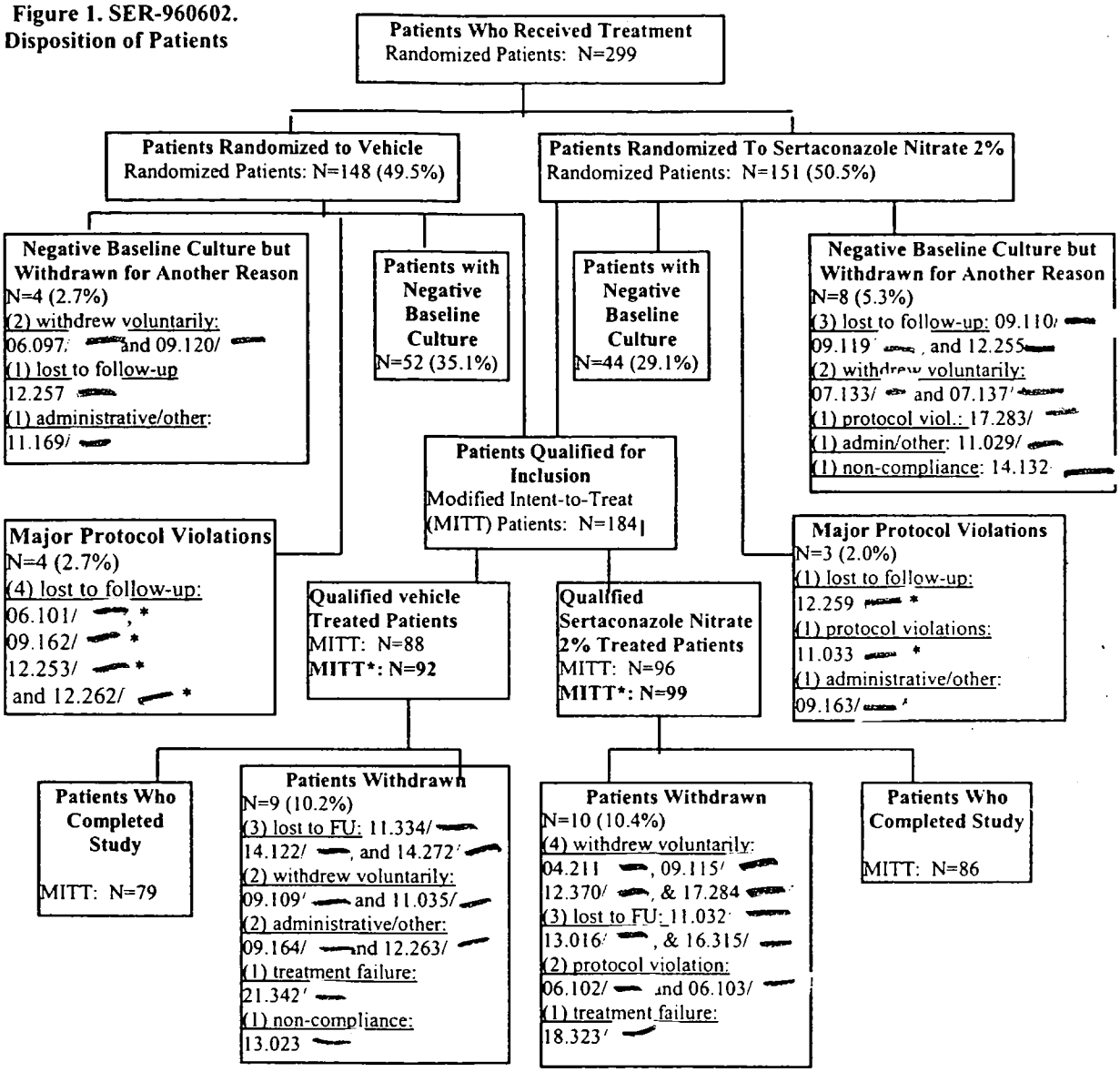
Demographic and Other Baseline Characteristics
The following table indicates the number of patients who enrolled and who completed the study:

Table 8 . SER-960602. Number of Patients.

Planned:	286	(143 vehicle and 143 sertaconazole nitrate 2% cream).
Entered:	299	(148 vehicle and 151 sertaconazole nitrate 2% cream).
Analyzed for Efficacy:		
Modified Intent-to-Treat:	191	(92 vehicle and 99 sertaconazole nitrate 2% cream)
Per-Protocol (at baseline):	148	(71 vehicle and 78 sertaconazole nitrate 2% cream)
Analyzed for Safety:	299	(148 vehicle and 151 sertaconazole nitrate 2% cream)

Populations enrolled/analyzed.
A total of 299 (148 vehicle and 151 sertaconazole nitrate 2% cream) patients entered this study. Of these, 108 patients (56 vehicle and 52 sertaconazole nitrate 2% cream) had negative baseline cultures and were discontinued. Of these, 12 patients (4 vehicle and 8 sertaconazole nitrate 2% cream) had other reasons for being discontinued. Seven patients (4 vehicle and 3 sertaconazole nitrate 2% cream) were considered major protocol violators. The following figure illustrates the disposition of patients.

Figure 1. SER-960602.
Disposition of Patients



Note: * these patients were excluded from MITT population by Sponsor but have been included by the Agency.
Data Source: Summary Tables DEM.1, DEM.4, EFF.7.1, EFF.7.2, EFF.8.1, and EFF.8.2 and Patient Data Listings DEM.1, DEM.3, and DEM.5.

Protocol Deviations and Patient Withdrawals

Four vehicle and three sertaconazole nitrate 2% cream-treated patients were considered major protocol violations. Five subjects with positive baseline KOH and cultures failed to return for at least one post-baseline visit (06.101/ , 09.162/ , 12.253/ , 12.259 , and 12.262/ ; and were considered major protocol violators and not included in efficacy analyses by Sponsor but were included by the Agency. Patient 12.263/ had a negative baseline culture due to insufficient sampling. The Visit-2 culture was positive during the same time frame and the lab reported the patient as baseline positive, while the clinical site

discontinued the patient as a negative baseline culture. This patient was left in the efficacy analyses and was listed as discontinued due to administrative/ other reasons.

Nine subjects had unknown KOH at Visit-6. Five of these were failures. The remaining four were labeled by Sponsor as "effectively treated" (01.203/ [redacted] 11.331 [redacted], 13.020 [redacted], 17.279 [redacted]). These were considered as failures in the Agency's analysis.

Table 9. SER-960602. Patient Withdrawals for Randomized and for the MITT patients.

	All randomized patients (N=299)		MITT patients (N=191)	
Withdrawal Reason	Vehicle N=148	SertaconazoleN=151	Vehicle N=92	Sertaconazole N=99
Withdrawals Number (%)	69 (46.6)	65 (43.0)	13 (14.13)	13 (13.13)
Negative Baseline Culture	52 (35.1)	44 (29.1)		
Lost to follow-up	8 (5.4)	7 (4.6)	7 (37.60)	4 (4.04)
Withdrew Voluntarily	4 (2.7)	6 (4.0)	2 (2.3)	4 (4.2)
Administrative/Other	3 (2.0)	2 (1.3)	2 (2.3)	1 (1.01)
Protocol Violation	0 (0.0)	4 (2.6)	0 (0.0)	3 (3.03)
Treatment Failure	1 (0.7)	1 (0.7)	1 (1.1)	1 (1.0)
Non-Compliance	1 (0.7)	1 (0.7)	1 (1.1)	0 (0.0)

Data Source: Patient Data Listing DEM.1.table 4, page 8-2-149

The primary reason for patient withdrawal in the randomized patients group was negative baseline culture. This affected 35.1% (52/148) of vehicle-treated patients and 29.1% (44/151) of sertaconazole nitrate 2% cream-treated patients. Excluding negative baseline culture, the primary reason for patient withdrawal was "lost to follow-up" with 5.4% (8/148) of vehicle-treated patients and 4.6% (7/151) of sertaconazole nitrate 2% cream-treated patients. The number of randomized patients withdrawn from the study at sites with more than seven patients, ranged from three (1.0%; 3/299) at site 21 (Hickman) to 17 (5.7%, 17/299) at site 09 (Kraus).

Table 10. SER-960602. Randomized Patients. Failed Inclusion/Exclusion Criteria

Failed Inclusion/Exclusion Criteria Randomized (N=299)	Vehicle N=148	Sertaconazole N=151
Number (%) of Patients not Meeting Inclusion/Exclusion	7 (4.7)	7 (4.6)
Liver Function Tests >2 x Upper Limit of Normal, n(%)	2 (1.4)	4 (2.6)
Topical Anti-fungal Therapy to Feet Within 30 Days, n(%)	3 (2.0)	1 (0.7)
HgA1c ≥ 10%, n(%)	2 (1.4)	1 (0.7)
Onychomycosis, n(%)	0 (0.0)	1 (0.7)

Data Source: Table 5, page 8-2-150

Seven of the 148 vehicle-treated patients (4.7%) and seven of the 151 sertaconazole nitrate 2% cream-treated patients (4.6%) failed to meet an inclusion and/or exclusion criteria. Topical anti-fungal therapy to the feet within 30 days was the primary criteria not met within the vehicle treatment group. Liver function tests greater than twice the upper limit of normal was the primary criteria not met within the sertaconazole nitrate 2% cream treatment group. *Reviewer comment: There were no study discontinuations due to treatment related adverse events. The distribution of protocol violations was similar for sertaconazole and for vehicle. Although the Sponsor excluded from efficacy analysis several patients because of missing*

data or patient withdrawal from the trial, all patients who were randomized and had a positive KOH and culture were included in the MITT efficacy analysis conducted by the Agency.

Patient demographic data and baseline characteristics for the all treated patient populations including interdigital tinea pedis infections are displayed in:

Table 11. SER-960602. Randomized Patients. Demographic Characteristics.

Characteristics	Vehicle N=148	Sertaconazole N=151	Total N=299
Age, years			
Mean ± SE, Range (min-max)	35.7 ± 1.12 (12-86)	37.1 ± 1.14 (12-71)	36.4 ± 0.80 (12-86)
Gender, n (%)			
Male	107 (72.3)	113 (74.8)	220 (73.6)
Female	41 (27.7)	38 (25.2)	79 (26.4)
Race, n (%)			
Caucasian	99 (66.9)	97 (64.2)	196 (65.6)
Black	36 (24.3)	36 (23.8)	72 (24.1)
Hispanic	13 (8.8)	13 (8.6)	26 (8.7)
Asian	0 (0.0)	4 (2.6)	4 (1.3)
Other	0 (0.0)	1 (0.7)[a]	1 (0.3)
Height, inches			
Mean ± SE Range (min-max)	68.1 ± 0.33 (59-77)	68.5 ± 0.31 (56-77)	68.3 ± 0.23 (56-77)
Weight, pounds Mean ± SE ,(min-max)	182.5 ± 3.45 (85-302)	183.8 ± 3.41 (70-358)	183.2 ± 2.42 (70-358)

[a] Patient 12.260/ — SE = Standard error.
Data Source: Summary Tables DEM.3.1, PHYSEXAM.1, and TINEAHX.1. table 11, page 8-2-160

Table 12. SER-960602. Randomized Patients. Baseline Disease Characteristics.

Disease Factors	Vehicle N=148	Sertaconazole N=151	Total N=299
Location			
One Foot	29 (19.6)	33 (21.9)	62 (20.7)
Both Feet	119 (80.4)	118 (78.1)	237 (79.3)
Duration of Current Episode			
<1 Month	16 (10.8)	19 (12.6)	35 (11.7)
1-3 Months	35 (23.6)	40 (26.5)	75 (25.1)
>3-6 Months	17 (11.5)	21 (13.9)	38 (12.7)
>6 Months	80 (54.1)	71 (47.0)	151 (50.5)
Number of Previous Episodes			
Mean ± SE (min-max)	8.5 ± 1.24 (0-120)	10.9 ± 2.12 (0-275)	9.7 ± 1.24 (0-275)

[a] Patient 12.260/ — SE = Standard error.
Data Source: Summary Tables DEM.3.1, PHYSEXAM.1, and TINEAHX.1. table 11, page 8-2-160

The majority of randomized patients were Caucasian (65.6%) and male (73.6%), with a mean (± SE) age of 36.4 (± 0.80) years. Baseline mean (± SE) height and weight in the randomized population were 68.3 (± 0.23) inches and 183.2 (± 2.42) pounds, respectively.

