be related to therapy (see 10.1.1). There were no reports designated as a congenital anomaly.

Post-Marketing

Spontaneous Case Reports

There were 8 cases considered serious spontaneous case reports to Novartis for terbinafine cream from October 10, 1990 through December 31, 1997.

Table 26. Spontaneous Case Reports

Novartis Assigned Case #	Adverse Event (COSTART TERM)	Outcome	Causality (assessed by the reporter)
GB/94/00125/LAS	Epidermal Necrolysis	Death	Remote
CDN/97/00122/LAS	Rash Pustular	Recovered	Probable
USA/96/01939/LAS	Dermatitis Exfoliative	Not provided	Not Related
USA/94/01688/LAS	Myasthenia Gravis	Recovered	Remote
USA/92/10069/LAS	Angina Severe	Improved	Not Assessable, Remote
GB/96/00568/LAS	Spontaneous Abortion	Not provided	Not Related
D/97/02425/LAS	Exanthema Maculopapular, Angioedema	Improved	Probable/Possible (oral and topical)
USA/97/02620/LAS	Contact Dermatitis, Overdose	Not provided	Yes

Case GB94 was complicated by the concomitant usage of oral fluconazole and ibuprofen, both of which have been associated with conditions similar to the presentation of this patient. Case CDN97 was a patient treated for local examthemous pustulosis which was attributed to the terbinafine cream. Case USA 96 was an exfoliative dermatitis at the application site which may have been due to the cream but which was attributed by the investigator to cellulitis. Case USA94 was determined to be preexisting myasthenia gravis. Case USA92 (angina) is a common condition and unlikely to be caused by the terbinafine cream. Cases GB96 (spontaneous abortion), D97 (maculopapular exanthem) and USA97 were compicated by concomitant oral terbinafine therapy (Case 97 may indeed have been an example of the antiepileptic syndrome).

The American Association of Poison Control Center (AAPCC)

The sponsor presented information from the database of The American Association of Poison Control Centers' (AAPCC). This database collects information on AAPCC consultations called the Toxic Exposure Surveillance System (TESS). The TESS database is useful for constructing a profile of the patients and effects of exposure. Comparisons of variables such as age, gender, or circumstance of exposure between substances can be made.

The sponsor queried the database for records of all reported human exposures in the TESS database to terbinafine HCl 1% cream in addition to patients exposed two OTC products (either to clotrimazole 1% cream or to miconazole 2% cream) from 1993 through 1996. For terbinafine, the there were a total of 154 exposures. Six of the cases were deleted. According to the sponsor, the reason for the deletion of the six records was concurrent exposure to another substance.

There were 148 evaluable records. Of the reported cases, infants and children (80%) were primarily exposed. Nearly all exposures were accidental and occurred in the patient's home. Most often the route of exposure:

ingestion	(78%)
dermal	(7%)
ocular	(5%)

The three indicators of severity of exposure provided by the TESS data are:

1) whether or not the exposure resulted in any symptoms;
2) whether the patient was seen in a health care facility (HCF); and
3) the rating of the medical outcome made by the Specialist in Poison Information(SPI).

Table 27. Symptoms by Route of Exposure to Terbinafine

N (% of Total Patients)

	Ingestion	Dermal	Ocular	Other	Multiple	Total (N=148)
Symptoms						
No Symptoms	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)

The rating of the medical outcome was made by the Specialist in Poison Information (SPI). One case was judged to be moderate in severity which involved the skin. No other data were provided. All others were judged to be mild in severity. There were no major effects or deaths reported. Severity of symptoms follow (N=148):

No Effect	26%
Unknown, judged nontoxic	30%
Unknown, judged minimally toxic	35%
Minor	7%
Moderate	1%
Unrelated effect	1%

Clinical Effects Related to Exposure

The ocular symptoms were judged to be related to exposure. The most common ocular symptom was irritation/pain.

10.1 Significant/Potentially Significant Events

10.1.1 Deaths

There have been a total of four reported deaths:

- Three deaths occurring during clinical trials of terbinafine (one on terbinafine, one on a comparator, and one on placebo) were reported.
  - Study 3-1, cause of death listed as asthma which occurred 18 days after discontinuation of terbinafine cream during a clinical trial.
  - Study 4-6, the cause of death listed as peritonitis in one patient on active control (ketoconazole cream).
  - One placebo treated patient died, cause of death was listed as bronchopneumonia, during a terbinafine emulsion gel clinical trial.
- One post-marketing/spontaneous report, cause of death was toxic epidermal necrolysis (TEN).

