CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-385

MEDICAL REVIEW

Medical Officer's Review of NDA 21-385

NDA submission number: 21-385 (AZ)
HFD# 313626
Date of submission: 10/09/03
CDER stamp date: 10/10/03
Date review completed: 11/14/03
Date review returned and completed 12/08/03

Applicant identification: Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Rd
PO Box 4310
Morgantown, WV 26504-4310

Pharmcologic category Topical antifungal.

Indication: [redacted]

Drug name: sertaconazole nitrate, 2%.

Marketing name: Ertaczo cream.

Dosage form: Twice daily for 4 weeks.

Route of adminsitration: Topical cream.

I. EXECUTIVE SUMMARY:

Recommendations:

From the clinical perspective, it seems reasonable to approve sertaconazole 2% cream, pending acceptance by the Sponsor of the proposed labeling, and acceptance of the commitment to conduct the Phase 4 study as recommended by Pharamcology/Toxicology, as follows:

> Non-Clinical Toxicology: Conduct a dermal carcinogenicity study. The need for a dermal carcinogenicity study is guided by the chronic nature or rate of recurrence of the indication and not by systemic absorption of the drug substance or the absence of genotoxicity. (ICH S1A, "For pharmaceuticals used frequently in an intermittent manner in the treatment of chronic or recurrent conditions, carcinogenicity studies are generally needed.").

The Sponsor should identify sertaconazole products being marketed as shampoo and as nail lacquer, which are not identified in the updated safety report but for which information is available in the internet.

II. RESUME

This NDA was submitted on 9/28/01 and the medical review was completed on 5/29/02.

On 7/22/02 the Sponsor was informed that the application had been reviewed and was approvable.

Before this application may be approved, however, the Sponsor would have to submit an amendment responding to all the deficiencies listed:

1 [redacted]

2. Revised draft labeling for the drug as indicated in the enclosed draft labeling.

In addition, the Sponsor was informed the following studies would provide useful information in labeling for the safe and effective use of ERTACZO™ Cream 2%, and could be in the course of further development prior to approval or as postmarketing commitments:

a. Pharmacology/Toxicology: A dermal carcinogenicity study.

[redacted]

d. Clinical: Updated safety information, including data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

d.1. Detailed description of any significant changes or findings in the safety profile.

d.2. Description of any discontinuations due to adverse events, serious adverse events, and common adverse events, providing narrative summaries for serious adverse events.

d.3. Retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies.

d.4. Case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event.

d.5. Information that would suggest a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

d.6. Summary of worldwide experience on the safety of this drug, including an updated estimate of use for drug marketed in other countries.

The present submission includes the following responses *(verbatim)* by the Sponsor:

1. Mylan has opted to amend the application to provide for the —— free formulation as the proposed market formulation. Since the currently proposed market formulation (—— -free) is the same as that used to dose the pivotal trials submitted in support of the referenced application, the need for a —————— is no longer necessary.

Reviewer comment: This response is acceptable from the clinical point of view. I defer to the Chemistry Review for other outstanding issues that may arise from choosing to market the —— free formulation.

2. Four copies of revised draft labeling for the carton, tube and prescribing information are provided in Attachment #2. A redlined, annotated copy of the revised prescribing information noting and explaining the differences between Mylan's proposed labeling and the Agency's draft labeling is provided in Attachment #3.

Reviewer comment: A review of the submitted draft labeling is included later on in this review.

3. Safety Issues.

3.1 As described in the 5/22/02 NDA Safety Update, no new studies have been conducted or initiated in the US since the submission of NDA 21-385. In addition, there have not been any significant changes or findings in the safety profile described in the world-wide pharamcovigilance survey conducted by Ferrer International since that submitted on 5/22/02 and in the review of published literature. Ferrer's most current Periodic Safety Update Report for sertaconazole (1/1/1998- 1/1/03) is provided in Attachment #17.