The majority of randomized patients had disease involvement of both feet (237/299; 79.3%) and a duration of disease (current episode) of greater than 6 months (151/299; 50.5%) at baseline. The mean (± SE) number of previous episodes was 9.7 (± 1.24).

Table 13. SER-960602. Baseline Pathogen. MITT

Characteristics	Vehicle N=92	Sertaconazole N =99	Total N=191
Pathogen			
T. rubrum	77 (83.65)	78 (78.78)	155 (81.15)
T. mentagrophytes	7 (8.0)	10 (9.4)	17 (8.90)
E. floccosum	8 (9.1)	10 (10.4)	18 (9.8)
T. kanei*	0 (0.0)	1 (1.0)	1 (0.5)

*this pathogen was not identified in the NDA submission but was identified in the electronic submission data file set02\culture.xpt. It was identified as a Trichophyton sp. at baseline, and as T. kanei at weeks-2 and 4.
Data Source: Summary Tables DEM.3.2, EFF.4.2, EFF.5.1, and PATHOG.2 and Patient Data Listings EFF.1 and DEM.3. table 12, page 8-2-161

Medical History

No significant prior medications were used by patients within this study. No patients were discontinued from the trial because of developing medical histories.

Concomitant Medications

No significant prior medications were used by patients within this study and there were no significant concomitant medications taken during this study. The most common medications taken during the trial were ibuprofen, acetylsalicylic acid, and acetaminophen, in similar numbers for both study arms.

Reviewer comment: No significant differences were noted between treatment groups for demographic variables (age, gender, and race) or disease factors (severity, medical and medication history, and pathogen) at baseline in the randomized population. The primary pathogen found at baseline was T. rubrum (81.15%).

Efficacy Endpoint Outcomes

The primary efficacy variable used to assess the antifungal efficacy of sertaconazole nitrate 2% cream applied twice daily for 4 weeks versus vehicle cream was the proportion of patients who demonstrated Successful Treatment Outcomes, which was defined as those patients who experienced a Complete Cure, i.e. complete resolution of all signs and symptoms and negative KOH and culture at the Point of Cure at the week-6 evaluation, two weeks after completion of treatment. The population analyzed for efficacy was the Modified Intent to Treat (MITT) population, comprised of all patients randomized who had a positive KOH and Culture at baseline, had clinical disease, and were dispensed medication, with last observation carried forward (LOCF) and missing values treated as failures (MVTF).

MITT Population analysis

The Agency's MITT population was slightly different from the Applicants. The Agency's efficacy analysis is reflected on the following table:

Table 14 SER-960602. Efficacy Results. MITT

MITT	Vehicle	Sertaconazole	p-value
Complete Cure	3/92 (3.3%)	13/99 (13.1%)	0.0101
Effective Treatment	11/92 (12.0%)	32/99 (32.3%)	0.0010
Mycological Cure	18/92 (19.6%)	49/99 (49.5%)	<0.0001

Reviewer comment: vehicle showed little effect and sertaconazole produced a Complete Cure rate that was statistically significant over vehicle. Efficacy reaches statistical significance for the primary efficacy variable "complete cure" at 13.1%. The difference between arms was 10 patients at the point of cure. For the secondary efficacy variable "effective treatment" statistical significance is reached at 32.3%. Mycological cures, reached statistical significance at 49.5%. These numbers are fairly low, considering that they result after treatment twice daily for 4 weeks. The Agency's results basically paralleled those of the Sponsor, which are shown later in this review.

Examination of subgroups:

The trial was not powered to detect treatment differences among subgroups. By center analysis is summarized in the next table. P-values are not calculated because the numbers for each center are very small.

Table 15. SER960602. Complete Cure. Analysis by Site. MITT

Site	Vehicle*	Sertaconazole*
01	0/6	0/8
03	0/12	5/14
04	½	0/2
05	0/1	1/3
06	0/6	1/5
07	0/0	0/0
08	0/0	0/0
09	0/8	0/9
10	0/2	0/3
11	1/14	1/17
12	0/5	1/3
13	1/8	1/7
14	0/10	0/9
15	0/1	0/3
16	0/7	0/7
17	0/2	0/4
18	0/4	½
19	0/0	0/0
20	0/0	1/1
21	0/4	½

* number of complete cures/number in MITT

Table 16. Complete Cure Rates. Effect of site #3. LOCF. MVTF

Sites	Vehicle	Sertaconazole	p-value
All	3/92 (3.3%)	13/99 (13.1)	0.0101
Site 3	0/12 (0%)	5/14 (36%)	
All minus 3			
	3/80 (3.8%)	8/85 (9.4%)	0.1092
	3/80 (3.8%)	9/85 (10.58%)	0.0673

Reviewer comment: The small number of patients at most sites makes comparison of sites difficult. Eight (8) sites had no complete cures. Site #3 seems to carry the weight of the successes in this trial since it is the only one that had more than one success. Without the data for site #3, this trial would not have shown statistical significance for the primary efficacy variable: Complete Cure. An investigation by D.S.I. of this site revealed no improprieties.

A test for non-homogeneity across centers did not reach significance.

Table 17. SER-960602. Efficacy Analyzed By Age of Patient. MITT.

	Vehicle	Sertaconazole	p-value[a]
Complete Cure			
Age ≤ 17	0/6 (0.0%)	3/8 (37.5%)	0.2088
18 – 35	2/45 (4.4%)	5/45 (11.1%)	0.4340
36 – 64	1/39 (2.6%)	5/42 (11.9%)	0.2030
≥ 65	0/2 (0.0%)	0/4 (0.0%)	NA
Effective Treatment			
Age ≤ 17	0/6 (0.0%)	5/8 (62.5%)	0.0310
18 – 35	5/45 (11.1%)	17/45 (37.8%)	0.0062
36 – 64	5/39 (12.8%)	9/42 (21.4%)	0.3842
≥ 65	½ (50.0%)	¼ (25.0%)	0.9333
Mycological Cure			
Age ≤ 17	1/6 (16.7%)	5/8 (62.5%)	0.1375
18 – 35	8/45 (17.8%)	24/45 (53.3%)	0.0080
36 – 64	8/39 (20.5%)	17/42 (40.5%)	0.0591
≥ 65	½ (50.0%)	¾ (75.0%)	>0.999

Reviewer comment: when analyzed by age, no age group achieves statistical significance for the primary endpoint of Complete Cure. Even for the secondary endpoints, statistical significance is only reached for participants younger than 35. However, in an exploratory post-hoc logistic regression model of clinical cure, the age covariate was not significant (p≥0.2250).

Complete Cure

The following table indicates the number and percentage of patients achieving complete cure for each subgroup at week-6, which is two weeks post treatment..

Table 18. SER-960602. Complete Cure Analyzed by Gender, Race, and Pathogen. MITT

Complete Cure		Vehicle	Sertaconazole	p-value[a]
Gender	Male	2/67 (3.0%)	8/75 (10.7%)	0.1025
	Female	1/25 (4.0%)	5/24 (20.8%)	0.0983
Race	Caucasian	1/62 (1.6%)	11/71 (15.5%)	0.0055
	Black	1/21 (4.8%)	1/18 (5.6%)	>0.999
	Asian	0/0	0/2 (0.0%)	NA
	Hispanic	1/9 (11.1%)	0/7 (0.0%)	>0.999
	Other	0/0	1/1 (100%)	NA
Pathogen	T. rubrum	3/77 (3.9%)	10/78 (12.8%)	0.0788
	T. mentagrophytes	0/7 (0.0%)	2/10 (20.0%)	0.4853
	E. floccosum	0/8 (0.0%)	1/10 (10.0%)	>0.999
	T. kanei			

[a] Fisher's Exact Test

Reviewer comment: Statistical significance is reached only for Caucasians.

Effective Treatment

The following table indicates the number and percentage of patients achieving effective treatment for each subgroup at week-6, which is two weeks post treatment..

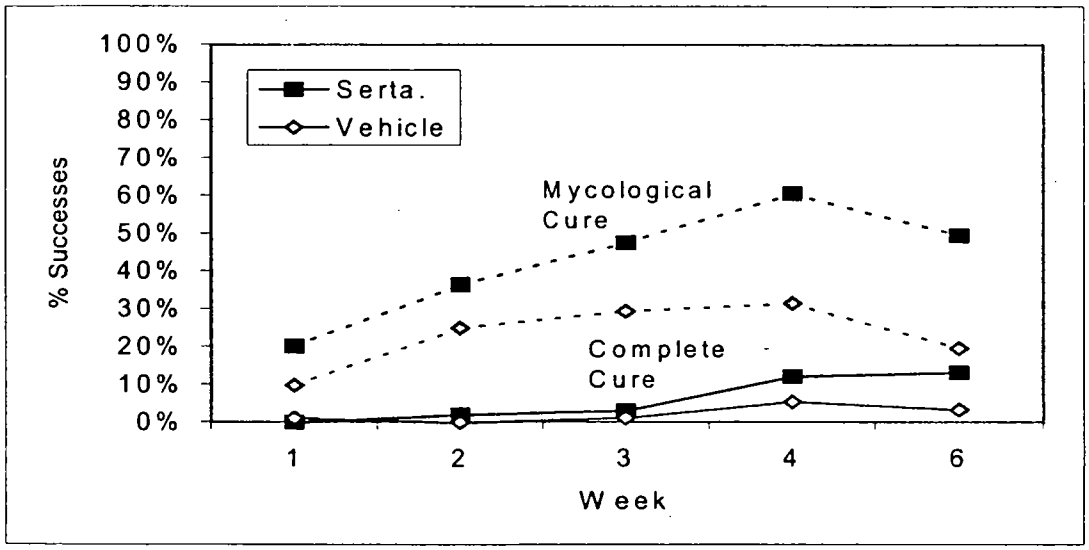
Table 19. SER-960602. Effective Treatment Analyzed By Gender, Race, and Pathogen. MITT

Effective Treatment	Vehicle	Sertaconazole	p-value[a]
Gender Male	8/67 (11.9%)	25/75 (33.3%)	0.0028
Female	3/25 (12.0%)	7/24 (29.2%)	0.1706
Race Caucasian.	8/62 (12.9%)	25/71 (35.2%)	0.0044
Black	1/21 (4.8%)	3/18 (16.7%)	0.3183
Asian	0/0	0/2 (0.0%)	NA
Hispanic	2/9 (22.2%)	3/7 (42.8%)	0.5962
Other	0/0	1/1 (100%)	NA
Pathogen T. rubrum	9/77 (11.7%)	25/78 (32.1%)	0.0032
T. mentagrophytes	1/7 (14.3%)	5/10 (50.0%)	0.3043
E. floccosum	1/8 (12.5%)	3/10 (30.0%)	0.5882
T. kanei			

[a] Fisher's Exact Test

Reviewer comment: Statistical significance is reached for "effective treatment" only for Caucasians, males, and for T. rubrum.

Figure 2– SER 960602. Complete Cure and Mycological Cure Rates by Week



Biostatistics Reviewer Graphic.

Reviewer comment: It is of interest that after 4 weeks of treatment complete cure had not reached statistical significance (p=0.1138). Complete cure rate reaches statistical significance only at week-6, the Point of Cure (p=0.0101). This effect was mostly the result of two vehicle Complete Cures being lost from week-4 to week-6, since complete cures for sertaconazole only increased by 1 from week-4 to week-6. Mycological cures were higher at week-4 than at week-6, both for vehicle and for sertaconazole.

Per Protocol population analysis:
The Per Protocol (PP) population includes participants who met the inclusion criteria, were randomized and treated and had evaluable efficacy data for Week-6 and were not delayed exclusion. The Agency's efficacy analysis is reflected on the following table:

Table 20. SER- 960602 Efficacy Results. Per Protocol (PP) population, Observed Cases

Per Protocol	Vehicle	Sertaconazole	p-value
Complete Cure	2/67 (3.08%)	12/72 (16.7%)	0.0062
Effective Treatment	10/67 (14.9%)	27/72 (37.5%)	0.0057
Mycological Cure	15/67 (22.4%)	42/72 (58.3%)	<0.0001

Reviewer comment: The "complete cure" rate reached statistical significance but the overall rate was very low, only 16.7%. The rate for "effective treatment" also reached statistical significance but was also rather low, 37.5%, specially considering these are the patients who more rigorously used treatment twice daily for 4 weeks. Mycological cures for this population of patients reached 58.3% and was statistically significant. Again, the rate of mycological cure was rather low, considering the length of the treatment. These success rates are supportive of the efficacy seen in the MITT population. The cure rates in the per protocol population and the MITT are similar, suggesting that treatment effect is low regardless how well the protocol is adhered to.