It was the opinion of the medical reviewer of NDA 20-192 that the deaths were not related to therapy (Medical Officer's Review, pages 174 and 207). The reporting physician of the post-

marketing/spontaneous report of the death of a 94 y.o. female assessed an unlikely association to the topical use of terbinafine cream. The causal relationship is uncertain but felt to be remote. The patient was receiving concomitant medications in addition to terbinafine cream prior to the onset of TEN. Some of the concomitant medications (e.g., oral fluconazole, ibuprophen) have been reported in association with development of TEN; however, a causal relationship has not been established.

10.1.2 Other Significant/Potentially Significant Events

A comprehensive literature search for reports of adverse events with use of terbinafine cream was undertaken by the sponsor. No relevant reports of adverse events from meeting abstracts, journal letters to the editor, etc. were identified from 1985 to January 1998 using multiple medical databases.

10.1.3 Overdose Experience

Risk of overdosage from terbinafine cream is felt to be low. A 30 gm tube contains 300 mg of terbinafine cream. The standard oral dose of terbinafine tablet is 250 mg daily.

10.2 Other Safety Findings

Oral terbinafine has been associated with the antiepileptic drug hypersensitivity syndrome (Schlienger et al, Epilepsia 1998 Suppl 7:S3-7). Additional serious adverse events from oral therapy were reported by Gupta et al (British Jrn Derm, 1998, Mar;138(3):529-32) in a summary of 10 severe cutaneous adverse reactions associated with terbinafine treatement which required discontinuation of the oral agent: erythema multiforme(5 patients), erythroderma (one), severe urticaria (one), pityriasis rosea (one) and worsening of pre-existing psoriasis (two). There are also reports of the development/worsening of psoriasis in patients on oral terbinafine therapy (Gupta et al J Am Acad Dermatol 1997 May; 36 858-62). A Medline search revealed no reports of these adverse events related to the topical use of terbinafine cream. The sponsor did not address this topic in the Summary of Safety.

10.2.1 ADR Incidence Tables Note: The following Adverse Events Tables (8,10,11,12, 13, 17, 18, and 19) were extracted verbatim from the sponsor's submission (Vol. 10). Tables 8, 10, 11,12, and 13 are based on a total exposure of 550 patients to terbinafine HCl cream, 1% enrolled in nine clinical studies reported in this NDA. Tables 17, 18, and 19 addresses post-marketing adverse event experience.

Table 8 **All Reported Adverse Events and Event Rates by Treatment and Trial Design**

N (% of Column Total)