3.2 Since the 5/22/02 NDA Safety Update there is no new safety data to incorporate and no additional clinical studies have been conducted.

3.3 No new studies have been initiated or conducted since the NDA was originally filed, therefore no new trends or patterns have been identified and there is no data regarding premature study discontinuation.

3.4 Since no studies have been conducted since the NDA was filed, there are no additional case report forms or narrative summaries for patients who may have died during the study or withdrew from the study due to an adverse event.

3.5 Subsequent to the filing of the NDA safety update in 5/02 no new safety data has been obtained.

3.6 Ferrer's Periodic Safety Update Report summarizing the world-wide experience with sertaconazole is provided in Attachment 17.

3.7 The Ferrer's current Core Safety Data Sheet is provided in their Periodic Safety Update Report in Attachment 17/
Reviewer comment: A review of the safety update is included later on in this review.

Please refer to reviews by Chemistry, Biopharmaceutics, Pharmacology /Toxicology , and by Clinical Microbiology for comments to the Sponsor's answers in those areas.

III. REVIEW OF SAFETY UPDATE

The submission includes a Periodic Safety Update Report provided by Ferrer, for the period 1/1/98 to 1/1/03. Following is a summary of the findings reported by the Sponsor for each of the products in the report:

1. Changes to reference safety information. Core Data Sheets:

1.1 Zalain/Dermofix cream, powder, solution, and gel, and they include the following safety information:

Side-effects: The Sponsor states there have been reported some cases of slight and transient local erythematous reaction during the first days of treatment, and that treatment discontinuation has not been required.

1.2 Gine-Dermofix and they include the following safety information:

Side-effects: The Sponsor states the adverse effects of this medication have been in general light and transitory, and that the more important secondary effects could be:

-occasionally: alterations genitor-urinary (sensation of heat urethral, vaginal pruritus, vaginitis, urinary incontinence, cystitis).

-rarely: alterations allergical/dermatological (erythema, eruptions exanthematicals, pruritus, dermatitis for contact) and neurological (cephalea). The treatment should be suspended immediately, in case the patient experiences some intense episode of cephalea, irritation and/or hypersensitivity.

Both Data sheets include the following:

"Pregnancy/Lactation: No plasma levels have been detected after the application of important amounts of the drug; in spite of this, its innocuousness in pregnant women has not been demonstrated and, therefore, the risk-benefit ratio should be evaluated before its use during pregnancy and lactation."

2. Worldwide market authorization status:

Sertaconazole cream is being marketed in 84 countries. The following other formulations are listed, but for fewer countries: for cutaneous use: powder, solution, and gel; for vaginal use: cream, tablet, and suppositories.

3. Update of regulatory authority or market authorization holder taken for safety reasons:

The Sponsor states that Sertaconazole has not been withdrawn from the market, nor have any drugs suspensions or regulatory actions directed to labeling of new safety aspects for Sertaconazole or restrictions to distribution been brought into effect. It further states that no amendment to the Company Core Safety Information or other safety related action has been brought into effect.

4. Patent Exposure: The Sponsor states that the exposure was calculated using I.M.S. data for Spain and the sales data facilitated for the rest of the countries. It is being marketed under the trade names Dermofix, Zalain, Gino-Dermofix, Gino-Zalain, Dermoseptic, Mykosert, Monazol, Sertacream, Sertaderm, Sertadie, Sertopic, Sertagyn, Tromderm. The total Sponsor-reported sales for sertaconazole amount to [redacted] units.

Reviewer comment: This reviewer has also found references to sertaconazole shampoo and to sertaconazole nail lacquer.

The Sponsor states that during the last 5 years in commercialization of Sertaconazole, Ferrer received a total of 47 reports of suspicious, non-serious, adverse reactions in 9539754 patients treated that indicates a proportion of 0.49 non-serious adverse reactions for each 100000 patients treated.
Reviewer comment: The actual Adverse Reaction rates may be many times the reported rates.

