CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-385

MICROBIOLOGY REVIEW

Product Quality Microbiology Review

Review for HFD-540
15 FEB 2002

NDA:	21-385
Name of Drug:	Sertaconazole Nitrate Cream, 2%
Review Number:	1
Submission Date:	28-Sept-01
Applicant:	Mylan Pharmaceuticals Inc.
Name of Reviewer:	Neal Sweeney, Ph.D.

Product Quality Microbiology Data Sheet

A. 1. **NDA:** 21-385

2. **REVIEW NUMBER:** 1

3. **REVIEW DATE:** 15-Feb-02

4. **TYPE OF SUPPLEMENT:** N/A

5. **SUPPLEMENT PROVIDES FOR:** N/A

6. **APPLICANT/SPONSOR:**

Name:	Mylan Pharmaceuticals Inc.
Representative:	Frank R. Sisto
Telephone:	304-599-2595

7. **MANUFACTURING SITE:** DPT Laboratories (San Antonio, TX)

8. **DRUG PRODUCT NAME:**
Proprietary: Not Assigned
Non-proprietary: Sertaconazole Nitrate Cream, 2%
Drug Priority Classification:

9. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Topical cream, sertaconazole nitrate 2% packaged in 2 g, 15 g, and 30 g tubes.

10. **METHOD(S) OF STERILIZATION:** None (Non-sterile drug product)

11. **PHARMACOLOGICAL CATEGORY:** Broad spectrum antifungal agent indicated for

B. 1. **DOCUMENT/LETTER DATE:** 28-Sept-01
2. **RECEIPT DATE:** 28-Sept-01
3. **CONSULT DATE:** 19-Dec-01
4. **DATE OF AMENDMENTS:** 01-Jan-02
5. **ASSIGNED FOR REVIEW:** 28-Jan-02
6. **SUPPORTING/RELATED DOCUMENTS:** None

C. **REMARKS:** Volumes 1and 3 were provided for product quality microbiology consult review.

Executive Summary

I. Recommendations

A. Recommendation on Approvability – NDA 21-385 is recommended for approval from the standpoint of product quality microbiology. See "Product Quality Microbiology Assessment" section of this review.

B. Recommendation on Phase 4 Commitments and/or Agreements, if Approvable - N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The non-sterile emulsion product (pH [redacted] is [redacted] methylparaben [redacted] w/w) and sorbic acid [redacted] w/w). The [redacted] was shown to be effective after [redacted] storage at 25°C/60%RH and [redacted] storage at 30°C/60%RH. Additionally a [redacted] formulation met USP Antimicrobial Effectiveness Testing acceptance criteria.

B. Brief Description of Microbiology Deficiencies – No product quality microbiology deficiencies were identified for this submission.

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____

B. **Endorsement Block**
Microbiologist: Neal Sweeney/15-Feb-02
Microbiology Supervisor: Peter Cooney/15-Feb-02

C. CC Block
cc:
Original NDA 21-385
HFD-540/Division File
HFD-540/F. Cross
HFD-805/N. Sweeney/Consult File

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/s/

Neal Sweeney
2/27/02 10:37:34 AM
MICROBIOLOGIST

Peter Cooney
2/27/02 11:00:59 AM
MICROBIOLOGIST

DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)
MICROBIOLOGY REVIEW
DERMATOLOGY (HFD-540) CONSULT
NDA: 21-385 DATE REVIEW COMPLETED: 29Apr02

Reviewer: Fred Marsik, Ph.D.

Date Company Submitted: 28Sep01 CDER Date Received: 1Oct01
Date Assigned: 14Jan02

Sponsor: Mylan Pharamaceuticals
781 Chestnut Ridge Rd.
PO Box 4310
Morgantown, West Virginia 26504-4310

Frank R. Sisto
Vice President Regulatory Affairs
304-599-2595

Established Name: Sertaconazole Nitrate Cream, 2%

Proprietary Name: Not Assigned

Other Names/Numbers: FI-7045

Chemical Name: (±)-1-[2,4-Dichloro-β-[(7-chlorobenzo[b]thien-3yl)methoxy]phenethyl]imidazole nitrate

Empirical Formula: $C_{20}H_{15}Cl_3N_2OS \bullet HNO_3$

Molecular Weight: 500.8

Drug Category: Anti-fungal

Proposed Indication:

Dosage Form/Route of Administration: Cream/Topical

Proposed Dosage: 2% sertaconazole nitrate/gram applied twice daily for 4 weeks (i.e. 28 days) to cover the infected areas and the immediately surrounding healthy skin. Each gram of sertaconazole nitrate cream, 2% contains 20 mg of sertaconazole.

Supporting Documents: IND 50,726

Background and Summary:

The Applicant has submitted data to support their application for a topical cream containing 2% sertaconazole to treat interdigital tinea pedis caused by the dermatophytes *Epidermophyton floccosum*, *Trichophyton mentagrophytes*,and *Trichophyton rubrum*. Sertaconazole is an antifungal of the imidazole class.

DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)
MICROBIOLOGY REVIEW
DERMATOLOGY (HFD-540) CONSULT
NDA: 21-385 DATE REVIEW COMPLETED: 29Apr02

EXECUTIVE SUMMARY:

The Applicant has provided in vitro susceptibility data for sertaconazole against the three most common causes of tinea pedis (*Epidermophyton floccosum*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum*) as well as clinical study results using sertaconazole to treat tinea pedis interdigitalis caused by each of these organisms. The in vitro data for *E. floccosum* was for one isolate of the organism while for *T. mentagrophytes* and *T. rubrum* there were data for 62 and 34 isolates respectively. Statistically significant results as compared to placebo for the treatment of tinea pedis interdigitalis caused by these organisms was only seen for *T. rubrum*. The statistically significant results were seen in each study in "Mycology Cures" but no statistical significance was seen for "Complete Cure" when analyzed by pathogen. However, the study was not powered for subgroup analysis.