COSTART Body System	COSTART Term	Terb/Veh*	Veh	Terb/Clo*	Clo	Terb*	Terb/All*	Total All Treatments
Body as a Whole	ALLERG REACT				1 (1.7)			1 (0.5)
	CELLULITIS				1 (1.7)			1 (0.5)
	HEADACHE	2 (15.4)	1 (9.1)	2 (2.4)			4 (3.6)	5 (2.7)
	INFECT	4 (30.8)	1 (9.1)	17 (20.0)	9 (15.0)		21 (18.9)	31 (17.0)
	INFECT BACT				1 (1.7)			1 (0.5)
	INFECT FUNG					1 (7.7)	1 (0.9)	1 (0.5)
	INFECT VIRAL			11 (12.9)	1 (1.7)		11 (9.9)	12 (6.6)
	INJURY ACCID	1 (7.7)	1 (9.1)	3 (3.5)	2 (3.3)		4 (3.6)	7 (3.8)
	PAIN		1 (9.1)	6 (7.1)	10 (16.7)		6 (5.4)	17 (9.3)
	PAIN ABDO				1 (1.7)			1 (0.5)
	PAIN BACK		1 (9.1)	2 (2.4)	1 (1.7)		2 (1.8)	4 (2.2)
	PAIN CHEST				1 (1.7)			1 (0.5)
Cardiovascular	ANGINA PECTORIS			1 (1.2)			1 (0.9)	1 (0.5)
	MIGRAINE		2 (18.2)	1 (1.2)			1 (0.9)	3 (1.6)
	SYNCOPE				1 (1.7)			1 (0.5)
Digestive	DIARRHEA			2 (2.4)			2 (1.8)	2 (1.1)
	DYSPEPSIA			2 (2.4)			2 (1.8)	2 (1.1)
	ESOPHAGITIS				1 (1.7)			1 (0.5)
	GINGIVITIS			1 (1.2)			1 (0.9)	1 (0.5)
	NAUSEA			1 (1.2)			1 (0.9)	1 (0.5)
	RECTAL DIS				2 (3.3)			2 (1.1)
	TOOTH DIS			1 (1.2)			1 (0.9)	1 (0.5)
Metabolic & Nutritional	EDEMA			1 (1.2)	1 (1.7)		1 (0.9)	2 (1.1)
Musculoskeletal	ARTHRITIS			1 (1.2)			1 (0.9)	1 (0.5)
	MYALGIA			1 (1.2)			1 (0.9)	1 (0.5)
Nervous	ANXIETY					1 (7.7)	1 (0.9)	2 (1.1)
	CONVULS				1 (1.7)			1 (0.5)
	PARESTHESIA	1 (7.7)		1 (1.2)			2 (1.8)	2 (1.1)
	THINKING ABNORM				1 (1.7)			1 (0.5)
	VERTIGO				1 (1.7)			1 (0.5)
Respiratory	ASTHMA	1 (7.7)						1 (0.5)
	COUGH INC		1 (9.1)	1 (1.2)			1 (0.9)	1 (0.5)
	PHARYNGITIS			2 (2.4)			1 (0.9)	2 (1.1)
	PNEUMONIA			2 (2.4)		2 (15.4)	4 (3.6)	4 (2.2)
	RESPIRAT DIS				1 (1.7)		2 (1.8)	2 (1.1)
	RHINITIS		1 (9.1)	4 (4.7)	1 (1.7)			1 (0.5)
	SINUSITIS	2 (15.4)		3 (3.5)			4 (3.6)	6 (3.3)
Skin and Appendages	ACNE			1 (1.2)			5 (4.5)	5 (2.7)
	DERM CONTACT				1 (1.7)		1 (0.9)	1 (0.5)
	ECZEMA				1 (1.7)	1 (7.7)		1 (0.5)
	HERPES SIMPLEX			1 (1.2)			1 (0.9)	2 (1.1)
	NAIL DIS				2 (3.3)	1 (7.7)	1 (0.9)	1 (0.5)
	PRURITUS	1 (7.7)	1 (9.1)	9 (10.6)	8 (13.3)	1 (7.7)	1 (0.9)	3 (1.6)
	RASH			1 (1.2)	3 (5.0)	1 (7.7)	11 (9.9)	20 (11.0)
	RASH MAC PAP				1 (1.7)		2 (1.8)	5 (2.7)
	RASH VESIC BULL		1 (9.1)		1 (1.7)			1 (0.5)
	SKIN DIS	1 (7.7)		2 (2.4)	2 (3.3)	3 (23.1)	6 (5.4)	2 (1.1)
	URTICARIA				1 (1.7)			8 (4.4)
Special Senses	AMBLYOPIA			1 (1.2)				1 (0.5)
	CONJUNCTIVITIS			1 (1.2)			1 (0.9)	1 (0.5)
	TASTE PERVERS			1 (1.2)			1 (0.9)	1 (0.5)
Urogenital	DYSURIA			1 (1.2)			1 (0.9)	1 (0.5)
	INFECT URIN TRACT			1 (1.2)			1 (0.9)	1 (0.5)
	MONILIA VAGINA			1 (1.2)		1 (7.7)	2 (1.8)	2 (1.1)
	PROSTAT DIS				1 (1.7)	1 (7.7)	1 (0.9)	2 (1.1)
					1 (1.7)			1 (0.5)
	TOTAL ADVERSE EVENTS*	13 (100.0)	11 (100.0)	85 (100.0)	60 (100.0)	13 (100.0)	111 (100.0)	182 (100.0)
	TOTAL PATIENTS	211	212	240	234	99	550	996
	TOTAL PATIENTS REPORTING AEs	8	9	54	39	11	73	121
	Rate (Total Pts Reporting AEs)/ (Total Pts) as %	3.8	4.2	22.5	16.7	11.1	13.3	12.1
	Rate (Total AEs)/(Total Pts)	0.06	0.05	0.35	0.26	0.13	0.20	0.18

*TERB/VEH = AEs in terbinafine-treated patients in vehicle controlled trials; TERB/CLO = AEs in terbinafine-treated patients in active-treatment (clotrimazole) controlled trials; TERB = AEs in uncontrolled trials; TERB/ALL = total terbinafine AEs for all trials