5. Adverse Reactions:

The Sponsor includes a table listing 47 adverse reactions reported to Ferrer from worldwide sources. The following table indicates the country of origination and the products object of the reports:

PRODUCT	NUMBER AND COUNTRY OF REPORTS
sertaconazole cream	Chile (4) Korea (10) Spain (8) Portugal (1) Germany (11)
sertaconazole vaginal cream	Germany (1) Korea (1)
sertaconazole vaginal tablet	Korea (2) Spain (1)
sertaconazole gel	Chile (4)
sertaconazole vaginal suppository	France (3)

Reviewer comment: Most reported adverse events are "spontaneous", and originate from only a few countries, which suggest possible under-reporting from all other countries.

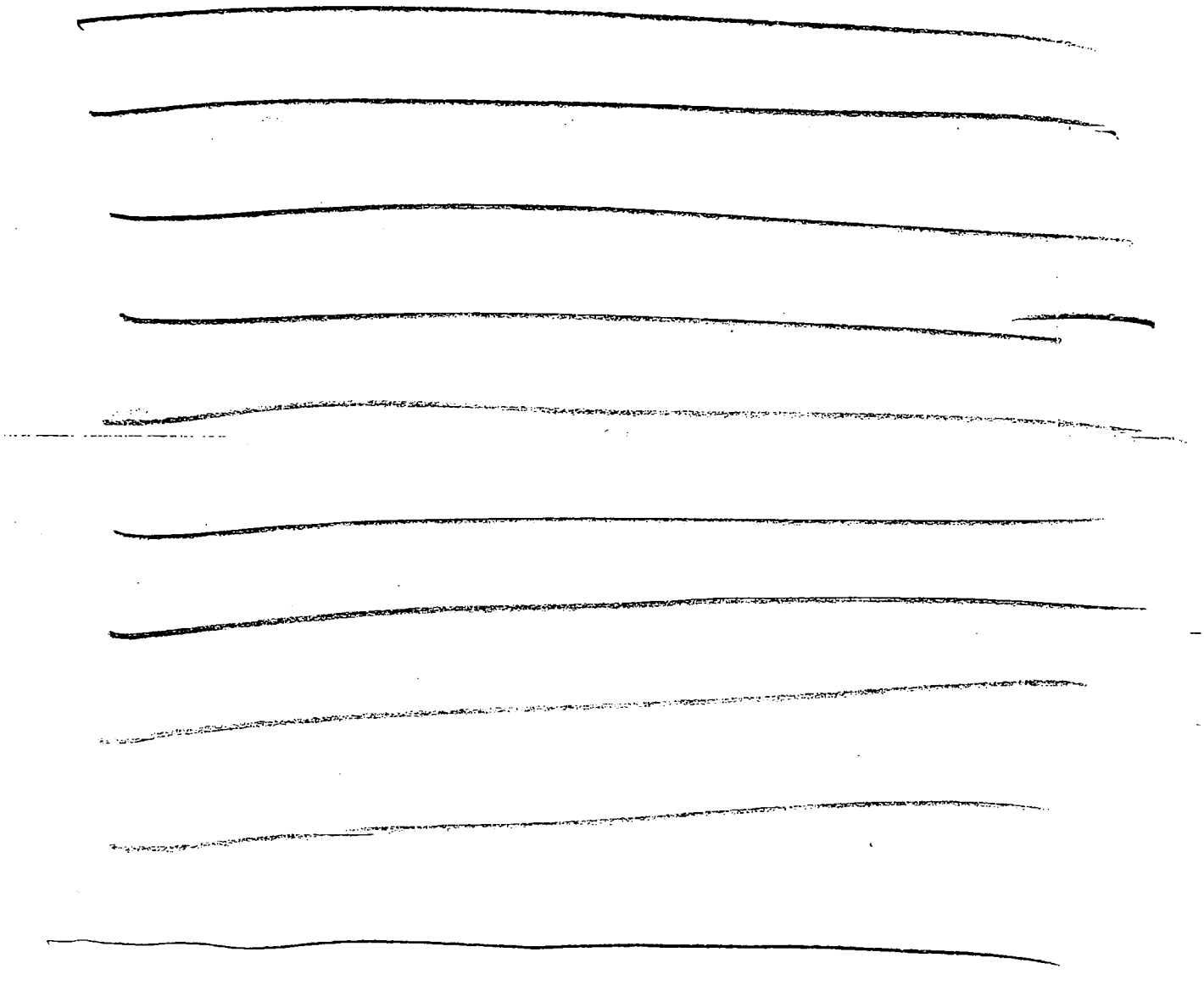
The type of adverse reports include:

e. Erythema/heat/desquamation (most common)
f. Erythema/heat/pruritus
g. Erythema/exhudation
h. Dermatitis
i. Erythema/vesicles
j. Skin higher pigmentation
k. Rhagades
l. Pruritus
m. Rash
n. Burning
o. Urticaria
p. Allergic reaction
q. Contact dermatitis
r. Flushing
s. Swelling/diarrhea/dyspnea
t. Decoloration skin
u. Nausea

Reviewer comment: All reported adverse reactions are listed as "non-serious." The outcome for most of these adverse reactions is listed as "unknown", the causality is given as "probable" in one case, for all others it is either "unknown", "possible", or "unrelated."

6. Studies: The Sponsor identifies the following studies as those conducted during the period 1/1/98-1/1/03, in which no safety concern has been identified:

Title of trial	Safety sample	Country	Trial start	Status
Assessment of efficacy and speed of action of a treatment combining sertaconazole nitrate vaginal suppository and cream in vulvovaginal candidiasis	N=98	France	2/99	completed



Reviewer comment: Most reported studies are for the indication candidiasis, which is not an approved indication in the US for sertaconazole. The safety profile for candidiasis could differ from dermatophytosis.

7. Other information:

The Sponsor states no new important information was received during the period of review involving relevant lack of efficacy that might represent a significant hazard to the treatment population.