Table 21 – SER 960602. Mycological Cure by Baseline Pathogen. MITT.

Pathogen	Vehicle	Sertaconazole	p-value[a]
T. rubrum	15/77 (19.5%)	38/78 (48.7%)	0.0002
T. mentagrophytes	2/7 (28.6%)	5/10 (50.0%)	0.6221
E. floccosum	1/8 (12.5%)	6/10 (60.0%)	0.0656

[a] p-values based on Fisher's Exact test. Source: Reviewer Analysis

Reviewer comment: Mycological cure reaches statistical significance only for T. rubrum.

6.3.1.9 Efficacy Conclusions

For the efficacy endpoint Complete Cure, this trial has demonstrated a small but statistically significant effect over vehicle. For secondary endpoints Effective Treatment and Mycological Cure, statistical significance was also reached.

6.3.2 Protocol # SER-960603. Title A Double-Blind, Randomized, Vehicle-Controlled, Multicenter, Parallel Group Evaluation of the Efficacy and Safety of Sertaconazole 2% Cream in Patients with Interdigital Tinea Pedis, **Conducted from** September 24, 1997 **to** March 27, 1998

The details of this protocol are the same as for the first protocol, except the participating sites and patients were different.

Subject Disposition

This trial included 15 study sites. The following table presents the site numbers, the investigators, and the number of patients who were randomized and who completed the study for each arm of each site.

Table 22. SER-960603. Study Sites, Investigators, Number of Patients Randomized and in MITT.

Site	Principal Investigator	Patients [1] Randomized P/S [3]	Patients [2] MITT P/S [3]
25	Raza Aly, Ph.D.	9/9	6/6
26	Gerald F. Davis, M.D.	3/3	1/0
27	Charles Fishman, M.D.	14/15	9/10
28	Joseph F. Fowler, M.D.	4/3	2/2
29	Terry M. Jones, M.D.	21/21	19/17
30	Joseph Jorizzo, M.D.	1/1	0/0
31	Kathryn Kroeger, M.D.	4/3	2/1
32	Marketa Limova, M.D.	10/10	8/8
33	Anne Lucky, M.D.	2/4	2/3
34	Ann Martin, M.D.	18/20	13/13
35	David M. Pariser, M.D.	6/6	3/2
36	Phoebe Rich, M.D.	18/18	10/13
37	David Rodriguez, M.D.	21/21	19/19
38	Bruce Brod, M.D.	11/10	8/9
39	Manuel Morman, M.D.	½	1/0

[1]from page 8-9-237 [2] from page 8-9-236, modified by the Agency [3]P = vehicle, S = sertaconazole

The following table indicates the number of patients who were enrolled and who completed the study:

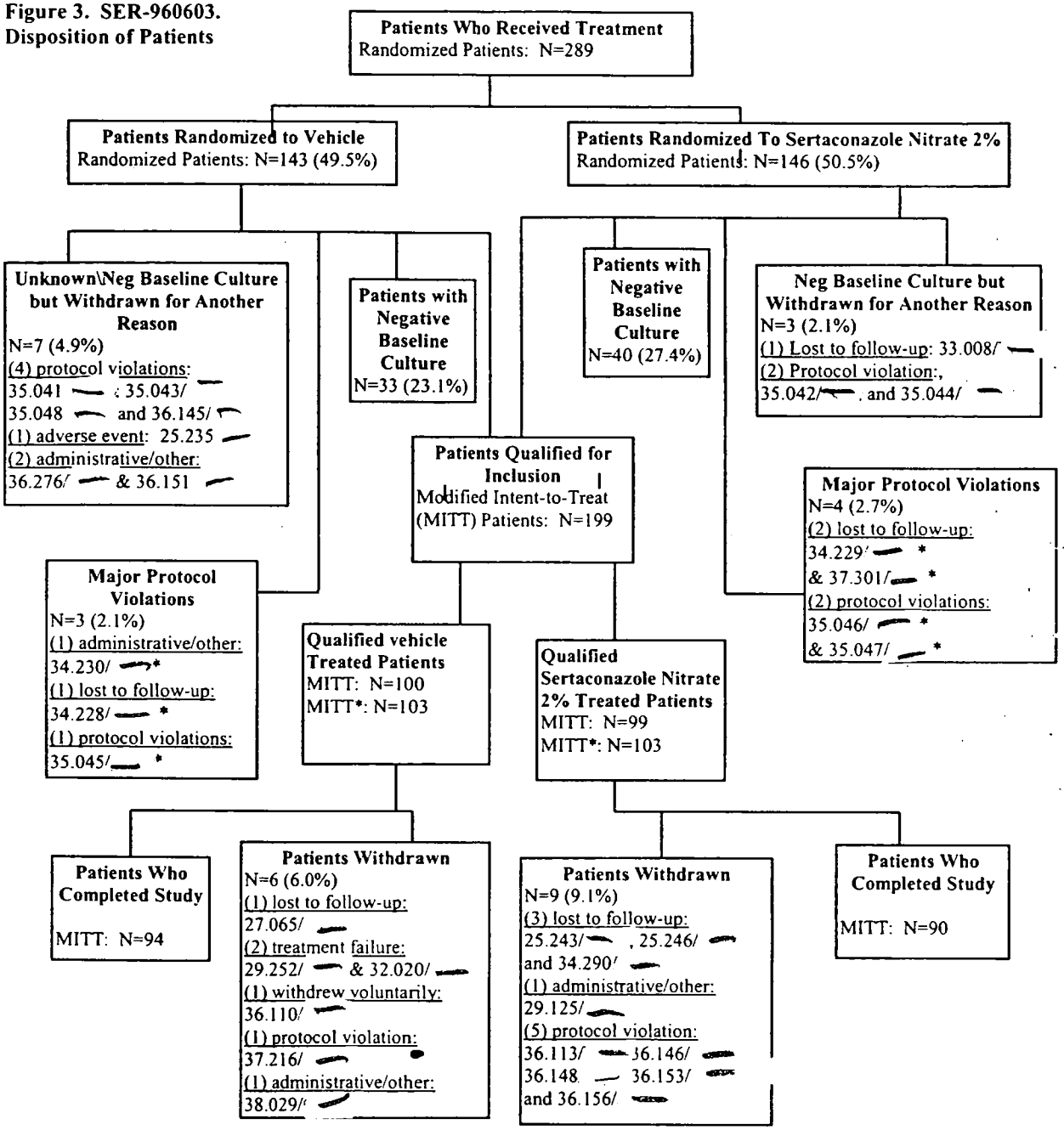
Table 23. SER 960603. Number of Study Participants.

Planned:	286	(143 vehicle and 143 sertaconazole nitrate 2% cream) patients
Entered:	289	(143 vehicle and 146 sertaconazole nitrate 2% cream) patients
Analyzed for Efficacy:		
Modified Intent-to-Treat:	206	(103 vehicle and 103 sertaconazole nitrate 2% cream) patients
Per-Protocol	183	(89 vehicle and 94 sertaconazole nitrate 2% cream) patients
Analyzed for Safety:	289	(143 vehicle and 146 sertaconazole nitrate 2% cream) patients

A total of 289 (143 vehicle and 146 sertaconazole nitrate 2% cream) patients entered this study. Of the 289 patients who entered the study, 83 patients (40 vehicle and 43 sertaconazole nitrate 2% cream) had negative baseline cultures. Seventy-three (73) patients (33 vehicle and 40 sertaconazole nitrate 2% cream) of the 83 patients with a negative baseline culture, were discontinued for this reason alone, while 10 patients (7 vehicle and 3 sertaconazole nitrate 2% cream) were discontinued due to multiple reasons excluding negative baseline culture. Seven patients (3 vehicle and 4 sertaconazole nitrate 2% cream) were considered major protocol violators.

The following figure indicates the number of patients who had negative cultures at baseline, and those who had protocol violations leading to elimination from the study.

Figure 3. SER-960603.
Disposition of Patients



Note: * these patients were not included by Sponsor into MITT for efficacy analysis but were included by the Agency

Data Source: Summary Tables DEM.1, DEM.4, EFF.7.1, EFF.7.2, EFF.8.1, and EFF.8.2 and Patient Data Listings DEM.1, DEM.3, and DEM.5.

A total of 289 patients entered the study (143 vehicle, 146 sertaconazole). Negative baseline culture was the reason for exclusion for 83 (40 vehicle, 43 sertaconazole) but 10 of these

patients (3 vehicle, 4 sertaconazole) had other reasons as well. Three vehicle and four sertaconazole nitrate 2% cream-treated patients were considered major protocol violations and excluded from MITT by the Sponsor but included by the Agency.
Three subjects had unknown KOH at Visit-6. One of these was a failure. The remaining two were labeled by Sponsor as "effectively treated" (34.174, 36.146). These were considered as failures in the Agency's analysis.

Table 24 provides reasons for patient withdrawal.

Table 24. SER-960603. Patient Withdrawals for Randomized Patients and for MITT.

	Randomized patients (N=289)		MITT patients (N=199)	
Withdrawal Reason	Vehicle N=143	Sertaconazole N=146	Vehicle N=103	Sertaconazole N=103
Withdrawals Number (%)	49 (34.3)	56 (38.4)	9 (8.73)	13(12.62)
Negative Baseline Culture	33 (23.1)	40 (27.4)	-	-
Lost to follow-up	2 (1.4)	6 (4.1)	2 (1.94)	5(4.85)
Withdrew Voluntarily	1 (0.7)	0 (0.0)	1(1.0)	-
Administrative/Other	4 (2.8)	1 (0.7)	2(1.94)	1(1.0)
Protocol Violation	6 (4.2)	9 (6.2)	2(1.94)	7(6.79)
Treatment Failure	2 (1.4)	0 (0.0)	2 (2.0)	-
Non-Compliance	1 (0.7)	0 (0.0)	-	-
Adverse event experience	1(0.7)	-	-	-

Data Source: Patient Data Listing DEM.1.table 4, page 8-2-144 to 148

The primary reason for patient withdrawal in randomized patients was negative baseline culture (Vehicle 23.1% (33/143), and sertaconazole 27.4% (40/146). Excluding negative baseline culture, the primary reason for patient withdrawal was protocol violation (Vehicle 4.2% (6/143), sertaconazole 6.2% (9/146). The percentage of randomized patients withdrawn from the study ranged from 1.7% (5/289) at sites 32 and 38 (Limova and Brod, respectively) to 6.6% (19/289) at site 36 (Rich).

Table 25 provides a listing of number of patients who failed inclusion/exclusion criteria, by the type of criteria that was not met, for the all-treated patient population.

Table 25. 960603. Randomized Patients. Failed Inclusion/Exclusion Criteria.

Failed Inclusion/Exclusion Criteria Randomized patients (N=289)	Vehicle N=143	Sertaconazole N=146
Number (%) of Patients not Meeting Inclusion/Exclusion	6 (4.2)	8 (5.5)
Onychomycosis, n(%)	1 (0.7)	4 (2.7)
Liver Function Tests ≥ 2 x Upper Limit of Normal, n(%)	3 (2.1)	2 (1.4)
Patient Less Than 12 Years Old, n(%)	1 (0.7)	0 (0.0)
Topical Anti-fungal Therapy to Feet Within 14 Days, n(%)	1 (0.7)	1 (0.7)
Lactating, n(%)	0 (0.0)	1 (0.7)

Data Source: table 5, page 8-9-145

Six of the 143 vehicle-treated patients (4.2%) and eight of the 146 sertaconazole nitrate 2% cream-treated patients (5.5%) failed to meet an inclusion and/or exclusion criteria. The primary criteria not met in the vehicle and sertaconazole nitrate 2% cream treatment groups were onychomycosis and liver function tests greater than twice the upper limit of normal, respectively.

Reviewer comment: there were no study discontinuations because of treatment-related adverse events. One participant treated with vehicle withdrew from the study because of an adverse event before being discontinued from the study due to a negative baseline culture. The distribution of protocol violations was similar for vehicle and for sertaconazole. Although the Sponsor excluded from efficacy analysis several patients because of missing data or patient withdrawal, all patients who were randomized and had a positive KOH and culture were included in the MITT efficacy analysis by the Agency.