Table 29

Table 10 All Adverse Events by Treatment and Severity*

		Terbinafine (N=550)				Vehicle (N=212)			Clotrimazole (N=238)			All Treatments (N=996)			
COSTART BODY SYSTEM	COSTART TERM	<>	mld	mod	sev	mld	mod	sev	mld	mod	sev	<>	mld	mod	sev
Body as a Whole	ALLERG REACT								1				1		
	CELLULITIS									1				1	
	HEADACHE		3	1		1							4	1	
	INFECT		15	6			1		8	1			23	8	
	INFECT BACT									1				1	
	INFECT FUNG	1										1			
	INFECT VIRAL		4	5	2					1			4	6	2
	INJURY ACCID		1	3			1		1	1			2	5	
	PAIN		1	4	1	1			3	2	5		5	6	6
	PAIN ABDO									1				1	
	PAIN BACK		2				1			1			2	2	
	PAIN CHEST									1				1	
Cardiovascular	ANGINA PECTORIS		1										1		
	MIGRAINE				1		2							2	1
	SYNCOPE								1				1		
Digestive	DIARRHEA		1	1									1	1	
	DYSPEPSIA		1	1									1	1	
	ESOPHAGITIS									1				1	
	GINGIVITIS			1										1	
	NAUSEA			1										1	
	RECTAL DIS									2				2	
	TOOTH DIS			1										1	
Metabolic and Nutritional	EDEMA				1					1				1	1
Musculoskeletal	ARTHRITIS			1										1	
	MYALGIA			1										1	
Nervous	ANXIETY	1										1			
	CONVULS									1				1	
	PARESTHESIA		2										2		
	THINKING ABNORM									1				1	
	VERTIGO								1				1		
Respiratory	ASTHMA				1										1
	COUGH INC		1			1							2		
	PHARYNGITIS	2		1	1							2		1	1
	PNEUMONIA			2										2	
	RESPIRAT DIS								1				1		
	RHINITIS		2	1	1	1				1			3	2	1
	SINUSITIS		2	3									2	3	
Skin and Appendages	ACNE		1										1		
	DERM CONTACT								1				1		
	ECZEMA	1							1				1		
	HERPES SIMPLEX		1									1	1		
	NAIL DIS	1											1		
	PRURITUS		3	4	4			1		2		1		2	
	RASH	1			1				3	3	2		6	7	7
	RASH MAC PAP								2		1	1	2		2
	RASH VESIC BULL					1				1				1	
	SKIN DIS	3	2	1							1		1		1
	URTICARIA								1	1		3	3	2	
Special Senses	AMBLYOPIA			1						1				1	
	CONJUNCTIVITIS				1									1	
	TASTE PERVERS		1												1
Genitourinary	DYSURIA		1										1		
	INFECT URIN TRACT	1		1								1	1		
	MONILIA VAGINA	1								1		1		1	
	PROSTAT DIS									1		1		1	
														1	
Total Adverse Events		12	45	40	14	5	5	1	24	27	9	12	74	72	24
Total Patients with AEs		10	35	34	12	5	4	1	17	24	6	10	57	62	19
Rate: Pts with AE/ Tot Pts as %		1.8	6.4	6.2	2.2	2.4	1.9	0.5	7.3	10.3	2.6	1.0	5.7	6.2	1.9
Rate: Total AEs/Total Pts		0.022	0.082	0.073	0.025	0.024	0.024	0.005	0.103	0.115	0.038	0.012	0.074	0.072	0.024

*<> = no indicated severity; mld = mild; mod = moderate; sev = severe

(Table 11) Adverse Events by Drug and Investigator-Perceived Relationship* to Drug for all Events at Least Possibly Related** to Treatment