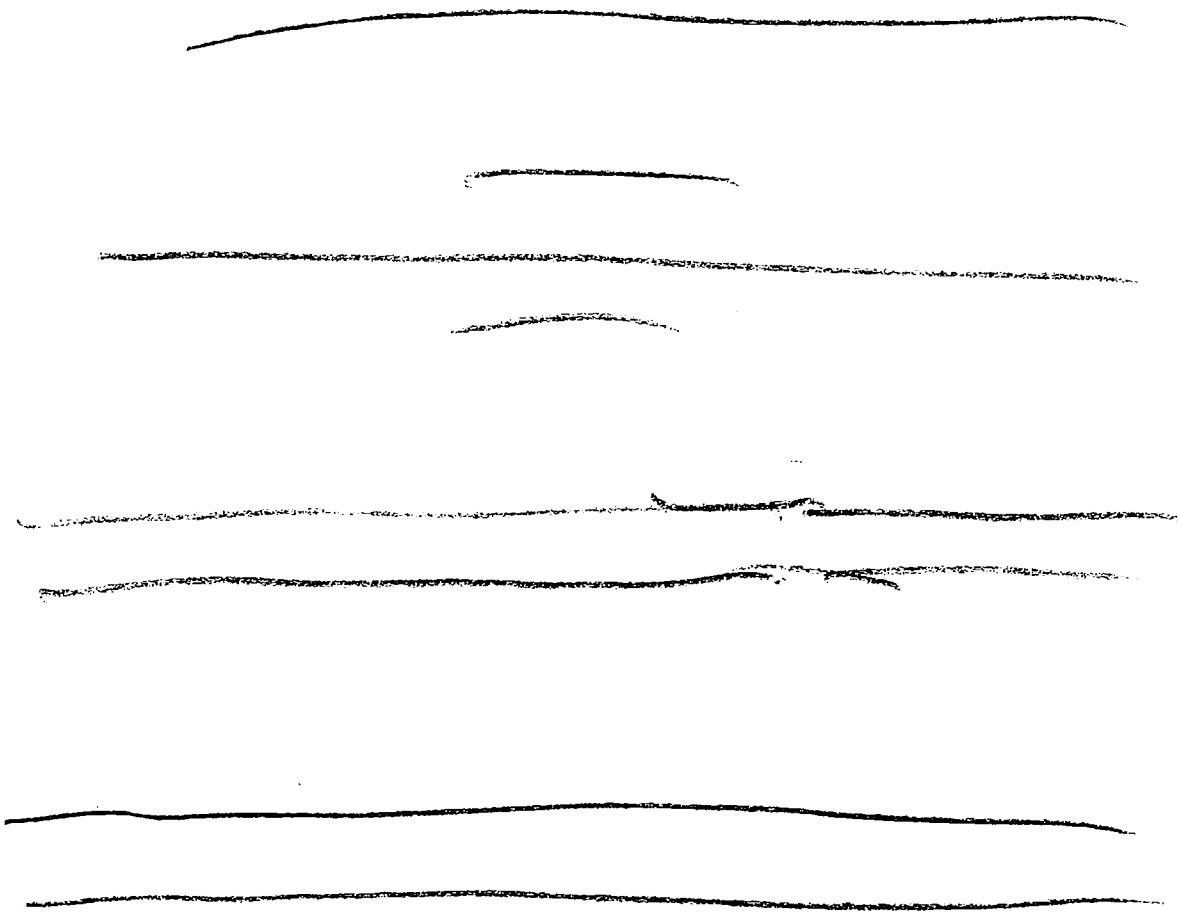
8. Overall safety evaluation: The Sponsor states no additional safety signal was identified. Ferrer summarizes that "the frequency of appearance and severity of the reported adverse drug reaction, as well as their comparison with the drugs of the same family, show that the safety profile of Sertaconazole is excellent and similar to that of the treatments of its therapeutic group, and no change is foreseeable in the safety profile of the molecule."

9. Publications: Ferrer includes references to 21 publications. Four of them are dated as of 2000 and make reference to the gynecological use of sertaconazole. The others are much older and were already reviewed originally for the NDA.