[redacted]

From a Microbiology perspective the product is approvable for the treatment of tinea pedis interdigitalis caused by *Trichophyton rubrum*.

DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)
MICROBIOLOGY REVIEW
DERMATOLOGY (HFD-540) CONSULT
NDA: 21-385 DATE REVIEW COMPLETED: 29Apr02

TABLE OF CONTENTS

INTRODUCTION:

Sertaconazole is a synthetic imidazole antifungal. The imidazoles have been shown to have activity against fungi that cause cutaneous skin infections (dermatophytes). The applicant is proposing that 2% sertaconazole in a topical cream be used to treat interdigital tinea pedis caused by *Epidermophyton floccosum, Trichophyton mentagrophytes*, and *Trichophyton rubrum.* These three dermatophytic fungi are commonly involved in tinea pedis interdigital infections in the United States (1, 2).

Epidemiology of tinea pedis:

Trichophyton mentagrophytes, *T. rubrum* and *E. floccosum* are commonly involved in tinea pedis interdigital infections in the United States (1, 2). Tinea pedis interdigital is the most common type of tinea pedis with the plantar form of tinea pedis being the second most common form of the infection. Tinea pedis interdigital is characterized by maceration, scaling, and fissuring, particularly in the web space between the fourth and fifth toes. In mild cases, fungi can usually be recovered from the digital interspaces. In more severe cases, with more maceration and hyperkeratosis, fungi are recovered less than half the time, and the infection is characterized by overgrowth of aerobic bacteria (1).

IN VITRO MICROBIOLOGY FOR SERTACONAZOLE

Mechanism of action:

The applicant has provided information as to the mechanism of action of sertaconazole using the yeast *Candida albicans* for these studies (Vol. 24 pg. 7-1-43). The studies showed that sertaconazole inhibits the synthesis of ergosterol, which is a key component of the fungal cell membrane. The inability to produce ergosterol causes the cell membrane of the fungi to become leaky. This leaky membrane results in the loss of vital cytoplasmic fluid that eventually causes the death of the fungus. Results of other studies provided by the Applicant suggest sertaconazole also interferes with the production of intracellular ATP (Vol. 25 pg. 7-2-66). The information provided by the Applicant on the mechanism of action of sertaconazole is consistent with the reports of other investigators on the action of imidazole antifungals against fungi (3).

Spectrum of activity:

The applicant has provided in this application in vitro susceptibility data for sertaconazole against a variety of fungi. This review will focus on the data that pertains to *E. floccosum*, *T. mentagrophytes*, and *T. rubrum* since these are the three organisms which the applicant desires to have in the labeling for 2% sertaconazole topical cream for the treatment of tinea pedis interdigital. At the time (1985-1995) the in vitro susceptibility of *E. floccosum*, *T. mentagrophytes*, and *T. rubrum* to sertaconazole were determined and to this date there is no standardized method of performing susceptibility testing of dermatophytic fungi. Therefore testing was done in a number of different

ways (different forms of inoculum, different inoculum concentrations, different media, different incubation conditions, different methods of reading end points). The effect these different conditions can have on the susceptibility test results is illustrated in a study that the applicant has provided in this submission (Vol. 24 pg. 7-1-123, Vol. 25 pg. 7-2-53, and Vol. 25 pg. 7-2-309). This does not negate the results of these tests but makes it difficult to compare the results from one investigator to another. Test inoculum was made in a variety of different ways. Test organisms were exposed to varying concentrations of sertaconazole in a variety of growth media. The inoculated media were incubated between 28^0 to 35^0 C with test results were read at between at 24 and 48 hours by some investigators and between 7 and 10 days by other investigators. The MIC end point for some investigators was the concentration of sertaconazole that inhibited the growth of the test organism more than 95%, as compared to the positive growth control while for other investigators it was approximately 80% inhibition compared to the positive growth control. Table 1 represents a compilation of the results provided by the Applicant from a number of studies. The study numbers from which the data came are in Table 1. As can be seen in Table 1 in vitro susceptibility data for one isolate of *E. floccosum* was provided by the Applicant. The data also suggest that the MIC of sertaconazole against these organisms is lower if read 24 hours after exposure rather than 48 hours or 7 to 10 days. In addition Table 1 gives the minimal lethal concentration (MLC) of sertaconazole from a few studies for some of the isolates for *T. mentagrophytes*, *T. rubrum*, and *E. floccosum*. The MLC is the fungicidal concentration of sertaconazole. One of the striking differences in Table 1 is the log difference between the MIC and MLC. In terms of therapeutic outcome, the MLC may be a better indicator of the efficacy of sertaconazole, but the test conditions and especially the duration of incubation with the drug which is essential for MLC estimation, have not been standardized. The correlation of the MIC and the MLC values with clinical outcome is not known.