	TERBINAFINE (N=550)				CLOTRIMAZOLE (N=234)				VEHICLE (N=212)				ALL TREATMENTS (N=996)			
COSTART TERM	POS	PROB	REL	UNC	POS	PROB	REL	UNC	POS	PROB	REL	UNC	POS	PROB	REL	UNC
HEADACHE												1				1
PAIN	1			3	4	2		1	1				6	2		4
NAUSEA				1											1	
EDEMA			1													
PARESTHESIA		2												2		1
ECZEMA								1								
PRURITUS	3	2		4		1		5			1		3	3	1	9
RASH			1			2		1						2	1	1
RASH MAC PAP								1								1
RASH VESIC BULL											1				1	
SKIN DIS		1		1										1		1
CONJUNCTIVITIS		1												1		
TASTE PERVERS	1												1			
Total Adverse Events	5	6	2	9	4	5	0	9	1	0	2	1	10	11	4	19
Total Pts with AE at least Possible	3	5	1	8	3	3	0	5	1	0	1	1	7	8	2	14
Pts with AE at least Possible/Total Pts as %	0.55	0.91	0.18	1.45	1.28	1.28	0.00	2.14	0.47	0.00	0.47	0.47	0.70	0.80	0.20	1.41
Total AEs/Total Pts	0.009	0.011	0.004	0.016	0.017	0.021	0.000	0.038	0.005	0.000	0.009	0.005	0.010	0.011	0.004	0.019

*POS = possible; PROB = probable; REL = related; UNC = uncertain

**Adverse events judged unrelated, related to an intercurrent illness or improbably related were omitted from this table.

Table 31.

(Table 12) Adverse Events at Least Possibly Related to Treatment by Treatment and Severity

COSTART BODY SYSTEM	COSTART TERM	TERBINAFINE			VEHICLE			CLOTRIMAZOLE		
		MILD	MOD	SEV	MILD	MOD	SEV	MILD	MOD	SEV
Body as a Whole	HEADACHE				1					
	PAIN		4		1			1	2	4
Digestive	NAUSEA		1					1		
Metabolic & Nutritional	EDEMA			1						
Nervous	PARESTHESIA	2								
Skin & Appendages	ECZEMA							1		
	PRURITUS	3	4	2			1	3	3	
	RASH			1				2		1
	RASH MAC PAP				1				1	
	RASH VESIC BULL									
	SKIN DIS	1	1							
Special Senses	CONJUNCTIVITIS			1						
	TASTE PERVERSION	1								
TOTAL		7	10	5	3	0	1	7	6	5

Table 32.

(Table 13) Complaint Rate* for Skin and Appendages and All Body Systems

COMPLAINT**	TERB/VEH***	VEH***	TERB/CLO***	CLO***	TERB***	TERB/ALL***	TOTAL ALL TREATMENTS
IRRITATION	1(33.3)	1(33.3)	4(21.1)	10(37.0)	4(80.0)	9(33.3)	20(35.1)
BURNING	1(33.3)	1(33.3)	6(31.6)	9(33.3)		7(25.9)	17(29.8)
PRURITUS	1(33.3)	1(33.3)	9(47.4)	8(29.6)	1(20.0)	11(40.7)	20(35.1)
DRYNESS	0	0	0	0	0	0	0
TOTAL AEs for Skin	3(100.0)	3(100.0)	19(100.0)	27(100.0)	5(100.0)	27(100.0)	57(100.0)
TOTAL Pts with Skin AEs	2	2	12	15	5	19	36
Total Adverse Events for All Body Systems	13	11	85	60	13	111	182
Total Patients	211	212	240	234	99	550	996
Rate Pts with Skin AEs/ Total Patients as %	0.95	0.94	5.0	6.4	5.1	3.5	3.6
Rate (Total Skin AEs)/ (Total Patients)	0.014	0.014	0.079	0.115	0.051	0.049	0.057
Rate (Total AEs)/ (Total Patients)	0.062	0.052	0.354	0.256	0.131	0.202	0.183

*Complaint rate is the total number of complaints reported by the patient population. Some patients reported more than one complaint.

**COMPLAINT definitions

IRRITATION includes: rash, skin cracking, erythema, skin irritation, local irritation and vesicles
BURNING includes: pain, burning, stinging, tenderness, and tingling
DRYNESS includes: dryness of the skin
PRURITIS includes: pruritus and itching

***TERB/VEH = AEs in terbinafine-treated patients in vehicle controlled trials; TERB/CLO = AEs in terbinafine-treated patients in active-treatment (clotrimazole) controlled trials; TERB = AEs in uncontrolled trials; TERB/ALL = total terbinafine AEs for all trials

Table 33

(Table 17) **FDA SRS Adverse Event Data for Topical Terbinafine, Non-Foreign Reports by Costart Term by Year**