Of the 289 patients who entered the study, 206 (103 vehicle and 103 sertaconazole nitrate 2% cream-treated patients) qualified for inclusion in the modified intent-to-treat population by having positive baseline cultures, and no major protocol violations.

Patient demographic data and baseline characteristics for the randomized populations are displayed in Table 26.

Table 26. SER-960603. Randomized Patients. Demographic Characteristics

Characteristics	Vehicle N=143	Sertaconazole N=146	Total N=289
Age, years			
Mean ± SE, Range (min-max)	34.1 ± 1.14 (11 - 76)	35.2 ± 1.14 (13 - 74)	34.6 ± 0.81 (11 - 76)
Sex, n (%)			
Male	112 (78.3)	104 (71.2)	216 (74.7)
Female	31 (21.7)	42 (28.8)	73 (25.3)
Race, n (%)			
Caucasian	88 (61.5)	88 (60.3)	176 (60.9)
Hispanic	32 (22.4)	27 (18.5)	59 (20.4)
Black	21 (14.7)	24 (16.4)	45 (15.6)
Asian	1 (0.7)	6 (4.1)	7 (2.4)
Other	1 (0.7)	1 (0.7)[b]	2 (0.7)
Height, inches			
Mean ± SE, Range (min-max)	68.4 ± 0.33 (57 - 79)	68.3 ± 0.36 (58 - 78)	68.3 ± 0.24 (57 - 79)
Weight, pounds			
Mean ± SE, Range (min-max)	181.1 ± 3.57 (100 -321)	184.4 ± 3.21 (83-310)	182.7 ± 2.4 (83 - 321)

a Patient 39.109/ [redacted] b Patient 32.278 [redacted] c N=142 d N=288 SE = Standard error.
Data Source: Summary Tables DEM.3.1, PHYSEXAM.1, and TINEAHX.1.table 10 page 8-9-154

Table 27. SER-960603. Randomized Patients. Baseline Disease Characteristics.

Disease Factors	Vehicle N=143	Sertaconazole N=146	Total N=289
Location			
One Foot	33 (23.1)	29 (19.9)	62 (21.5)
Both Feet	110 (76.9)	117 (80.1)	227 (78.5)
Duration of Current Episode			
<1 Month	20 (14.0)	27 (18.5)	47 (16.3)
1-3 Months	37 (25.9)	45 (30.8)	82 (28.4)
>3-6 Months	17 (11.9)	8 (5.5)	25 (8.7)
>6 Months	69 (48.3)	66 (45.2)	135 (46.7)
Number of Previous Episodes			
Mean ± SE, (min-max)	9.7 ± 1.66[c] (0 - 125)	11.9 ± 4.68 (0 - 672)	10.8 ± 2.5[d] (0 - 672)

a Patient 39.109 — b Patient 32.278/ — c N=142 d N=288 SE = Standard error.
Data Source: Summary Tables DEM.3.1, PHYSEXAM.1, and TINEAHX.1.table 10 page 8-9-154

The majority of randomized patients were male (74.7%) with a mean (± SE) age of 34.6 (± 0.81) years, and were Caucasian (60.9%). Baseline mean (± SE) height and weight in randomized patients were 68.3 (± 0.24) inches and 182.7 ± 2.4 pounds, respectively.

The majority had disease involvement of both feet (227/289; 78.5%) and a duration of disease (current episode) of greater than 3 months to 6 months or greater than 6 months (160/289; 55.4%) at baseline. The mean (± SE) number of previous episodes was 10.8 (± 2.5).

Table 28. SER-960603. Baseline Pathogen. MITT.

Pathogen	Vehicle N=103	Sertaconazole N=103	Total N=206
T. rubrum	78 (75.72)	82 (79.61)	160 (77.69)
T. mentagrophytes	20 (20.0)	18 (18.2)	38 (19.1)
E. floccosum	5 (5.0)	3 (3.0)	8 (4.0)

Data Source: Summary Tables DEM.3.2, EFF.4.2, EFF.5.1, and PATHOG.2 and Patient Data Listings EFF.1 and DEM. 3. Table 11, page 8-9-156

A slightly higher percentage of sertaconazole nitrate 2% cream-treated patients (80%; 8/10) had *T. rubrum* at Site 38 (Brod) as compared to vehicle-treated patients (45.5%; 5/11).

Medical History

Two patients (36.153 and 36.156) treated with sertaconazole nitrate 2% cream entered the study on Day 14 of Lotrimin washout (minor protocol violations). No patient was excluded from efficacy analysis because of developing medical history.

Concomitant Medications

There were no significant concomitant medications taken during this study. Most commonly taken medications during the trial included multivitamins, ibuprofen, acetylsalicylic acid, and acetaminophen.

Reviewer comment: The patient demographic data (age, gender, race, baseline pathogen, medical and medication history, and severity of involvement) for the modified-to-treat

population paralleled that of all randomized patients and was similar for both study arms. Similar to the other protocol, the predominant pathogen was T. rubrum (77%), but in this study there were twice as many T. mentagrophytes isolates than in the other study.

6.3.2.1 Results. Efficacy Endpoints Outcomes

MITT Population analysis

The reviewer will present next the Agency's MITT analysis. The Sponsor's MITT analysis will be discussed in section 6.3.3, Overview of Efficacy for the Indication Interdigital Tinea Pedis (page 42). The Agency's efficacy analysis is reflected on the following table:

Table 29. SER-960603. Efficacy Results MITT.

MITT	Vehicle	Sertaconazole	p-value
Complete Cure	5/103 (4.9%)	28/103 (27.2%)	<0.0001
Effective Treatment	16/103 (15.5%)	52/103 (50.5%)	<0.0001
Mycological Cure	20/103 (19.4%)	71/103 (68.9%)	<0.0001

Reviewer comment: As in the first protocol, vehicle showed little effect and sertaconazole was statistically significantly more effective than vehicle. The sertaconazole effect(27%) in this trial is about double that of the first trial (13%). Efficacy reaches statistical significance for the primary efficacy variable "complete cure," as well as for the secondary efficacy variables.

Table 30. SER 960603 Complete Cure. Analysis by Site. MITT

Site	Vehicle *	Sertaconazole *
25	0/6	2/6
26	0/1	0/0
27	0/9	2/10
28	0/2	½
29	0/19	7/17
30	0/0	0/0
31	0/2	0/1
32	0/8	3/8
33	0/2	2/3
34	2/13	3/13
35	0/3	0/2
36	1/10	4/13
37	0/19	2/19
38	2/8	3/9
39	0/1	0/0

* number complete cures/ number in MITT

Reviewer comment: The small number of patients in most sites makes comparison of efficacy rates by site difficult. Only one site had more than 4 successes.

Table 31. SER-960603. Efficacy Analyzed By Age of Patient. MITT.

	Vehicle	Sertaconazole	p-value[a]
Complete cure			
Age ≤ 17	0/6 (0.0%)	3/7 (42.9%)	0.1923
18 – 35	3/54 (5.6%)	14/43 (32.6%)	0.0008
36 – 64	2/40 (5.0%)	10/49 (20.4%)	0.0582
≥ 65	0/3 (0.0%)	¼ (25.0%)	>0.999
Effective treatment			
Age ≤ 17	1/6 (16.7%)	6/7 (85.7%)	0.0291
18 – 35	10/54 (18.5%)	26/43 (60.5%)	<0.0001
36 – 64	5/40 (12.5%)	19/49 (38.8%)	0.0077
≥ 65	0/3 (0.0%)	¼ (25.0%)	>0.999
Mycological cure			
Age ≤ 17	2/6 (33.3%)	7/7 (100%)	0.0210
18 – 35	13/54 (24.1%)	30/43 (79.80%)	<0.0001
36 – 64	5/40 (12.5%)	32/49 (65.3%)	<0.0001
≥ 65	0/3 (0%)	2/4 (50.0%)	0.4286

Complete Cure

Table 32. SER-960603. Complete Cure. Analysis by Gender, Race, and Pathogen. MITT.

Complete Cure	Vehicle	Sertaconazole	p-value[a]
Gender Male	1/78 (1.3%)	23/71 (32.4%)	<0.0001
Female	4/25 (16.0%)	6/32 (18.8%)	>0.999
Race Caucasian	5/60 (8.3%)	23/61 (37.7%)	0.0002
Black	0/15 (0.0%)	0/12 (0.0%)	NA
Asian	0/1 (0.0%)	2/5 (40.0%)	>0.999
Hispanic	0/26 (0.0%)	3/24 (12.5%)	0.1033
Other	0/1 (0.0%)	1/1 (100%)	>0.999
Pathogen T. rubrum	2/78 (2.6%)	23/82 (28.1%)	<0.0001
T. mentagrophytes	3/20 (15.0%)	5/18 (27.8%)	0.4381
E. floccosum	0/5 (0.0%)	1/3 (33.3%)	0.3750

[a] Fisher's Exact Test

Reviewer comment: Complete Cure reached statistical significance for males, Caucasians, and for T. rubrum.

Effective Treatment

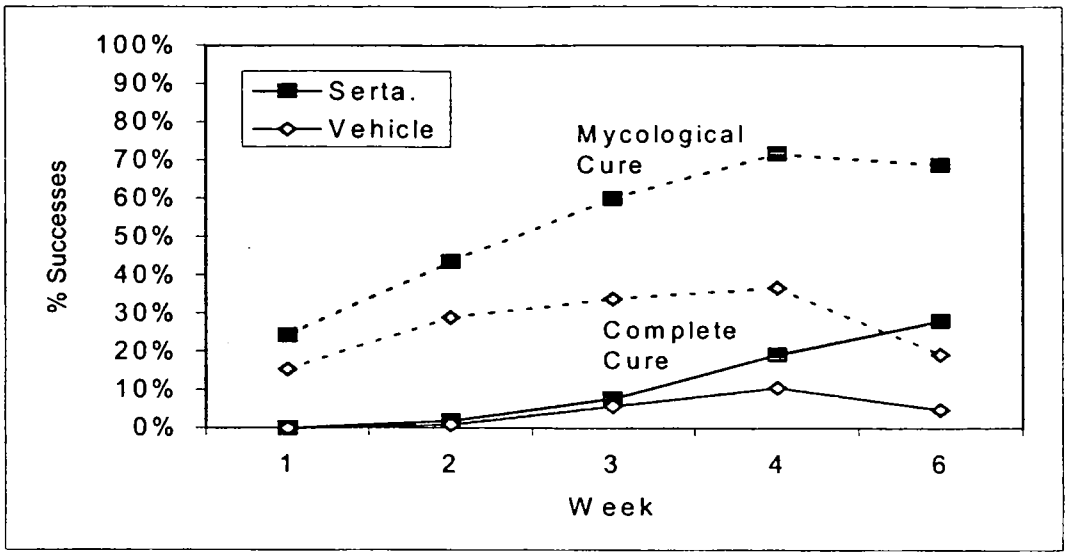
Table 33. SER-60603. Effective treatment Analyzed by Gender, Race, and Pathogen. MITT.

Effective treatment	Vehicle	Sertaconazole	p-value[a]
Gender Male	10/78 (12.8%)	38/71 (53.5%)	<0.0001
Female	6/25 (24.0%)	14/32 (43.8%)	0.1649
Race Caucasian	15/60 (25.0%)	36/61 (59.0%)	0.0002
Black	1/15 (6.7%)	3/12 (25.0%)	0.2940
Asian	0/1 (0.0%)	3/5 (60.0%)	>0.999
Hispanic	0/26 (0.0%)	9/24 (37.5%)	0.0005
Other	0/1 (0.0%)	1/1 (100%)	>0.999
Pathogen T. rubrum	13/78 (16.7%)	43/82 (52.4%)	<0.0001
T. mentagrophytes	3/20 (15.0%)	8/18 (44.4%)	0.0741
E. floccosum	0/5 (0.0%)	1/3 (33.3%)	0.3750

[a] Fisher's Exact Test

Reviewer comment: Statistical significance for Effective Treatment was reached for males, Caucasians, and for T. rubrum.

Figure 4- SER 960603Complete Cure and Mycological Cure Rates by Week.



Biostatistics Reviewer Graphic.

Reviewer comment: It is of interest that after 4 weeks of treatment complete cure had not reached statistical significance (p=0.0941). Complete cure rate reaches statistical significance only at week-6, the Point of Cure (p<0.0001). This effect was the result of six vehicle Complete Cures being lost from week-4 to week-6, as well as an increase of 8 complete cures for sertaconazole from week-4 to week-6. Mycological cures were higher at week-4 than at week-6, both for vehicle and for sertaconazole.