Table 1. In vitro susceptibility test results for sertaconazole against *Epidermophyton floccosum*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum* as provided in NDA 21-385

Organism/Study No.	Number Tested	MIC (µg/mL) 24/48 hr. reading	MIC (µg/mL) 7-10 day reading	MLC* (µg/mL) Range 24/48 hr. reading
E. floccosum				
Ph-I.1	1		4	
T. mentagrophytes				
M-2285	5		2	
M-2285	1		0.5	
MSERT-001	2	≤ 0.125/≤0.125		16/>64
M-2486	30		2.6	
Ph-I.1	7		2	

Ph-I.1	12		4	
Ph-I.1	3		8	
AD Ph-I.17	2	≤0.09/≥50		≥50/≥50
T. rubrum				
MSERT-001	7	≤0.125/≤0.125		≤0.125-0.5/1-64
MSERT-002	8	≤0.125/≤0.125		0.25-16/2->64
MSERT-002	3	0.25/0.25		0.25-32/0.25->64
MSERT-002	3	0.5/0.5		0.5-16/0.5->64
M2486	10		0.4	
Ph-I.1	2		2	
Ph-I.1	1		4	

*Minimal lethal concentration.

In addition to MIC and MLC data the Applicant provided data that measured the ability of sertaconazole to cause inhibition of growth of fungi (Vol. 24 pg. 7-1-55, Vol. 24 pg. 7-1-99). This inhibition was determined by the size of colonies of the fungi exposed to sertaconazole compared to the size of colonies not exposed to sertaconazole. This data provides evidence that sertaconazole apparently can inhibit the growth of fungi at lower concentrations than the MIC or MLC. This data provides a crude method by which to determine that sertaconazole has activity against fungi but its relevance to clinical outcome is not known.

Table 2 gives the in vitro susceptibility test results for sertaconazole against other dermatophytic fungi. The Applicant provided the data presented in Table 2. The Applicant is not asking for any of these organisms to be included in their label. However, it is important to have some understanding of the activity of sertaconazole against these organisms because based on clinical presentation and microscopic examination of skin scrapings taken from the infected area it is difficult to know the exact dermatophyte etiology of the infection. Therefore sertaconazole has the potential of being used in infections caused by these fungi. Here as in Table 1 the minimal lethal concentration of sertaconazole is given for some of the dermatophytes. In terms of therapeutic outcome, the MLC may be a better indicator of the efficacy of sertaconazole, but the test conditions and especially the duration of incubation with the drug which is essential for MLC estimation, have not been standardized. The correlation of the MIC and the MLC values with clinical outcome is not known. The data in Table 2 indicates that the concentration of sertaconazole that inhibits these fungi is similar to the concentrations that inhibit the fungi in Table 1. However, the ability of sertaconazole to treat infections caused by these organisms was not presented in this application.

Table 2. In vitro susceptibility test results for sertaconazole against dermatophytes other than *T. mentagrophytes, T. rubrum and E. floccosum*

Organism/Study No.	Number	MIC (µg/mL)	MIC (µg/mL)	MLC* (µg/mL) Range

The Applicant also provided the in vitro activity of sertaconazole against a variety of *Candida* species and other yeasts in this submission. This data is not presented here because the Applicant is not requesting labeling for yeast organisms. Yeast infections of the feet can be distinguished from dermatophytic infections by their clinical presentation and examination of skin scrapings from the infected area under the microscope (1, 2).

Information on the activity of sertaconazole against gram positive bacteria was provided in this submission (Vol. 25 pg. 7-2-118). This data did not give the names of the bacteria against which sertaconazole was tested but simply listed them by number. Supposedly they were staphylococci and streptococci. The method used to determine the susceptibility of the organisms to sertaconazole also was not given in detail. Therefore the data cannot be evaluated.

Mechanism(s) of resistance:

Resistance to the azole antifungals occurs because: 1) there is a modification in the quality or quantity of the enzyme associated with the production of ergosterol, 2) there

is reduced access to the target enzyme, and 3) there is a combination of 1 and 2. At this time there are no reports of modification of azole antimicrobials as a mechanism of resistance (5). The applicant did not provide any experimental data relating to mechanisms of resistance.

The Applicant has provided the results of two experiments intended to induce resistance to sertaconazole. The one experiment (Vol. 24 pg. 7-1-217) was done by subculturing susceptible organisms in media containing sub-inhibitory concentrations of sertaconazole. The MICs of the organisms subcultured under the test conditions were compared to those initially obtained for the same organisms. The organisms that were used were two isolates of *Candida albicans* and one isolate of *Candida pseudotropicalis*. Induction of resistance was done both on agar and in a broth medium. After 8 passages on agar medium and 6 in the broth medium the original MICs of the isolates did not change. The other experiment used an isolate of *C. albicans* and an *isolate of T. rubrum*. These experiments were done in an agar medium. The *C. albicans* was transferred a total of eight times and the *T.* rubrum transferred once. There were no changes in the MICs of these organisms after the transfers.

Post antibiotic effect (PAE):

The Applicant has provided the results of experiments that were done to determine if sertaconazole exhibited post antibiotic effect (Vol. 25 pg. 7-2-298). The conclusion of the investigator doing this experiment was that sertaconazole does not exhibit post antibiotic effect. The investigator notes that this conclusion is consistent with the conclusions of Craig and Gunmunsdon (6) who concluded in their studies that oral antifungals are devoid of PAE effect.

IN VIVO

Pharmacokinetics/Pharmacodynamics:

The Applicant has provided information on the amount of sertaconazole at the site of application 24 hours after a single application of 2% sertaconazole cream (Study Report CL-PH-1b). Each application of sertaconazole nitrate cream, 2% contains 20 mg of sertaconazole. Seven individuals had the 2% sertaconazole cream applied simultaneously to 8 sites. The results of this study showed that 82% to 89% of the 2% sertaconazole penetrated the stratum corneum after this one dose.