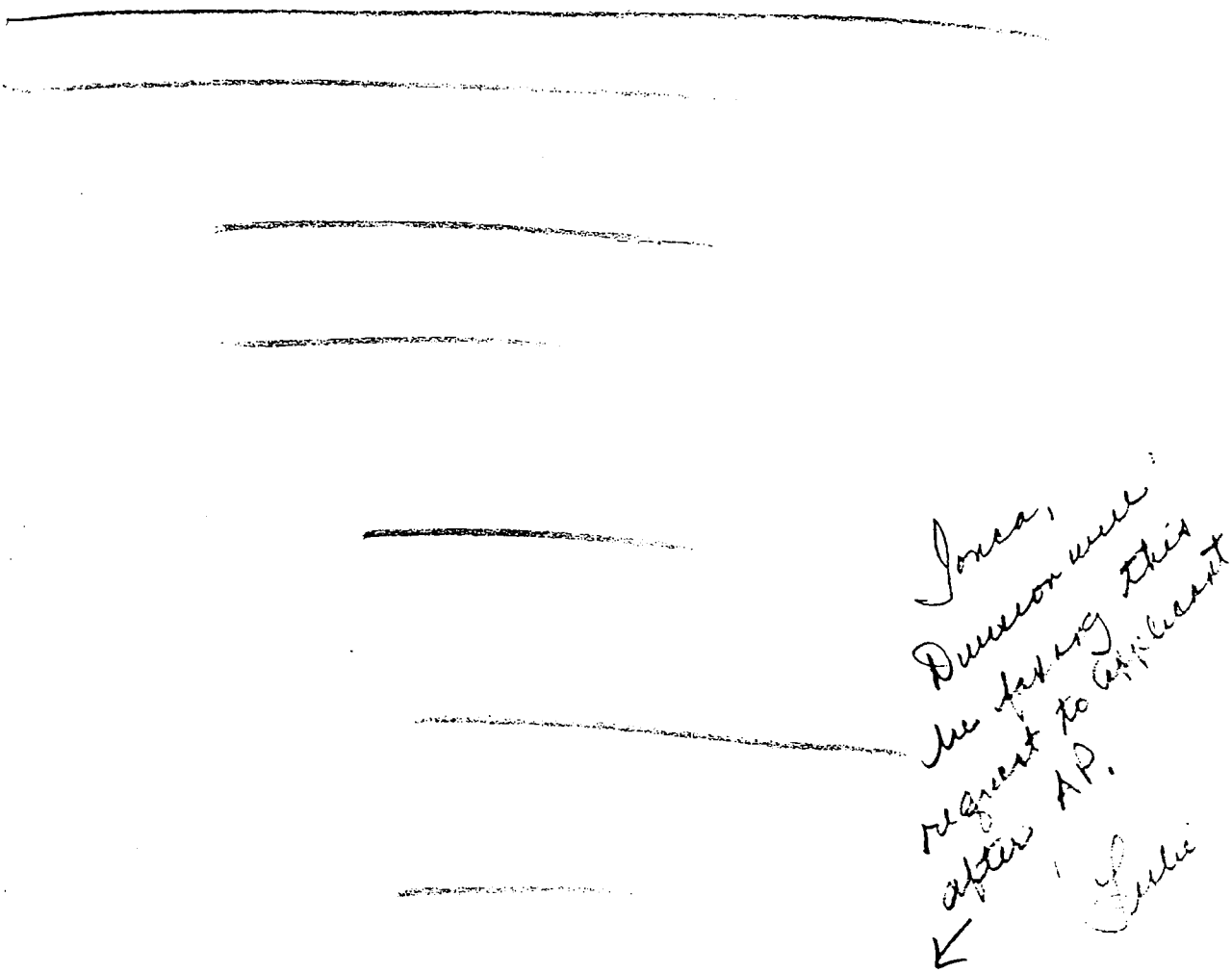
Reviewer comment: The reported safety update does not point to any particular safety concerns. Overall, the proposed drug product seems to have an overall safety profile similar to that of other topical antifungals marketed in the US.

IV. REVIEW OF SUBMITTED DRAFT LABELING

Reviewer comment: The Sponsor proposed labeling, which this reviewer finds acceptable, is shown next.



6 Draft Labeling Page(s) Withheld



V. **CONCLUSIONS:** The Sponsor should identify sertaconazole products being marketed as shampoo and as nail lacquer.

From the clinical perspective, it seems reasonable to approve sertaconazole 2% cream, with the acceptance by the Sponsor of the proposed labeling, and acceptance of the commitment to conduct the Phase 4 studies as recommended by other disciplines.

Non-Clinical Toxicology: Conduct a dermal carcinogenicity study. The need for a dermal carcinogenicity study is guided by the chronic nature or rate of recurrence of the indication and not by systemic absorption of the drug substance or the absence of genotoxicity. (ICH S1A, "For pharmaceuticals used frequently in an intermittent manner in the treatment of chronic or recurrent conditions, carcinogenicity studies are generally needed.").

Recommended comments to be conveyed to sponsor: (List here will be CUT/PASTED by PM into fax to sponsor.

For the updated safety report, please provide information about sertaconazole formulations not included in the latest report: sertaconazole shampoo and sertaconazole lacquer.