Per Protocol population analysis:

Defining the Per Protocol (PP) population as including those study participants who met the inclusion criteria, were randomized and treated and had evaluable efficacy data for Week-6 and were not delayed exclusion, the Agency's efficacy analysis is reflected on the following table:

Table 34 SER-960603 Efficacy Results. Per Protocol. Observed Cases

Per Protocol	Vehicle	Sertaconazole	p-value
Complete Cure	5/88 (5.7%)	27/92 (29.4%)	<0.0001
Effective Treatment	16/88 (18.2%)	51/92 (55.4%)	<0.0001
Mycological Cure	19/88 (21.6%)	70/92 (76.1%)	<0.0001

Reviewer comment: the "complete cure" rate reached statistical significance at 28% but the overall rate was low. Rates for all three efficacy variables were similar to those obtained for the MITT population, suggesting that a greater adherence to treatment did not improve efficacy.

Table 35 SER-960603 Mycological Cure by Baseline Pathogen. MITT.

Pathogen	Vehicle	Sertaconazole	p-value[a]
T. rubrum	15/78 (19.2%)	60/82 (73.2%)	<0.0001
T. mentagrophytes	5/20 (25.0%)	10/18 (55.6%)	0.0960
E. floccosum	0/5 (0.0%)	1/3 (33.3%)	0.3750

[a] p-values based on Fisher's Exact test. Source: Reviewer Analysis

Reviewer comment: Statistical significance is reached for Mycological Cure only for T. rubrum.

6.6.3.2 Efficacy Conclusions

For the efficacy endpoint Complete Cure, this trial has demonstrated a small but statistically significant effect over vehicle. For secondary endpoints Effective Treatment and Mycological Cure, statistical significance was also reached.

6.3.3 Overview of Efficacy for the Indication Interdigital Tinea Pedis.

The results from each trial differ in the degree of success, which is higher in the second trial for all three efficacy variables. A statistically significant difference over vehicle has been demonstrated for sertaconazole nitrate cream 2% in the treatment of tinea pedis interdigitalis for 4 weeks, twice a day. However the overall efficacy is small, particularly considering these results have been obtained after 4 weeks of treatment with a twice a day dosage.
The following table summarizes the combined results from both trials.

Table 36. Combined Studies. Efficacy Results Analyzed By Age. MITT.

Combined Studies	Vehicle N=195	Sertaconazole N=202	p-value[a]
Complete Cure			
Age ≤ 17	0/12 (0.0%)	6/15 (40.0%)	0.0200
Age 18 – 35	5/99 (5.1%)	21/88 (21.9%)	0.0002
Age 36 – 64	3/79 (3.8%)	15/91 (16.5%)	0.0108
Age ≥ 65	0/5 (0.0%)	1/8 (12.5%)	>0.999
Effective Treatment			
Age ≤ 17	1/12 (8.3%)	11/15 (73.3%)	0.0014
Age 18 – 35	15/99 (15.2%)	46/88 (52.3%)	<0.0001
Age 36 – 64	10/79 (12.7%)	28/91 (30.8%)	0.0055
Age ≥ 65	1/5 (20.0%)	2/8 (25.0%)	>0.999
Mycological Cure			
Age ≤ 17	3/12 (25.0%)	12/15 (80.0%)	0.0071
Age 18 - 35	22/99 (22.2%)	57/88 (64.8%)	<0.0001
Age 36 - 64	14/79 (17.7%)	50/91 (55.0%)	<0.0001
Age ≥ 65	1/5 (20.0%)	5/8 (62.5%)	0.2657

Reviewer comment: Statistical significance is reached for patients less than 64 years old for all of the efficacy variables.

The following table summarizes the combined results of both trials by gender, race, and pathogen.

Table 37 Combined Studies. Complete Cure Analyzed by Gender, Race, and Pathogen. MITT.

Complete Cure	Vehicle N=195	Sertaconazole N=202	p-value[a]
Gender Male	3/145 (2.0%)	30/146 (20.6%)	<0.0001
Female	5/50 (10.0%)	11/56 (19.6%)	0.1865
Race Caucasian	6/122 (4.9%)	34/132 (25.8%)	<0.0001
Black	1/36 (2.8%)	1/30 (3.3%)	>0.999
Asian	0/1 (0.0%)	1/7 (14.3%)	>0.999
Hispanic	1/35 (2.9%)	3/31 (9.7%)	0.3346
Other	0/1 (0.0%)	2/2 (100%)	0.3333
Pathogen T. rubrum	5/155 (3.2%)	32/160 (20.0%)	<0.0001
T. mentagrophytes	3/27 (11.1%)	7/28 (25.0%)	0.2955
E. floccosum	0/13 (0.0%)	2/13 (15.4%)	0.4800
T. kanei			

Reviewer comment: Significance is only reached for males, Caucasians, and for T. rubrum, even after pooling both trials.

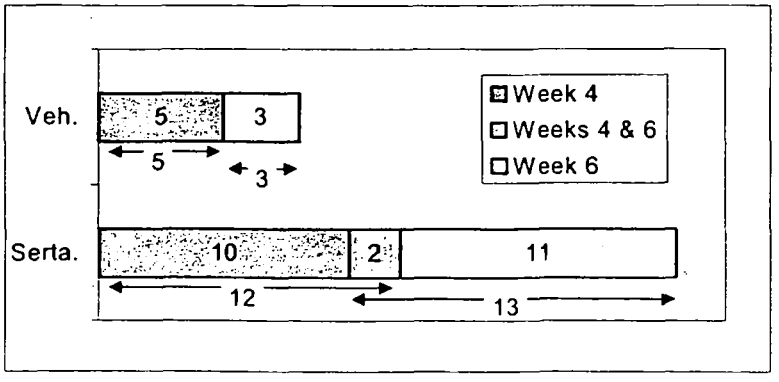
Table 38 Combined Studies Analyzed By Gender, Race, and Pathogen. MITT.

Effective Treatment.	Vehicle N=195	Sertaconazole N=202	p-value[a]
Gender Male	18/145 (12.4%)	63/146 (43.2%)	<0.0001
Female	9/50 (18.0%)	21/56 (37.5%)	0.0317
Race Caucasian	23/122 (18.9%)	61/132(46.20%)	<0.0001
Black	2/36 (5.6%)	6/30 (20.0%)	0.1278
Asian	0/1 (0.0%)	3/7 (42.9%)	>0.999
Hispanic	2/35 (5.7%)	12/31 (38.7%)	0.0018
Other	0/1	2/2	0.3333
Pathogen T. rubrum	22/155 (14.2%)	67/160 (41.9%)	<0.0001
T. mentagrophytes	4/27 (14.8%)	13/28 (46.4%)	0.0186
E. floccosum	1/13 (7.7%)	4/13 (30.8%)	0.3217
T. kanei			

Reviewer comment: Effective treatment reached statistical significance in the pooled studies for males and females, for Caucasians and Hispanics, for T. rubrum and for T. mentagrophytes.

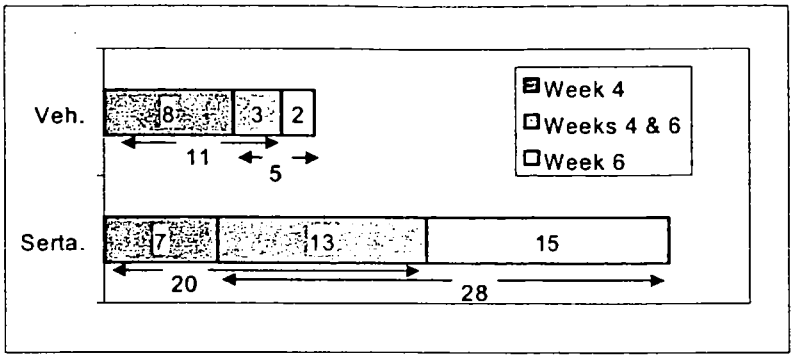
The following two figures indicate the number of patients who had a Complete Cure at week-4 and week-6.

Figure 5 – SER-960602. Number of Subjects with Complete Cure at Weeks 4 and 6.



Biostatistics Reviewer Graphic.

Figure 6 – SER 960603. Number of Subjects with Complete Cure at Weeks 4 and 6



Biostatistics Reviewer Graphic.

Reviewer comment: In trial 602, only 2 out of 12 (17%) of the sertaconazole patients who had a Complete Cure at week-4 also had Complete Cure at week-6. For 603, it was 13 out of 20 (65%). One could expect vehicle treated patients who appear as Complete Cure at week-4 to appear as failures by week-6. It is harder to explain the variability in results between week-4 and week-6 for sertaconazole treated patients. Those that improved from week-4 to week-6 could represent patients who finally cleared residual symptoms. Those who worsened after week-4 suggest poor efficacy of the drug treatment. Other explanations are also possible, such as an initial improvement of symptoms resulting from an antiinflammatory effect of sertaconazole which could be expected to be temporary; persistence of drug in the skin samples could also account for negative cultures at week-4 on patients who finally have a positive culture at week-6, once sertaconazole is no longer present in the skin sample.

Review of Mycology Studies

In this section the reviewer will make comments about the mycology studies, including both trials.

Table 39. Combined Studies. Pathogen identified .

Pathogen	Vehicle N = 195	Sertaconazole N= 202	Total N= 397
T. rubrum	155	160	315 (79.34%)
T. mentagrophytes	27	28	55 (13.85%)
E. floccosum	13	13	26 (6.54%)
T. kanei	0	1	1 (0.25%)

The pathogen most often reported in these trials was Tricophyton rubrum, which was isolated from 315 (79.34%) of the study patients. T. mentagrophytes was reported in only 55 (13.85%) patients.

Table 40. Mycological Cures. Combined Results from both trials.

	Vehicle	Sertaconazole
T. rubrum		
Complete Cure	5/155 (3.22%)	32/160 (20.0%)
Effective Treatment	22/155(14.19%)	67/160(41.87%)
Mycological Cure	30/155(19.35%)	98/160(61.25%)
T. mentagrophytes.		
Complete Cure	3/27 (11.11%)	7/28 (27.8%)
Effective Treatment	4/27 (14.81%)	13/28 (44.4%)
Mycological Cure	7/27 (25.9%)	15/28 (55.6%)
E. floccosum		
Complete Cure	0/13 (0.0%)	2/13 (15.2%)
Effective Treatment	1/13 (7.60%)	4/13 (30.76%)
Mycological Cure	1/13 (7.60%)	7/13 (53.84%)

Reviewer comment: Of the 160 sertaconazole treated patients with T. rubrum at baseline, 98 had a mycological cure by week-6 but only 32 of these had a Complete Cure. At week-6, 67 still had minimal signs and symptoms, and 31(19.37%) had greater than minimal symptomatology. It would have been of interest to know whether these patients would have later on had a positive culture.

Of the 28 sertaconazole treated patients with T. mentagrophytes at baseline, 15 reached a mycological cure but only 7 had a Complete Cure.
Of the 13 sertaconazole treated patients with E. floccosum at baseline, 7 had a mycological cure by week-6 but only 2 had a Complete Cure.

Table 41. SER-960602 and SER-96063. Number of positive cultures per pathogen, per visit in the MITT population.

SER-960602	Visit	1	2	3	4	5	6	Total
T. rubrum								
	Vehicle	77	47	38	33	34	45	274
	Sertacolazole	78	33	22	14	6	9	162
T. mentagrophytes								
	Vehicle	7	7	2	3	2	2	23
	Sertacolazole	10	3	3	2	1	0	19
E. floccosum								
	Vehicle	8	5	6	6	5	5	35
	Sertacolazole	10	1	0	0	0	1	12
SER-960603								
T. rubrum								
	Vehicle	78	44	38	34	36	46	276
	Sertacolazole	82	35	21	11	9	5	163
T. mentagrophytes								
	Vehicle	20	10	6	3	4	8	51
	Sertacolazole	18	3	5	0	1	1	28
E. floccosum								
	Vehicle	5	3	4	3	4	4	23
	Sertacolazole	3	0	0	0	0	2	5

Reviewer comment: In both trials T. rubrum was recovered from patients 875 times, T. mentagrophytes 121 times, and E. floccosum 75 times. T. mentagrophytes was recovered twice as often from the vehicle treated arm in 960603 than in 960602. The number of cultures that are positive rebounded in both studies about 130% after treatment is stopped when the pathogen is T. rubrum and the treatment is vehicle. This effect is either not noticed or negligible when the treatment is vehicle for either of the other two pathogens.