In another experiment called cutaneous retention of sertaconazole (Vol. 25 pg. 7-2-237) investigators applied 2% sertaconazole cream to the depilated skins of guinea pigs. Then 24, 48 and 72 hours post sertaconazole application they inoculated the skin of the guinea pigs with a suspension of *T. mentagrophytes* (inoculum approximately $1x10^5$ cfu/mL, sertaconazole MIC not provided) and observed the infected animals with and without sertaconazole for 21 days. In the groups to which sertaconazole was applied and then the animals infected 42 and 48 hours later there was no recovery of the infecting organism from any of the animals (0/16) at days 12 and 19. In the group that

was infected 72 hours after sertaconazole application 5 of the 16 guinea pigs had the infecting organism recovered at day 12. At day 19 there was no recovery from any of the 16 animals. Of the infected controls at day twelve 87.5% had the infecting organism isolated from the infected area and at day nineteen 68.5% had the organism isolated from the infected area. The investigators concluded that the result of this experiment indicated that there was retention of sertaconazole at the application site for at least 72 hours. In a similar experiment by the same investigator (Vol. 25 pg. 7-2-246) sertaconazole cream was applied at 12, 24, 48, and 48 hours prior to infection with *T. mentagrophytes* to each of four animals in a group. The results that were obtained from this study were similar to the results of the previously described study. In both of these experiments the 2% sertaconazole was applied in a topical cream base. The control animals in each experiment did not have the topical cream base without the sertaconazole applied to the skin. Therefore it is not known what effect the topical cream base might have on the infection.

Animal models of infection:

The Applicant has provided data from studies of the effect of sertaconazole on experimentally induced trichophytosis in animal models. These experiments involved the use of guinea pigs. In one of the experiments (Vol. 25 pg. 7-2-144) the guinea pigs were infected with *T. mentagrophytes* (the initial sertaconazole MIC of the infecting organism was not provided by the Applicant) and when infection was evident (3 days) the guinea pigs were randomly divided into two groups. One group served as the control and the other as the treatment group. Treatment was begun on day 3 with 2% sertaconazole cream applied topically to the infected skin and was continued for a total of 12 non-consecutive days. By the 17th day post-infection (10th day of treatment) no *T. mentagrophytes* could be isolated from the sertaconazole treated guinea pigs and the infection was well healed. By the 31st day post-infection still no *T. mentagrophytes* could be isolated and the infection was completely healed. In another experiment by the same investigator (Vol. 25 pg. 7-2-154) guineas pigs were infected as previously mentioned and treated with either 1% or 2% sertaconazole cream. The investigator concluded that the 2% sertaconazole cream performed better than 1% sertaconazole cream. In another experiment by the same investigator using the aforementioned guinea pig model (Vol. 25 pg. 7-2-191) the effects of treating *T. mentagrophytes* (sertaconazole MIC not provided) infected guinea pigs for 1, 5 and 12 days with 2% sertaconazole was investigated. The investigator concluded that treatment for 12 days showed the clearest decrease of symptoms and a total negativity in cultures performed on the 30th day post infection. In a similar experiment where the infected guinea pigs were treated for three days beginning the fourth day post-infection it was concluded that 2% sertaconazole treatment was somewhat better than treatment with 2% miconazole based on culture positivity and healing of lesions caused by the infection (Vol. 25 pg. 7-209).

In the experiments described above the control animals were not treated with the topical cream base without sertaconazole. Therefore the effect the topical cream base might have on the infection is not known. The results of the sertaconazole treatment

experiments suggests that 2% sertaconazole applied for at least 12 days is a more efficacious treatment than 2% used for fewer days or the use of 1% sertaconazole cream for any period.

Clinical studies (Vol. 49 pg. 8-24-11):

Two placebo-controlled clinical studies were conducted to determine the safety and efficacy of sertaconazole nitrate 2% cream in the treatment of interdigital tinea pedis. Both of these studies were conducted in the United States under identical protocols. Both Phase III studies were designed as 6-week multicenter, randomized, double-blinded, parallel group, placebo-controlled studies. Based of the Applicant's previous clinical experience with 2% sertaconazole cream the study medication was applied twice daily for 4 weeks (28 consecutive days), followed by a 2-week period of no treatment at the end of which time the reoccurrence rate was assessed. The sample size of 143 patients/treatment group (286 patients/study) was based on a 90% power to detect a 27% difference in therapeutic effectiveness between sertaconazole nitrate 2% cream and placebo, and a negative confirmatory fungal culture result of 40%.

Eligible patients were defined as patients aged 12 years or older with a clinical diagnosis of tinea pedis, based on clinical signs and symptoms of moderate erythema and scaling plus at least mild pruritus. The clinical diagnosis of tinea pedis was confirmed by direct microscopic examination of a KOH wet mount and by culture of scrapings acquired from the diseased area with the most extensive scaling.

After successful completion of screening procedures (including a positive KOH), patients who met the inclusion criteria were randomized at day 0 to receive either sertaconazole nitrate 2% cream or placebo (sertaconazole vehicle) for 4 weeks. Relapse (recurrence of infection) rates were determined during a Follow-up Visit, held 2 weeks after discontinuation of therapy for all patients completing therapy. Critical times for therapeutic evaluation were defined to be: Day 0 (i.e., visit 1; baseline; treatment initiation), Final treatment visit (Visit 5), and the Final Treatment visit + 2 weeks (point of Cure visit 6). The primary efficacy endpoint was to be the Point of Cure (Follow-up Visit 6). Mycological laboratory evaluations were performed using skin scrapings obtained from the diseased web site with the most extensive scaling at baseline Day 0 (visit1), during treatment on Days 7, 14, 21 and 28 (Visits 2 through 5); and at the 2-week follow-up (Visit 6). For any visit in which all interdigital web spaces appeared normal, the skin scrapings were obtained from the interdigital web space used at the preceding visit.
At the point of cure, a blinded qualified reviewer other than the investigator (central lab staff) was required to perform microscopic examination of the KOH wet mount preparation. This was done to rule out potential bias in which expectations of KOH negativity secondary to improved clinical appearance could reduce the tenacity of the search for fungal elements leading to the underreporting of fungal elements at the point of Cure.