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

cc: Orig NDA 21-385-000(AZ)
HFD-540 file
HFD-540/DIVDIR/Wilkin
HFD-540/DepDir/Kukich
HFD-540/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: 12/8/03

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

/s/

Joseph Porres
12/9/03 03:23:31 PM
MEDICAL OFFICER

Markham Luke
12/9/03 03:32:23 PM
MEDICAL OFFICER
PM: Comment to be conveyed to Sponsor on p
16 of MOR. Concur with Approval. TL interdisciplinary
summary to follow.

Jonathan Wilkin
12/9/03 04:06:41 PM
MEDICAL OFFICER

Team Leader's Addendum to Medical Officer's Review of NDA 21-385
Sertaconazole Nitrate Cream, 2%

Mylan Pharmaceuticals, Inc.
781 Chestnut Ridge Rd.
P.O. Box 4310
Morgantown, WV 26504-4310

Date of submission: 9/28/01
CDER Stamp Date: 10/1/01
Date of MO review: 5/22/02
Date of TL Addendum: 5/24/02

General Comments

In general, the Team Leader agrees with the analysis and conclusions in the well-crafted Medical Officer's Review.

The two pivotal trials demonstrate that sertaconazole nitrate cream, 2%, can be used to treat interdigital tinea pedis with a statistically significant population receiving benefit from this treatment. The rates of clinical cure in interdigital tinea pedis demonstrated for this product are low (ranging from 13% to 27% in the point estimates). These rates achieved significance in the setting of even lower rates seen in the vehicle arms of the studies (ranging from 3.3% to 4.9%). It is clear that other topical antifungals exist in the market that have similar or better rates of cure. There is no regulatory requirement that a new topical antifungal be an improvement to what is currently marketed. Since dose-ranging has not been performed, it is not clear where on the dose response curve we are with this topical product. However, this also, is not a regulatory reason for lack of sufficient efficacy with this drug product. Thus, there is agreement by the clinical team that this product is approvable from an efficacy point of view.

Regarding safety, the product has demonstrated minimal safety concerns in the U.S. study population and in studies abroad. Spontaneous adverse event reporting in Spain included one patient who reported hepatitis after applying sertaconazole nitrate cream for tinea versicolor, but the relationship to topical application of sertaconazole nitrate cream to the adverse event is not clear.

There is agreement among the clinical team that overall, the risk/benefit suggests that the studies submitted support approvability of this product with respect to both safety and efficacy when used for the treatment of interdigital tinea pedis. As of the date of this review, the Trademark name for the new product is still pending.

Regarding Indications and Usage

There has been some discussion regarding the organisms that should be included after interdigital tinea pedis under Indications and Usage in product labeling. While it is true that only Trichophyton rubrum demonstrates statistical signficance in each study, the Sponsor is correct in its assertion that previous antifungals may have been held to a different standard (see their submission to this regard), that allowed inclusion of other organisms based on similar data. The analysis of the clinical data for the organisms T.

mentagrophytes and E. floccosum show that the efficacy is approximately similar in the proportion of clinical cures. The efficacy for T. mentagrophytes is seen in the Table on Complete Cure with the two studies combined (Table 37 on page 44 of MOR) where the point estimate for Complete Cure with T. mentagrophytes is 25% vs. only 20% for T. rubrum. In vitro microbiological data is available (see Microbiology Review and Table 1, page 13 of MOR) for T. mentagrophytes (multiple isolates, but not for E. floccosum). Deferring to the microbiologists, who have recommended a [redacted] E. floccosum should not be placed in the Indications and Usage section until such information to substantiate the clinical supposition is available. In the meantime, it is recommended that treatment of interdigital tinea pedis caused by T. rubrum and T. mentagrophytes be included in the Indications and Usage section.

Acting Dermatology Team Leader,
Markham C. Luke, M.D., Ph.D.

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

/s/

Markham Luke
5/29/02 04:54:36 PM
MEDICAL OFFICER
TL addendum to MOR.