Negative baseline cultures

The number of baseline samples who had a negative culture is shown in the next table.

Table 42. Negative baseline cultures.

	Vehicle	Sertaconazole	
SER-960602	56 (N=148) 37.83%	52 (N=151) 34.43.13%	108 (N= 299) 36.12%
SER-960603	40 (N=143) 27.97%	43 (N=146) 29.45%	63 (N= 289) 21.79%
Total	96 (N= 291) 32.98%	95 (N= 297) 31.98	191 (N= 588) 32.48%

Reviewer comment: The percentage of negative baseline cultures was similar for both trials but was higher for both arms in trial 960602 than in 960603.

Table 43 Negative Baseline Cultures by Site.

Site	Randomized patients	Negative baseline cultures	% Randomized patients with negative cultures
SER-960602	Vehicle/Sertaconazole (Total)	Vehicle/Sertaconazole (Total)	
01	12/12 (24)	6/4 (10)	41
03	21/21 (42)	9/7 (16)	38
05	7/6 (13)	6/3 (9)	69
06	9/8 (17)	2/3 (5)	29
09	14/15 (29)	5/4 (9)	31
11	19/20 (39)	4/2 (6)	15
12	7/9 (16)	1/5 (6)	37
13	8/9 (17)	0/2 (2)	11
14	11/10 (21)	1/0 (1)	5
15	4/6 (10)	3/3 (6)	60
16	10/11 (21)	3 / 4 (7)	33
17	5/5 (10)	3/0 (3)	30
18	5/4 (9)	1 /2 (3)	33

Site	Randomized patients	Negative baseline cultures	% Randomized patients with negative cultures
SER-960603	Vehicle/Sertaconazole (Total)	Vehicle/Sertaconazole (Total)	
25	9/9 (18)	2/3	27
27	14/15 (29)	5/5	34
29	21/21 (42)	2/4	25
32	10/10 (20)	2/3	25
34	18/20 (28)	5/7	33
35	6/6 (12)	0/2	
36	18/18 (36)	5/5	27
37	21/21 (42)	2/2	16
38	11/10 (21)	3/1	19

Note: Centers with low enrollment numbers are not shown in these tables.

Reviewer comment: Some sites had a greater share of negative baseline cultures. The rate of negative baseline culture ranged from as low as 5% to as high as 69%. This data suggests sample collection and culturing techniques might have varied considerably from one center to another, influencing the likelihood that a culture will grow a pathogen fungus. Literature reports indicate an 84% successful recovery of a dermatophyte in cultures of uncomplicated tinea pedis interdigitalis, which can decrease to 55% in cases with considerable inflammation and maceration, referred to as "dermatophytosis complex" (Leyden J.J and Kligman A.M. Interdigital athlete's foot. Arch. Derm 1978; vol. 114: 1466-1472). In these trials, "dermatophytosis complex" cases had been excluded, and therefore a high rate of positive mycology cultures from patients at baseline could have been anticipated.

Table 44a. SER-960602. Negative cultures at visits 2-6.

								Number of negative intervening cultures
SER-960602								
Patient	Treatment	Culture-1	Culture-2	Culture-3	Culture-4	Culture-5	Culture-6	
01.201	P	1	1	0	0	0	1	3
03.152	P	1	0	1	1	0	1	2
03.379	P	1	0	0	0	0	1	4
03.381	P	1	1	0	1	0	1	2
03.406	P	1	0	0	0	0	1	4
04.213	P	1	1	1	1	0	1	1
04.215	S	1	1	1	0	0	1	2
06.106	S	1	0	1	0	0	1	3
09.238	P	1	1	1	1	0	1	1
10.041	P	1	0	0	0	0	1	4
10.042	P	1	1	0	1	0	1	2
11.030	P	1	1	1	0	0	1	1
11.031	S	1	0	0	0	0	1	4
11.036	P	1	1	1	0	0	1	2
11.171	S	1	1	1	0	0	1	2
11.332	P	1	0	1	1	0	1	2
11.391	S	1	0	0	0	0	1	4
13.244	P	1	0	unknown	1	0	1	3
14.128	P	1	1	0	1	0	1	2
14.267	S	1	1	0	0	0	1	3
14.268	P	1	1	0	0	0	1	3
14.273	S	1	0	0	1	0	1	3
16.233	P	1	1	0	0	0	1	3
16.234	P	1	0	0	1	0	1	3
Patients 24								63

Table 44b. SER-960603. Negative cultures at visits 2-6.

								Number of negative intervening cultures
SER-960603								
Patient	Treatment	Culture-1	Culture-2	Culture-3	Culture-4	Culture-5	Culture-6	
25.325	P	1	1	1	1	0	1	1
25.326	P	1	1	1	1	0	1	1
27.067	P	1	1	1	1	0	1	1
29.251	P	1	1	1	1	0	1	1
29.321	P	1	0	0	0	0	1	4
29.323	P	1	1	1	1	0	1	1
31.097	P	1	1	1	1	0	1	1
32.014	P	1	1	1	0	0	1	2
32.019	P	1	0	0	0	0	1	4
32.022	S	1	0	0	0	0	1	4
34.172	P	1	1	0	0	0	1	3
34.175	P	1	1	0	1	0	1	2
34.179	P	1	0	0	0	0	1	4
34.217	P	1	1	1	1	0	1	1
34.232	P	1	0	1	0	0	1	3
36.152	P	1	1	unknown	1	0	1	1
37.157	S	1	0	1	0	0	1	3
37.215	S	1	0	0	0	0	1	4
37.302	P	1	1	0	1	0	1	2
37.303	P	1	0	0	0	0	1	4
37.308	P	1	0	0	0	0	1	4
37.374	P	1	0	0	0	0	1	4
37.377	S	1	1	0	0	0	1	3
37.378	P	1	1	0	0	0	1	3
38.033	S	1	0	1	0	0	1	3
38.133	S	1	1	1	0	0	1	2
38.135	P	1	1	1	1	0	1	1
38.139	P	1	0	1	1	0	1	2
39.345	P	1	0	0	0	0	1	4
Patients 29								73
Total Patients 960602 and 960903 = 53								136

Treatment: P = vehicle, S = sertaconazole; Culture: 0= Negative, 1= Positive

Reviewer comment: There were a number of patients who had positive cultures at Week-6 but not at one or more intervening visits, suggesting the pathogen might have been present all along but not recovered.
It is hard to assess trials that depend on culture results when so many baseline and intervening cultures were negative. It signals a need for improvement and standardization of culture techniques.

Table 45 . Changes in Identified Pathogen Throughout the Study

Trial	Patient	Visit	Reported pathogen
960602	10.042	Baseline	T. rubrum
		1	T. mentagrophytes
		2	No growth
		3	T. mentagrophytes
		4	No growth
		5	T. mentagrophytes
	11.177	Baseline	T. mentagrophytes
		1	E. floccosum
		2	E. floccosum
		3	E. floccosum
		4	E. floccosum
		5	E. floccosum
			E. floccosum
	13.019[1]	Baseline	T. rubrum
		1	T. mentagrophytes
		2	No growth
		3	No growth
		4	No growth
		5	No growth
960603	29.059	Baseline	T. mentagrophytes
		1	T. mentagrophytes
		2	No growth
		3	T. rubrum
		4	No growth
		5	No growth
	38.033	Baseline	T. rubrum
		1	No growth
		2	T. mentagrophytes
		3	No growth
		4	No growth
		5	T. rubrum
	27.067	Baseline	T. mentagrophytes
		1	T. mentagrophytes
		2	T. mentagrophytes
		3	T. rubrum
		4	No growth
		5	T. mentagrophytes
	36.114	Baseline	T. rubrum
		1	No growth
		2	No growth
		3	No growth
		4	T. rubrum
		5	T. mentagrophytes
	37.164	Baseline	T. mentagrophytes
		1	No growth
		2	No growth
		3	T. rubrum
		4	No growth
		5	No growth
	37.307	Baseline	T. mentagrophytes
		1	No growth
		2	E. floccosum
		3	E. floccosum
		4	E. floccosum
		5	E. floccosum

[1]This patient achieved complete cure and effective treatment.

Reviewer comment: It can be expected that most tinea pedis interdigitalis result from infection with only one pathogenic fungus. However, the pathogen reported from 9 patients in these trials was different at various time points. If pathogens are misidentified, their respective cure rates and their statistical significance would change. False negative cultures and misidentification of isolates compound the difficulty in relying on culture results.

The Applicant has supplied two safety and efficacy trials in which sertaconazole nitrate 2% cream was used twice daily for 4 weeks, conforming to the proposed label. These studies support the efficacy of twice daily administration for interdigital tinea pedis. Efficacy has been demonstrated when the causative pathogen is T. rubrum but has not been demonstrated for T. mentagrophytes or E. floccosum, the other two pathogens included in the proposed label.

7. INTEGRATED REVIEW OF SAFETY

7.1 Brief Statement of Findings

A review of the data submitted by the sponsor has not revealed any safety concerns in the patients treated with sertaconazole nitrate 2% cream, twice-daily for a month, in the treatment of interdigital tinea pedis.

There were no deaths or treatment-related severe adverse events, clinical or laboratory, in either the sertaconazole- or the vehicle- treated patients in any of the US studies reported for this application.

Overall there were no clear differences between treatment groups in adverse events or in treatment-related adverse events.

7.2 Materials Utilized in the Review

The materials utilized for the review of safety of sertaconazole nitrate 2% cream are those supplied by the Sponsor with the application, which include the US studies and the foreign studies listed in table S-1 below and the results of pharmacovigilance in Spain and the results of a literature search conduced by the Sponsor. This information is collected in NDA 21-385 and it is scattered through volumes 1.1, 1.24, 1.26-1.62. Additionally, the review has utilized materials sent by the Sponsor as a result of requests from the Agency and which is collected in volumes 2.1, 3.1, and 4.1.

Sponsor has supplied an updated safety report which is reviewed in section 7.6

7.3 Description of Patient Exposure

Sponsor bases the analysis of safety on 3553 patients who participated in 29 US and foreign studies. Of these, 2047 received some formulation containing sertaconazole, of which all except 597 received sertaconazole 2% cream. IND 50,726 included 904 patients, of which 588 participated in the two pivotal studies, and 316 in the pharmacokinetic study (N=10) and dermal safety studies (N=306).

The table 3 (page 6) summarizes the exposure of patients to sertaconazole in US (613) and foreign (541) studies for which summary reports were available at the cutoff date of July 16, 1998.

Sponsor indicates that adverse events are reported less often in foreign trials than in US trials, so combined analysis artificially reduces the incidence of adverse events in sertaconazole treated patients. For this reason, although the Sponsor has combined US and foreign studies for analysis of safety in the NDA, this reviewer will focus mainly on the US studies.

To assess safety, Sponsor has combined the 588 patients from the US studies with the 541 from foreign studies that had CRFs available. Sponsor considers the foreign data as supportive of the US pivotal studies.

Table 46 summarizes the demography of the patients treated with sertaconazole in US trials that formed the database for analysis of safety, broken down by age, race, and gender.

Table 46. Demography of Sertaconazole Treated Patients in US Trials

	US		Foreign	
	Vehicle	Sertaconazole	Vehicle	Sertaconazole
Age				
<17 (N=24)	18	15		1
17-60 (N=728)	260	268		460
>60 (N=48)	13	14		34
Race				
Caucasian	187	185	-	-
Black	57	60	-	-
Other	47	52	-	-
Gender				
Male	219	217	-	180
Female	72	80	-	347[1]
Unknown	0	0	-	14

[1] Most females in foreign studies were treated for indications other than tinea pedis interdigitalis

Reviewer comment: Overall, there was a balanced distribution between the sertaconazole and the vehicle treated groups, regarding gender, race and age.

The average length of treatment in the US studies was 21 days, both for sertaconazole and for vehicle, and for each of the two pivotal studies. Table S-3 summarizes the duration of treatment.

Table 47. Number Of Patients and Length of Their Treatment with Sertaconazole Nitrate 2% Cream in the US Pivotal Trials.

Days	1-7	8-14	15-21	22-28	>29
Vehicle (N=291)	54	37	20	137	43
Sertaconazole (N=297)	47	47	14	149	40

Reviewer comment: There were no meaningful differences in duration of treatment between the age groups or the genders.