Mycological response was categorized as one of the following (vol. 49 pg. 8-24-23):

Mycological Cure: A negative KOH preparation and negative fungal cultures at the Final Treatment Visit (Visit 5; week 4) and at the 2 week Point of Cure Follow-Up visit (Visit 5; week6).

Mycological Failure: Presence of a positive KOH and/or positive fungal culture at the Final Treatment Visit (Visit 5: week 4) and the 2 week Point of Cure Follow-Up visit (Visit 6; week 6).

Mycological Relapse: A positive KOH preparation and/or positive fungal cultures at the Point of Cure from a patient who demonstrated "Mycological Cure" at a prior visit or visits prior to the Point of Cure.

Clinical Evaluation of Signs and Symptoms of Disease Severity (vol. 49 pg. 8-24-21):

In addition to the mycological response evaluation subjects were also clinically evaluated. Using the interdigital web space most clinically affected by the disease process, the following four point scale was used to grade the clinical signs and symptoms of interdigital tinea pedis:

Clinical response referred to the changes in visible signs and reportable clinical symptoms. Clinical response to study treatment was evaluated for each patient through investigator assessment. Except where noted, evaluation procedures and examinations were performed at the Treatment Initiation Visit (Day 0), Study Days 7, 14, 21 the Final Treatment Visit (Day 28) and at the 2-week follow-up visit (Day 42).

0	Absent = Normal appearing skin
1	Mild = Barely abnormal
2	Moderate = Distinctly present abnormality
3	Marked = Intense involvement or marked abnormality

Physician's Global Evaluation of Clinical Response to Treatment (Vol. 49 pg. 8-24-21):

The physician's evaluation of response to treatment was based on the clinical status of the tinea pedis and information provided by the patient. The investigator evaluated weekly the amount of change in the overall condition of the patient based on relative expectations for normal appearing skin. The categorizations are as follows.

Worsening of Clinical Status: Some baseline signs and symptoms of tinea pedis are more severe and/or new signs and symptoms are present.

Mild Clinical Improvement or No Change: Some baseline signs and symptoms of tinea pedis are decreased. Significant evidence of disease remains.

Moderate Clinical Improvement: Most baseline signs and symptoms of tinea pedis have shown definite decrease.

Effective Clinical Treatment: Physicians Global evaluation referring to marked improvement over baseline in the signs and symptoms of interdigital tinea pedis. At most, mild residual erythema and/or scaling in all treated interdigital web spaces remain without other signs of interdigital tinea pedis.

Clinical Cure: Physician's Global evaluation referring to normal appearance of skin in all treated interdigital web spaces. Signs and symptoms associated with tinea pedis have completely resolved.

Overall Assessment of Successful Treatment Outcome (Clinical Response plus Mycological Response) (Vol. Pg.8-24-20):

Successful treatment outcome required both clinical and mycological evidence of therapeutic benefit. Overall response to treatment pertaining to the assessment of antifungal efficacy of sertaconazole nitrate cream 2% applied for 4 weeks versus placebo cream (product vehicle) was the proportion of patients who demonstrate Successful Treatment Outcome. Assessment of Successful Treatment Outcome was performed at the 6-week Point of cure (i.e. the Final Treatment visit plus 2 weeks) using the interdigital web site with the most severe tinea pedis involvement on clinical examination. The Successful Treatment Outcome ("Clinical Win") was defined as either of the following:

Complete Cure:*	Clinical Cure on the Physician's Global Evaluation In combination with Mycological Cure.
Effective Treatment:	Effective Clinical Treatment on the Physician's Global Evaluation in combination with Mycological Cure.

NOTE: The only primary efficacy variable evaluated by the Agency was "Complete Cure".

Patients were considered Treatment Failures if evaluated as clinical failure and/or mycological failure at the 2-week Point of Cure follow-up visit.

Table 3 (Vol. 49 pg. 8-24-28) summarizes the number of subjects in the sertaconazole treatment group and those on the placebo treatment group that had one of the pathogens of interest.

Table 3. Summary of subjects (MITT populations) with *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum* from studies SER-960602 and SER-960603

Pathogen	Sertaconazole (% of 195)	Placebo (% of 188)

T. rubrum	154 (79.0)	148 (78.7)
T. mentagrophytes	27 (13.8)	27 (14.5)
E. floccosum	13 (6.7)	13 (6.9)
Other	1 (0.5)	0 (0.0)

Because this Reviewer had some concern that the culture results may not be reflecting the actual clinical treatment outcome the data was reviewed with and without physician assessment of the outcome. The data without physician assessment is the results as determined by culture and or microscopic examination of specimens taken from suspected lesions. The results for weeks 4 and 6 are presented here because week 4 is the last week of treatment and week 6 is the two-week follow up after discontinuation of treatment. Table 4 (Vol. 49 pg. 8-24-512 and correspondence dated 7Mar02) is a summary of treatment outcome by visit week and baseline pathogen in the MITT populations (missing values treated as failure) for studies SER-960602 and SER-960603 combined with and without physician assessment. As can be seen in Table 4 the cure rates without physician assessment are higher for both the treatment and placebo groups. While it is difficult to know which is correct this Reviewer believes that the results that take into account the physician's assessment would be closer to the true results. This is because it is difficult to obtain appropriate specimens for microscopic examination and culture thus visual examination of the infected site may be more accurate in evaluating treatment results.