COSTART BODY SYSTEM	COSTART TERM	1993	1994	1995	1996	1997	TOTAL (%)
BODY AS A WHOLE	ALLERG REACT	2	1		1	2	6 (4.9)
	CELLULITIS	1			1		2 (1.6)
	DRUG INTERACTION					2	2 (1.6)
	EDEMA FACE					1	1 (0.8)
	INFECT BACT				1		1 (0.8)
	NO DRUG EFFECT	1	1	1		5	8 (6.6)
	PAIN	4		2	1	2	9 (7.4)
	PAIN BACK		1				1 (0.8)
	REACT AGGRAV	1				1	2 (1.6)
CARDIOVASCULAR	HEADACHE VASC					1	1 (0.8)
DIGESTIVE	GGTP INC				1		1 (0.8)
ENDOCRINE	GOITER	1					1 (0.8)
	HYPOTHYR	1					1 (0.8)
HEME AND LYMPHATIC	LYMPHANGITIS	1					1 (0.8)
METABOLIC AND NUTRITIONAL DISORDERS	EDEMA	3			1		4 (3.3)
	EDEMA PERIPH	3	1				4 (3.3)
	GLUCOSE TOLER DEC					1	1 (0.8)
MUSCULOSKELETAL	CRAMPS LEG			1			1 (0.8)
	MYASTHENIA	1	1				2 (1.6)
NERVOUS	HYPESTHESIA	1					1 (0.8)
	PARESTHESIA	1	1	1			3 (2.5)
	URIN RETENT				1		1 (0.8)
SKIN AND APPENDAGES	APPLICAT SITE REACT	5	1	3	2	2	13 (10.7)
	DERM CONTACT	2	3		1		6 (4.9)
	DERM EXFOL				1		1 (0.8)
	DERM FUNG		1				1 (0.8)
	PRURITUS	1	1	1			3 (2.5)
	RASH	10	5	2	4	4	25 (20.5)
	RASH MAC PAP		1		2	1	4 (3.3)
	RASH VESIC BULL	1					1 (0.8)
	SKIN DIS			1			1 (0.8)
	SKIN DISCOLOR	1	1			1	3 (2.5)
	SKIN DRY		1				1 (0.8)
	SKIN STRIAE		1				1 (0.8)
	STEVENS JOHNSON SYND			1			1 (0.8)
	ULCER SKIN	1					1 (0.8)
	URTICARIA				1	1	2 (1.6)
SPECIAL SENSES	AMBLYOPIA					1	1 (0.8)
UROGENITAL	METRORRHAGIA				1		1 (0.8)
	PENIS DIS				1		1 (0.8)
	URIN TRACT DIS					1	1 (0.8)
Total Adverse Event Reports		42	21	13	20	26	122 (100.0)
Total Individual Cases		22	18	9	10	19	78

Table 34

(Table 18) **FDA SRS Adverse Event Data for Topical Terbinafine, Foreign and Non - Foreign Reports by Outcome by Year**

OUTCOME*	1993	1994	1996	1997	TOTAL
DIED		1			1
HOSPITALIZED		2	3		5
REQUIRED INTERVENTION TO PREVENT PERMANENT DAMAGE		1	2	3	6
NONE	16	9			25
OTHER			3		3
TREATED WITH RX DRUG	5				5
TOTAL CASES* WITH A REPORTED OUTCOME	21	13	8	3	45

*A case could have more than one reported outcome

Table 35

(Table 19) **SRS Adverse Event Data for Topical Terbinafine, Foreign and Non-Foreign Reports with Serious Outcomes by Costart Term by Year**

COSTART BODY SYSTEM	COSTART TERM	1994	1996	1997	Total (%)
BODY AS A WHOLE	CELLULITIS		1		1 (5.0)
	INFECT BACT		1		1 (5.0)
	PAIN			1	1 (5.0)
	PAIN BACK	1			1 (5.0)
	REACT AGGRAV			1	1 (5.0)
NERVOUS	EDEMA		1		1 (5.0)
SKIN AND APPENDAGES	URIN RETENT		1		1 (5.0)
	DERM CONTACT		1		1 (5.0)
	DERM EXFOL		1		1 (5.0)
	DERM FUNG	1			1 (5.0)
	EPIDERM NECRO	1			1 (5.0)
	PRURITUS	1			1 (5.0)
	RASH		1	2	3 (15.0)
	RASH MAC PAP		1	1	2 (10.0)
	SKIN DISCOLOR	1			1 (5.0)
UROGENITAL	ABORTION		1		1 (5.0)
	PENIS DIS		1		1 (5.0)
Total Adverse Events		5	10	5	20 (100.0)
Total Individual Cases		3	4	3	10