7.4 Safety Findings from Clinical Studies

In the evaluation of safety, the Sponsor employed the following convention:

- If a patient had more than one adverse event, it was counted as one for body system.
- If an event was recorded with various degree of intensity, the most severe was reported.
- Incidence reflects the number of patients reporting an event, rather than the number of events.

The overall sertaconazole population (N=838) reported an adverse event incidence of 10% (N=84), which results from a 19% (N=58) rate in the US and 5% (N=26) in foreign trials. Sponsor notes that there were 10 patients in foreign studies that reported 19 adverse events for which severity is unspecified in the case reports. In the US pivotal trials, no significant differences in adverse events were noted between sertaconazole and vehicle treated patients. Table 48 summarizes adverse event rates in the US studies.

Table 48. Summary of Adverse Events in the US Pivotal Trials.

	Vehicle			Sertaconazole (N=297)		
Overall	N=291	50 (17%)		N=297	58 (19%)	
SER-960602	N=148	23 (15.5%)		N=151	25 (16.6%)	
SER-960603	N=143	27 (18.9%)		N=146	33 (22.6%)	
Age <17	18[1]	4[1] (22%)		15[1]	2[1] (13%)	
Age 17-60	260	45 (17%)		268	54 (20%)	
Age >60	13[1]	1[1] (7%)		14[1]	2[1] (14%)	
Race						
Caucasian	187	40 (21%)		185	41 (22%)	
Black	57	3 (5%)[1]		60	11 (18%)	
Other	47	7 (15%)[1]		52	6 (11.5%)[1]	
			Possibly related			Possibly related
Body as a whole		23 (8%)			29 (10%)	
Cardiovascular		2 (0.7%)				
Digestive		3 (1%)			3 (1%)	
Metabolic/nutritional		3 (1%)			9 (3%)	
Musculoskeletal		1 (<1%)			3 (1%)	
Nervous		2 (0.7%)			2 (0.7%)	
Respiratory		14 (5%)			15 (5%)	
Skin		7 (2%)	4 (1.4%)		7 (2%)	2 (0.7%)
Special senses					2 (0.7%)	
Urogenital		3 (1%)			5(2%)	
Symptoms						
Headache		8 (2.7%)			11 (3.7%)	
Common cold		10 (3.4%)			7 (2.4%)	
Coughing		2 (0.7%)				
Nasal congestion					2 (0.7%)	
Contact dermatitis					2 (0.7%)	
Urinary tract infection		2 (0.7%)				
Severe adverse events						
Skin		2 (0.7%)			2 (0.7%)	

Note: only adverse events with an incidence of at least 0.5% are shown.
[1] these numbers are too small to draw comparisons

Age: In general, no age related trends were apparent. Because the number of adverse events was small, comparisons could not be made between age groups.

Gender: No gender related trends in adverse events were apparent.

Race: The rate of adverse events in blacks appears larger than for other races but given the low number of black participants (60 of 257 treated with sertaconazole) it is not possible to draw significant comparisons with other races. Only headaches were reported with a higher incidence in the sertaconazole treated group than in the vehicle group and these events did not appear to be related to treatment with sertaconazole.

Possibly related adverse events: None were reported more than once in either the vehicle or the sertaconazole groups. Possibly related adverse events rate in the US studies reached over 1% only for the skin and only on the vehicle arm.

Pregnancy: One pregnancy was reported in a patient treated with vehicle (SER-960602, table medhx.1 page 8-2-269) and one in a sertaconazole treated patient) SER-960603, tablebmedhx.1, page 8-9-260)
Reviewer comment: no adverse event trends were apparent in these trials in relation to gender, age, or race. The rate of adverse events was low and similar for both vehicle and sertaconazole.

Severe adverse events:
The overall incidence of severe adverse events was low, with no apparent marked differences between treatment groups in individual adverse events within any one body system. Sponsor indicates there were 7 sertaconazole treated patients with severe adverse events, 3 in the US studies and 4 in the foreign studies (page 8-28-65). These included headache, respiratory infection, upper respiratory infection, dermatitis, erythema, genital pruritus, and vaginal pain or burning (these were patients who were treated for conditions other than tinea pedis).

Sponsor does not indicate whether any of the severe adverse events were drug-related.
In the vehicle (vehicle) group, faint, periodontal abscess, contact dermatitis, and application site reaction were considered severe by the investigator. These were considered not-related to treatment.
Reviewer comment: the rate of severe adverse events during these trials was very low and there is no pattern that suggests that those reported are related to the treatment, for instance the increased incidence of headaches in Black patients.

Laboratory adverse events:
In the US trials, all testing was done at [redacted] a central clinical laboratory, except for pregnancy testing, which was done at each center. The protocol describes testing for pregnancy at baseline and at study end but does not include results of such testing and no pregnancies were reported during the study. The sponsor has been asked to further supply information on this aspect of laboratory testing but the requested information has not been supplied at the time of this review.

No laboratory adverse event was considered serious and none caused discontinuation of treatment. Within the sertaconazole treated group, only one event (hypercholesterolemia) was considered drug-related by the investigator. Overall, no laboratory evidence points to specific organ toxicity due to sertaconazole use. No laboratory adverse events were considered drug-related within the vehicle group. Laboratory adverse events are summarized in table S-5 as follows:

Table 49. Laboratory Adverse Events Reported In the US Pivotal Trials.

	Vehicle (N=291)		Sertaconazole (N=297)	
	Adverse events	Drug-related	Adverse events	Drug-related
Total	9 events in 6 patients		14 events in 10 patients	1 (0.3%)
SGPT	1		1 (0.3%)	
SGOT	1		1 (0.3%)	
Raised cholesterol			3 (1%)	1 (0.3%)
Raised Triglycerides	1		2 (0.7%)	
Raised WBC			2 (0.7%)	
Raised BUN			2 (0.7%)	
Glycosuria			1 (0.3%)	
Acetonuria	1			
Proteinuria	1			
Blood urine			1 (0.3%)	
Decreased platelets	1			

Note: only abnormal laboratory measurements that reached an incidence of at least 0.5% are listed

No pregnancies were reported during the US trials. The application did originally not include details of pregnancy test results. After requesting information on pregnancy test results, the Applicant supplied the following information:

Table 50. Results of pregnancy tests

Result	SER960602	SER-960603
Number of females	79	73
Not of childbearing potential (based on exclusion criteria)	12	27
Negative Baseline pregnancy test	67	46
Negative study end pregnancy test	57	43
Not done at study end: Dropped out	8	2
Refused test	1	0
Unknown	1	1

Reviewer comment: In a peri-postnatal study findings included a significant reduction in live birth indices and a significant increase in the number of stillborn pups. This type of fetotoxicity reflects a pregnancy category C. This will be reflected in the reviewer's comments to the proposed labeling (see Pharmacology review for further details)."

All potentially clinically significant laboratory values occurred at a rate of less than 0.3%. Fourteen abnormal laboratory tests results were reported in sertaconazole treated patients, only one being described as possibly related to the treatment: Patient 20.295 had mild hypercholesterolemia. The same patient also had slightly increased ALT/SGPT, AST/SGPT, which were not attributed to the treatment. The patient completed the treatment. No action or follow-up is reported for this patient.

Patient 34.174 had mildly elevated triglycerides and cholesterol throughout the entire study. Patient 34.224 had an elevated SGOT but patient was discontinued because of a negative baseline culture.

Patient 34.289 had elevated cholesterol and alkaline phosphatase but was dropped from the study because of negative baseline culture.

The number of laboratory adverse events was too small to make any significant comparisons by age, gender, or race.

The Sponsor indicates it does not include laboratory tests results obtained in foreign trials with those from the US because the foreign trials included many different laboratories with varying analytical methodology for testing, and normal values and ranges were not standardized (page 8-28-67). Sponsor indicates that the validity of laboratory data from studies CL-1, CL-2, CL-3, and CL-5/93 was questionable because of the way the data was collected and transcribed (page 8-28-69). Nevertheless, it is of interest that laboratory data from foreign trials also pointed to a mild increase in cholesterol/triglycerides values in sertaconazole-treated patients (page 8-28-87).
Reviewer comment: It is very difficult to assess whether the changes in cholesterol have any clinical significance due to the paucity of information supplied and because there could be other factors that could explain this finding.

Nine foreign protocols studied pharmacokinetic parameters of various sertaconazole-containing dosage forms. Abnormal laboratory tests results were reported only in CL-PH1, with mild elevations of SGOT and of SGPT in two participants, which returned to normal within 8 days and no direct link to treatment was established.
Reviewer comment: It is difficult to assess the meaning of these laboratory changes, which could be due to factors other than treatment with sertaconazole; there is no apparent trend of laboratory adverse events in these trials.

Dermal safety studies:
The dermal safety studies were conducted in the US and are summarized in table 51.

Table 51. US Dermal Safety Studies

Protocol US studies	Test	Number of patients enrolled/completed)
SERT-9625 (dermal safety)	Sensitization Repeat insult patch test	221/202
SERT-9626 (dermal safety)	Cumulative irritancy	30
SERT-9627 (dermal safety)	Phototoxicity	25
SERT-9628 (dermal safety)	Photoallergy	30/29
Total		306/286

SERT-9625: In this Repeated Insult Patch Test study, sertaconazole did not conclusively induce contact sensitization in human participants. During the Induction Phase, the vehicle cream and saline exhibited no reactions, sertaconazole exhibited ±1 reactions (4/202

subjects). During the challenge Phase, saline exhibited no reactions, vehicle and sertaconazole exhibited ± 1 reactions (4/202 and 8/202 respectively)

SERT-9626: In this Primary/Cumulative Irritation Test, with the semi-occlusive patches at 24 hours saline exhibited no irritation, and vehicle and sertaconazole exhibited negligible irritation. At 48 hours, no dermal irritation was exhibited by any of three test substances. With the occlusive patches, sertaconazole and vehicle exhibited negligible irritation, saline exhibited none. At 48 hours sertaconazole and saline exhibited negligible reaction and vehicle exhibited none. Because the occlusive tests elicited negligible reaction, the cumulative irritation tests were conducted with occlusive patches; saline elicited "minimal" irritation (score of 28/100, greater than erythema in 8 of 29 subjects) while a "moderate" reaction was exhibited for sertaconazole (score 41/100, greater than erythema in 8 of 29 subjects) and for vehicle (score 49/100, greater than erythema in 11/29).

SERT-9627: In this Phototoxicity Study, none of three test substances elicited a reaction.

SERT-9628: In this Dermal Photosensitization study, none of three test substances elicited a reaction.
Reviewer comment: dermal safety studies did not show a significant potential for irritancy or sensitization in either contact- or photo- testing.

Potential risks based on animal data:
In more than two dozen animal toxicity studies at fairly large dose levels using multiple routes of administration in several species, no significant irreversible adverse events were identified. In rats and rabbits, no maternal or embryo toxicity was identified. In a battery of assays, no mutagenicity or clastogenicity was detected. The cream formulation was found slightly irritating in animals. In a rat peri-postnatal study, a significant increase in the stillborn pups was observed at the highest dose level of 160 mg/kg/day.. This information is reflected in category C for pregnancy in labeling.

Reviewer comment: this type of fetotoxicity reflects a pregnancy category C. This will be reflected in the reviewer's comments to the proposed labeling (see Pharmacology review for further details).

7.5 Literature Review for Safety

Sponsor indicates a MEDLINE search has failed to reveal additional adverse events (page 8-28-92). However, an interesting adverse event is reported (page 8-28-479) of an allergic contact dermatitis to sertaconazole, with cross-sensitivity to miconazole and to econazole (Goday JJ et al. Contact Dermatitis 1995 Jun 32(6): 370-1) where a patient who had no prior use of antifungals, used sertaconazole cream and developed a contact dermatitis. On patch testing, he was shown to have a positive patch test to sertaconazole, miconazole, and econazole but not to ketoconazole, sulconazole, or clotrimazole.