Table 4. Summary of treatment outcome by visit week and baseline pathogens MITT (with missing values treated as failures) populations. Studies SER-960602 and SER-960603 combined.

Visit Week	Pathogen	Treatment Outcome	Sertaconazole Number (%) with Physician Assessment	Sertaconazole Number (%) without Physician Assessment	Placebo Number (%) with Physician Assessment	Placebo Number (%) without Physician Assessment
Week 4	*T. rubrum*	Success	73 (47.4)	102 (65.4)	28 (18.9)	47 (30.4)
		Failure	81 (52.6)	54 (34.6)	120 (81.1)	107 (69.5)
	T. mentagrophytes	Success	15 (55.6)	21 (75.0)	12 (44.4)	16 (59.3)
		Failure	12 (44.4)	7 (25.0)	15 (55.6)	11 (40.7)
	E. floccosum	Success	7 (53.8)	10 (76.9)	2 (25.4)	4 (30.8)
		Failure	6 (46.2)	3 (23.1)	11 (84.6)	9 (69.2)
	Other	Success				
		Failure				
Week 6	*T. rubrum*	Success	71 (46.1)	97 (62.2)	22 (14.9)	30 (19.5)
		Failure	83 (53.9)	59 (37.8)	126 (85.1)	124 (80.5)
	T. mentagrophytes	Success	13 (48.1)	15 (53.6)	5 (18.5)	7 (25.9)
		Failure	14 (51.9)	13 (46.4)	22 (81.5)	20 (74.1)
	E. floccosum	Success	4 (30.8)	7 (53.8)	1 (7.7)	1 (7.7)
		Failure	9 (69.2)	6 (46.2)	12 (92.3)	12 (92.3)

Other	Success	[redacted]
	Failure	

1. Successful outcome is defined as both (a) and (b), where a = mycological response: negative KOH and negative culture, and b = clinical response: clinical cure or effective treatment obtained from Physician's Global exam
2. Obtained from CMH test for general association adjusted by investigator

Table 5 gives the results seen in Table 4 for the results that include the physicians assessment along with the statistical significance of the treatment results. The only statistically significant outcome was for the treatment of infection due to *T. rubrum*. In an analysis of each of the studies (SER-960602 and SER 960603) in Table 5 individually no statistically significant results were found for treatment of infection with any of the organisms when compared to placebo (IND 21-385 correspondence dated 7Mar02 attachments 5 and 6). The statistically significant difference for sertaconazole treatment of *T. rubrum* infection compared to placebo treatment occurred only when the study results are combined.

Table 5. Summary of treatment outcome by visit week and baseline pathogens MITT (with missing values treated as failures) population. Studies SER-960602 and SER-960603 combined. The results take into account the physician's assessment of treatment.

Visit Week	Pathogen	Treatment Outcome	Sertaconazole Number (%)	Placebo Number (%)	P-Value
Week 4	*T. rubrum*	Success	73 (47.4)	28 (18.9)	<0.0001
		Failure	81 (52.6)	120 (81.1)	
	T. mentagrophytes	Success	15 (55.6)	12 (44.4)	0.3609
		Failure	12 (44.4)	15 (55.6)	
	E. floccosum	Success	7 (53.8)	2 (25.4)	0.1985
		Failure	6 (46.2)	11 (84.6)	
	Other	Success	[redacted]		
		Failure			
Week 6	*T. rubrum*	Success	71 (46.1)	22 (14.9)	<0.0001
		Failure	83 (53.9)	126 (85.1)	
	T. mentagrophytes	Success	13 (48.1)	5 (18.5)	0.0456
		Failure	14 (51.9)	22 (81.5)	
	E. floccosum	Success	4 (30.8)	1 (7.7)	0..2743
		Failure	9 (69.2)	12 (92.3)	

Other Success [redacted]
Failure

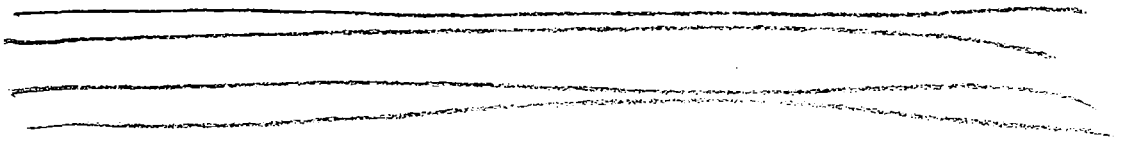
1. Successful outcome is defined as both (a) and (b), where a = mycological response: negative
KOH and negative culture, and b = clinical response: clinical cure or effective treatment obtained from Physician's Global exam
2. Obtained from CMH test for general association adjusted by investigator

REMARKS:

The sertaconazole in vitro susceptibility data that the Applicant has provided in this submission was performed by a number of investigators using different test methodologies. It is recognized that at the time these data were generated and to the time of this review there is not a recognized and standardized susceptibility test method for dermatophytic fungi. Because of the major differences in the susceptibility test results among the data submitted in this application it is difficult to determine what the true sertaconazole MIC is for the *T. mentagrophytes, T. rubrum* and *E. floccosum* isolates. In the case of *E. floccosum* susceptibility results were presented for only one isolate of this organism. This in itself is unsatisfactory. It is the recommendation of this Reviewer that [redacted]

CONCLUSION:

From a Microbiology perspective the information which the Applicant has provided on the in vitro activity of sertaconazole against *E. floccosum* is inadequate. This is because in vitro susceptibility data was only provided for one isolate of this organism. In addition there were only 13 patients with *E. floccosum* infection evaluated during clinical trials, which does not allow for a conclusion to be made on the efficacy of sertaconazole to treat tinea pedis interdigital caused by this organism. In the case of *T. mentagrophytes* infection treated with sertaconazole there was no statistically significant results when compared to placebo in each study (SER 960602 and SER 960603) evaluated individually or when the results of the study were combined. Therefore from a Microbiology perspective *E. floccosum* and *T. mentagrophytes* can not be included in the labeling for this product. Statistically significant results as compared to placebo for the treatment of tinea pedis interdigitalis caused *T. rubrum was* achieved. The statistically significant results were seen in each study for "Mycology Cures" but no statistical significance was seen for "Complete Cure" when analyzed by pathogen. However, the study was not powered for subgroup analysis.



From a Microbiology perspective the product is approvable for the treatment of tinea pedis interdigitalis caused by *Trichophyton rubrum.*

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2. Stein DH. 1998. Tineas –Superficial dermatophyte infections. Pediatric in Rev. *19*: 368-372.
3. Groll AH, TJ Walsh. 1997. Potential new antifungal agents. Current Opinion in Infectious Diseases. *10*: 449-458.
4. NCCLS. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Conidium-Forming Filamentous Fungi: Approved standard. 2000. NCCLS document M38-A (ISBN 1-56238-000-0). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA. 19087-1898.
5. Ghannoum MA, LB Rice. 1999. Antifungal agents: Mode of action, mechanism of resistance, and correlation of these mechanisms with bacterial resistance. Clin Microbiol Rev *12*:501-517.
6. V. Lorian (ed.) Antibiotics in Laboratory Medicine. 1986. 2nd ed. pg. 515-536. The Williams & Wilkins Co., Baltimore.
7. NCCLS. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Approved Standard. 1997. NCCLS document M27-A (ISBN 1-56238-328-0). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898.
8. NDA Holders Letter: CDER/FDA; 26January 1993.

DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)
MICROBIOLOGY REVIEW
DERMATOLOGY (HFD-540) CONSULT
NDA: 21-385 DATE REVIEW COMPLETED: 29Apr02

_____ Date_____
Frederic J Marsik, Ph.D.
Microbiology Reviewer

CONCURRENCE ONLY:

_____ Date_____
HFD-520/DepDir/L Gavrilovich

RD Initialed 4/30/02, Final 5/1/02
HFD-520/TLMicro/A T Sheldon

cc:
Original NDA 21-385
HFD-540 Divisional File
HFD-520/Micro/F Marsik
HFD-540/PHF/F Cross

DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)
MICROBIOLOGY REVIEW
DERMATOLOGY (HFD-540) CONSULT
NDA: 21-385 DATE REVIEW COMPLETED: 29Apr02

AGENCY PROPOSED MICROBIOLOGY PORTION OF THE PACKAGE LABEL

Microbiology

Sertaconazole is an antifungal that belongs to the imidazole class of antifungals. While the exact mechanism of action of this class of antifungals is not know it is believed that they act primarily by inhibiting the cytochrome P450-dependent synthesis of ergosterol. Ergosterol is a key component of the cell membrane of fungi and lack of this component leads to cell death primarily by leakage of key constituents in the cytoplasm from the cell.

[redacted]

Activity *In Vitro/In Vivo*: Sertaconazole nitrate has been shown to be active against [redacted] isolates of the following microorganisms, both *in vitro* and in clinical infections, as described in the INDICATIONS AND USAGE section:

~~*Epidermophyton floccosum*~~
~~*Trichophyton mentagrophytes*~~
Trichophyton rubrum

NOTE: The clinical efficacy of this product for the treatment of fungal infections other than tinea pedis caused by *T. rubrum* has not been shown.

[redacted]

Microbiology Comments on Applicant's Proposed Label:

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/s/

Frederic Marsik
5/20/02 03:15:58 PM
MICROBIOLOGIST

Albert Sheldon
5/21/02 10:01:24 AM
MICROBIOLOGIST

Lillian Gavrilovich
5/21/02 11:20:01 AM
MEDICAL OFFICER

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)
MICROBIOLOGY REVIEW
DERMATOLOGY (HFD-540) CONSULT

NDA: 21-385 DATE REVIEW COMPLETED: 4 November 2003
Document Date: 10 October 3003
Date Assigned: 22 October 2003
Requested due date: 17 November 2003

Sponsor: Mylan Pharamaceuticals
781 Chestnut Ridge Rd.
PO Box 4310
Morgantown, West Virginia 26504-4310

Angela Miller, R.Ph., Esq
Executive Director, Regulatory Affairs
304-599-2595

Established Name: Sertaconazole Nitrate Cream, 2%
Proprietary Name: Not Assigned
Other Names/Numbers: FI-7045
Chemical Name: (±)-1-[2,4-Dichloro-â-[(7-chlorobenzo[b]thien-3yl)methoxy]phenethyl]imidazole nitrate

Empirical Formula: $C_{20}H_{15}Cl_3N_2OS \cdot HNO_3$
Molecular Weight: 500.8
Drug Category: Anti-fungal
Proposed Indication: [redacted]

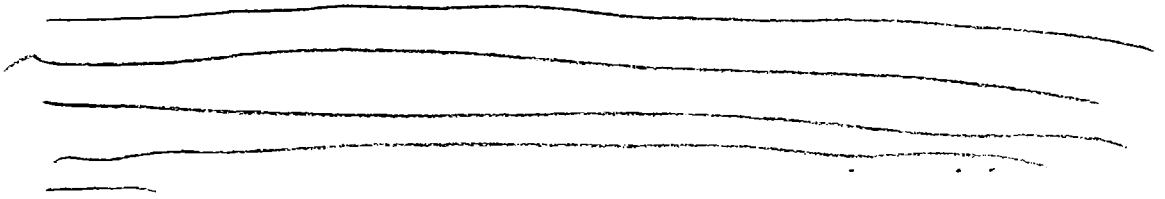
Dosage Form/Route of Administration: Cream/Topical