7.6 Postmarketing Surveillance

Table 52 indicates the sales of sertaconazole nitrate 2% cream up to October of 1998 as reported by the Sponsor (page 8-28-91):

Table 52. Units Of Sertaconazole Nitrate 2% Cream Sold In Countries Where It Is Approved

Country or Subcontinent	Units
Spain	[redacted]
Germany	
Portugal	
Brazil	
Rest of South America	
Central America	
Africa	
Pakistan	
Korea	
Philippines	
Total	

The Spanish Pharmacovigilance System has reported 14 communications with 20 untoward reactions. One reported case, taking place in 1996 and identified as a 20 year old female was reported as a fulminant hepatitis, long-lasting (4 months), life-threatening and requiring hospitalization, with eventual recovery for whom the following parameters are not known, length of treatment, surface area treated, and prior medical history. In non US post marketing surveillance for sertaconazole nitrate cream, 2%, most adverse events were mild, localized and temporary, with complete resolution (page 3-1-78, and 8-28-92): erythema, pruritus, vesiculation, hyperpigmentation, urticaria, hyperkeratosis, eczema, pain, pruritus, maculopapular eruption, pigmentation, and contact dermatitis.
Reviewer comment: It is difficult to assess the significance of these adverse events due to the paucity of details reported. Additional information has been requested from the Sponsor regarding the patient who developed hepatitis.

7.7 Safety Update.

The Sponsor submitted a safety update which is reviewed in the preceding section 7.6

7.8 Drug Withdrawal, Abuse, and Overdose Experience. Long term adverse events.

The maximum exposure to sertaconazole in the US studies was 35 days. No long-term (6 months or greater treatment) adverse events have been reported. Additionally, there were no reports of any clinical signs or symptoms consistent with withdrawal effects in patients discontinuing or completing treatment with sertaconazole. The applicant has not identified reports of overdose or accidental exposures to sertaconazole nitrate cream 2%.

7.9 Adequacy of Safety Testing

A review of the safety data supplied by the Sponsor has failed to indicate a potential safety signal when sertaconazole treatment is used twice daily for four weeks in the treatment of

interdigital tinea pedis in man and in women who are not pregnant or breast feeding and who are 17 years or older.

7.10 Labeling Safety Issues and Postmarketing Commitments

No clear need has developed for further studies to explore safety concerns. The dermal safety studies appear to have been conducted within what can be expected from this type of studies. The pivotal trials included the expected routine safety observations both for clinical events and for laboratory events.

This reviewer has not identified safety concerns that need to be reflected in labeling beyond what is proposed by the Sponsor in the submitted label.

Adverse Events As Reported In The Proposed Label

The proposed label includes the following:

"ADVERSE EVENTS:

Reviewer comment: this reviewer considers the preceding paragraph to be an adequate representation of the adverse event profile of the proposed drug to the consumer. To make more complete, this reviewer will recommend the addition of the following sentence:

7.11 Conclusion Of Safety Review

There were no meaningful differences in he incidence of adverse events to sertaconazole related to age, gender, or race. Results from the two pivotal US trials suggest sertaconazole 2% cream to be safe and well tolerated when used twice daily for 4 weeks for the treatment of

the indication tinea pedis interdigitalis, in patients age 17 to 60, who are not pregnant, nursing or who are sensitive to any of the ingredients in sertaconazole nitrate 2% cream or any of the other imidazole-type antifungals. The listing of adverse events in the proposed label appears to be adequate.

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

Selection of Doses in the Study

Sponsor states that Pre-phase 3 evidence indicated a potential therapeutic benefit with no increased safety risk for sertaconazole nitrate 2% cream versus sertaconazole nitrate cream 1%. Both at the PreIND meeting and the end-of Phase 2 meeting, the Agency requested a rationale for choosing 2% over 1% for sertaconazole cream. The information submitted by the Sponsor at the End-of-Phase 2 meeting in support of dose selection is summarized in vol. 26, page 8-1-34. Three studies compared the dosages 1% and 2% cream, as follows:

Table 53. Dose Selection Studies.

Trial	Indication	Subjects
CL-1	Pityriasis versicolor	10 per arm
CL-2	Candida albicans	10 per arm
CL-3	Dermatophytes	10 per arm

The Sponsor reports therapeutic differences were noted only in one of the three studies (submission 006, received 8/4/97, page 91) and were not significant. The Sponsor pooled the data from all three studies for meta-analysis and indicates that that the rates for "clinical heal" seemed higher at week-2 for the 2% dosage. However, by week-3 the advantage is lost, and it seems to be reversed by week-4. The latter study, Study CL-3 is the only one conducted on dermatophytes but it includes few patients and only 8 of them had tinea pedis without specifying interdigitalis or plantar type:

Site	Treatment with 1% sertaconazole nitrate	Treatment with 2% sertaconazole nitrate
Face	2	2
Trunk	1	2
Extremities	4	4
Hands	2	1
Feet	3	5

The number of isolates of each species is small and their site of origin is not identified:

Isolate	Treatment with 1% sertaconazole nitrate	Treatment with 2% sertaconazole nitrate
T. mentagrophytes	1	3
E. floccosum	1	1
T. rubrum	7	4
T. schoenleini	-	1
M. canis	1	1

At the time these data was presented, the Agency asked for further support for choosing the 2% product and Sponsor stated it would present additional dose ranging information to the Agency, addressing concentration, duration, and frequency of administration, but no additional data has not been provided.

Reviewer comment: It seems inappropriate to pool data from studies with different indications. This reviewer considers that no valid rationale has been provided for selecting for phase 3 trials and marketing the 2% dosage twice a day over once a day or over the 1% formulation. Although the drug sertaconazole has not demonstrated an adverse safety profile, one has to wonder whether it is appropriate to expose the population at risk to twice the amount of the drug for no validated reason.

9. Use in Special Populations

9.1 Evaluation of Applicant's Efficacy and Safety Analyses of Effects of Gender, Age, Race, or Ethnicity. Comment on Adequacy of the Applicant's Analyses.

Reviewer comment: no significant differences have been noted in safety or efficacy as it relates to gender, race or age. However, for some groups the number of patients was too small to draw conclusions, as was the case with races other than Caucasian, and for ages below 17 and above 60.

9.2 Pediatric Program

Sponsor is requesting a full waiver for pediatric subjects of —— of age or less on the basis that sertaconazole nitrate 2% cream does not represent a significant therapeutic alternative for this age group.

Under the Pediatric Rule, applications for new active ingredients, new indications, new dosage forms, dosing regimens or new routes of administration must contain a pediatric assessment unless the sponsor has obtained a waiver or deferral of pediatric studies. The Agency can also require pediatric studies of marketed drugs and biological products (1) that are used in a substantial number of pediatric patients for the claimed indications and where inadequate labeling could pose significant risks, or (2) that would provide a meaningful therapeutic benefit over existing treatments for pediatric patients and where inadequate labeling could pose significant risks (21 CFR 201.23).

In response to a request for data on use of sertaconazole nitrate 2% cream in countries where it is approved, according to age and indication, the Sponsor supplied on 2/6/2 the following information, where all patients age 12 to 19 are grouped together:

Table 54. Usage of Sertaconazole Nitrate 2% Cream In Spain by Age.

Indication		% prescriptions
	Tinea pedis	—
	Pityriasis versicolor	—
	Candidiasis	—
	Seborrheic dermatitis	—
	Seborrheic dermatitis (non-specific)	—
Age		
	0-1	—
	1-11	—
	12-19	—
	20-55	—
	>55	—

The pivotal trials included patients 18 and younger as shown in the following table:

Table 55. Subjects 18 And Younger Enrolled.

Age	Number enrolled			Number in MITT		
	SER 960602	SER960603	Total	SER960602	SER960603	Total
11		1 (0.3%)	1		0	1
12	4 (1.3%)	1 (0.3%)	5	3	1	4
13	4 (1.3%)	5 (1.7%)	9	3	2	5
14	5 (1.7%)	1 (0.3%)	6	2	1	3
15	1 (0.3%)	4 (1.4%)	5	1	2	3
16	2 (0.7%)	5 (1.7%)	7	1	4	5
17	7 (2.3%)	5 (1.7%)	12	4	3	7
18	7 (2.3%)	4 (1.4%)	11	5	4	9

There were 33 patients 16 or younger enrolled in the trials, of which 21 entered into the MITT population, and 19 into the Per-Protocol population.
Reviewer comment:

The number of patients in the pivotal trials younger than 17 years old is too small to substantiate safety and efficacy for patients 16 years old and younger. On the other hand, no particular safety concerns were identified in these patients.

Tinea pedis interdigitalis is not uncommon in the age group 3-18 years old (McBride A. Tinea pedis in children AJDC Vol. 146, 1992 p. 844-847) and it is considered underdiagnosed. In asymptomatic school children 11-14 years old, 8% had positive evidence of dermatophyte infection (English MP and Gibson MD Studies in the epidemiology of tinea pedis. Br. Med. J. 1959; 1:1442-6; Marples MJ and Chapman EN. Tinea pedis in a group of school children. Br. J. Dermatology 1959; 71:414-21). Nearly half of the children presenting with undiagnosed foot dermatitis had culture proven tinea (Kearse H.L. and Miller F. Tinea pedis in prepubertal children: Does it occur? J.A.A.D. 1988; 19:619-22; Caravati C.C. et al Cutis 1976; 17:313-4). Tinea pedis interdigitalis is even more likely if one of the parents has the condition (Gentles JC et al. Foot infections in swimming baths. Br. Med. J. 1973; 3:260-262) or if the patient frequents locales where other people walk around barefooted, such as swimming and sports facilities.

In markets where it is approved, nearly — of reported prescriptions were for tinea pedis, of which the more common type is the interdigital variety, and nearly —, of prescriptions were for patients 19 or younger. If sertaconazole is used in the US at rates similar to those reported here, substantial use could be anticipated for this indication in the age group 16 and younger.
Sertaconazole is a new molecular entity in the US but it is a member of the imidazole class of topical antifungal drug products which, as a class, has not demonstrated a significant risk signal within any age group. It seems reasonable to extrapolate efficacy and safety down to age 12. Below the age of 12 years old, it seems reasonable to expect that sertaconazole nitrate cream should not be frequently prescribed for the indication tinea pedis interdigitalis. This reviewer agrees with the Sponsor's statement that, for the pediatric population, sertaconazole does not represent a meaningful therapeutic benefit over existing treatments for interdigital tinea pedis. It would seem reasonable to extrapolate data on safety and efficacy to age 12 and to waive the requirement for pediatric studies for the indication tinea pedis

interdigitalis. .

9.3 Risk/Benefit analysis

From adverse events data collected in the US pivotal studies, there is no evidence of any significant health risk from the use of sertaconazole nitrate cream 2% in patients age 17 and above who are not pregnant or nursing. As with topically applied medications, cutaneous adverse events are seen but the rate has been low (1.3%). They have included contact dermatitis, erythema, irritation, stinging, tenderness, and body odor. Patients who become sensitized to sertaconazole might cross-react with other imidazole topical antifungals and should be switched to other imidazole antifungals with great care. Black patients have shown a greater tendency to react to sertaconazole but the small number of black patients enrolled into the pivotal trials makes generalizations difficult.

Efficacy has been demonstrated in the treatment of tinea pedis interdigitalis only when the causative organism was T. rubrum. In the absence of mycology culture proving the identity of the causative micro-organisms, practitioners might well consider selecting a topical antifungal with a proven wider spectrum of activity.

Females who are nursing or pregnant were excluded from the pivotal trials and therefore there is data as to effects during pregnancy or lactation. The Agency has requested the Sponsor includes information about pregnancies during the foreign studies in the upcoming safety update.

10. CONCLUSIONS, RECOMMENDATIONS, AND LABELING

10.1 Conclusions Regarding Safety and Efficacy

The data presented by the Sponsor does not suggest a safety signal when sertaconazole nitrate 2% cream is used in patients who are 17 years of age or older, who are not pregnant or nursing, and who are not allergic to imidazole-type antifungals or to any of the ingredients of sertaconazole nitrate 2% cream.

10.2 Recommendations on Approvability

Reviewer comment: This reviewer recommends approval of sertaconazole nitrate 2% cream for the

10.3 Labeling

Reviewer comment: Some portions of the label for which the reviewer is recommending changes are included next. Suggested deletions are shown with ~~strikeouts,~~ and additions are shown with underlining.

10 Draft Labeling Page(s) Withheld

Joseph M Porres, M.D., Ph.D.
Medical Officer/Dermatology

cc: Orig NDA 21-385
HFD-540 file
HFD-540/DIVDIR/Wilkin
HFD-540/Acting Clinical TL/Luke
HFD-540/MO/Porres
HFD-540/PHARM/Jacobs/Jacobs
HFD-540/CHEM/Decamp/Pappas
HFD-540/Stats/Alosh
HFD-540/Project Manager/Cross

Entered to DFS on: 5/29/02