Proposed Dosage: 2% sertaconazole nitrate/gram applied twice daily for 4 weeks (i.e. 28 days) to cover the infected areas and the immediately surrounding healthy skin. Each gram of sertaconazole nitrate cream, 2% contains 20 mg of sertaconazole.
Supporting Documents: IND 50,726

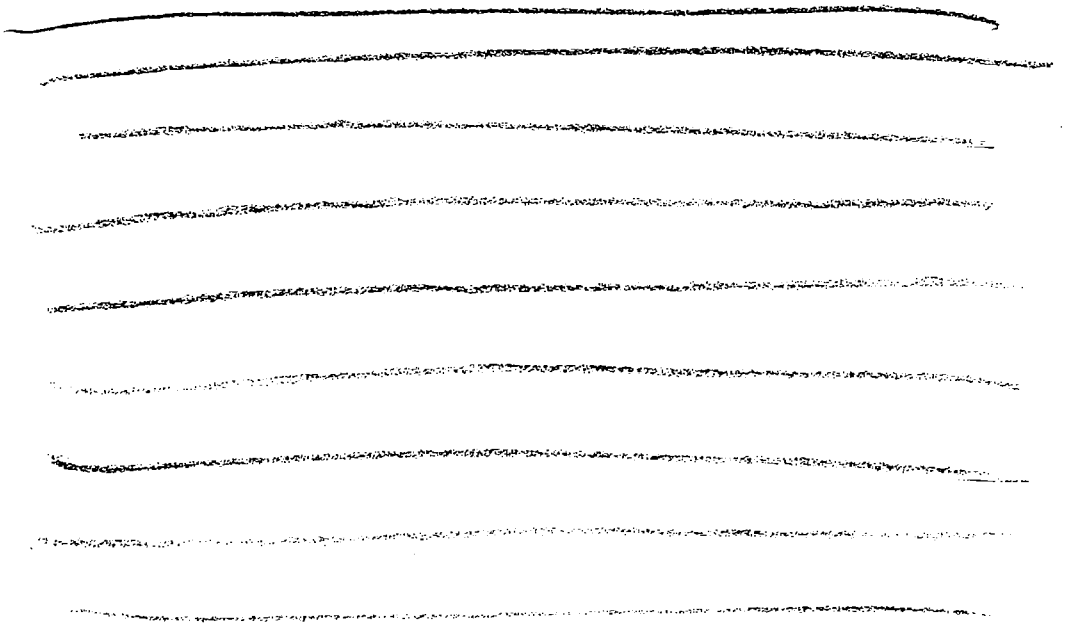
PURPOSE OF SUBMISSION:
In this submission, the sponsor provided a response to the deficiencies/comments outlines in the Agency's approvable letter dated 26 July 2002. The sponsor requested that the response be designated as a class 1 resubmission. The sponsor provided revised labeling, a safety update, and responses to the Agency's proposed Phase IV studies, updated stability data and other information clarifying the revision to the [redacted] free formulation.

BACKGROUND:

A microbiology review consult was provided on 29 April 2002. In the executive summary, the microbiology reviewer provided the following remarks:
"The Applicant has provided *in vitro* susceptibility data for sertaconazole against the three most common causes of tinea pedis (*Epidermophyton floccosum*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum*) as well as clinical study results using sertaconazole to treat tinea pedis interdigitalis caused by each of these organisms. The *in vitro* data for *E. floccosum* was for one isolate of the organism while for *T. mentagrophytes* and *T. rubrum* there were data for 62 and 34 isolates respectively. Statistically significant results as compared to placebo for the treatment of tinea pedis interdigitalis caused by these organisms were only seen for *T. rubrum*. The statistically significant results were seen in each study in "Mycology Cures" but no statistical significance was seen for "Complete Cure" when analyzed by pathogen. However, the study was not powered for subgroup analysis."



The microbiology reviewer also provided the following Proposed Phase IV Microbiology Studies:



The microbiology reviewer also reviewed the revised draft of the product label.

AGENCY PROPOSED MICROBIOLOGY PORTION OF THE PACKAGE LABEL

Microbiology

Sertaconazole is an antifungal that belongs to the imidazole class of antifungals. While the exact mechanism of action of this class of antifungals is not known, it is believed that they act primarily by inhibiting the cytochrome P450-dependent synthesis of ergosterol. Ergosterol is a key component of the cell membrane of fungi and lack of this component leads to cell death primarily by leakage of key constituents in the cytoplasm from the cell.

Activity *In Vitro/In Vivo*: Sertaconazole nitrate has been shown to be active against isolates of the following microorganism, both *in vitro* and in clinical infections, as described in the INDICATIONS AND USAGE section:

Connie R. Mahon, MS, CLS
Microbiologist, HFD-520
4 November 2003

Concurrence:
HFD-520/TLMicro/A.T. Sheldon
RD#1 Initialed 11/04/03, Final 11/13/03 ATS
HFD-520/Dept/Dir/L. Gavrilovich

REFERENCES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Connie Mahon
11/18/03 07:13:24 AM
MICROBIOLOGIST

Albert Sheldon
11/19/03 03:36:02 PM
MICROBIOLOGIST

Lillian Gavrilovich
11/26/03 05:14:49 PM
MEDICAL OFFICER