Jonathan Wilkin
5/30/02 02:02:28 PM
MEDICAL OFFICER
I concur with TL recommendation re T. mentagrophytes, if, and only if, the sponsor commits to all of the recommended

Medical Officer's Review of NDA 21-385

Original Submission

General Information

NDA submission number: 21-385

Applicant identification:

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Rd
PO Box 4310
Morgantown, WV 26504-4310
(304) 285-6407

Submission /review dates

Date of submission:	9/28/01
CDER stamp date:	10/1/01
Date submission received by reviewer:	10/9/01
Date review begun:	10/11/01
Date review completed:	5/22/02
Date review returned and completed	5/29/02

Drug identification

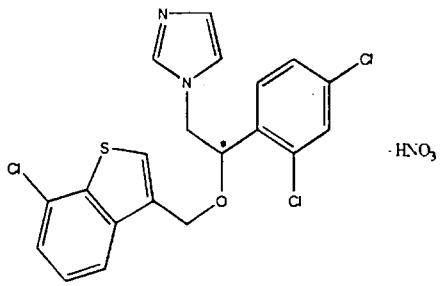
Generic name: sertaconazole nitrate

Proposed trade name: not given

Chemical name:

(±)-1-[2,4-DICHLORO-β-[(7-CHLOROBENZO[B]THIEN-3-YL)METHOXY]-2-(2,4-DICHOROPHENYL)ETHYL]-1H-IMIDAZOLE NITRATE

Chemical structure:



Pharmcologic category	Topical antifungal.
Dosage form:	Twice daily for 4 weeks for the indication interdigital tinea pedis.
Route of adminsitration:	Topical cream.

Table of Contents

List of Tables and Figures

The Executive Summary of the Primary Clinical Review

1. RECOMMENDATIONS

1.1 Recommendations on Approvability

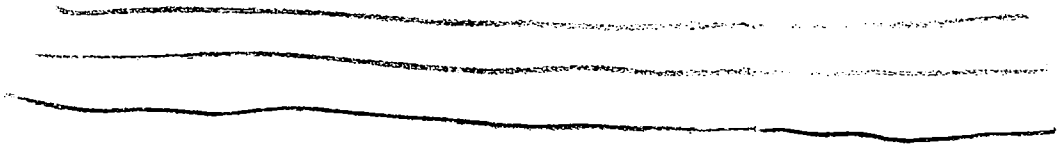
From a clinical perspective, the application is approvable for the indication of treatment for tinea pedis interdigitalis, depending upon the Sponsor's acceptance of revised labeling and commitment for phase 4 studies. Since no evidence has been provided that the addition of [redacted] to the to-be-marketed drug product does not effect its safety and efficacy, Sponsor will be requested to market the drug product without [redacted] or to commit to a postmarketing study of safety and efficacy comparing both formulations.

The risks of treatment with sertaconazole nitrate 2% cream appeared to be low in the patients treated in the pivotal trials. The benefit seen in the pivotal trials has been moderate; vehicle showed very little effect and sertaconazole was statistically superior to vehicle.

1.2 Recommendations on Postmarketing Studies

The following postmarketing studies are being requested of the applicant by other disciplines (please refer to relevant reviews):

[redacted]



5. A dermal carcinogenicity study. This requirement derives from the proposed indication, in which chronic repeated use is anticipated. (ICH S1A, "For pharmaceuticals used frequently in an intermittent manner in the treatment of chronic or recurrent conditions, carcinogenicity studies are generally needed.").

2 SUMMARY OF CLINICAL FINDINGS

2.1 Brief Overview of Clinical Program

Product name:	Sertaconazole nitrate cream 2%
Product class:	Imidazole type antifungal
Route:	Topical, twice a day for 4 weeks
Indication:	Interdigital tinea pedis

The trials conducted in the US include two Phase 3 studies for safety and efficacy, SERT-960602 and SERT-960603 (588 patients randomized, 349 completed); a pharmacokinetic phase 1 study, SERT-9758 (10 patients); a Phase 1 contact sensitization study, SERT-9625 (221 patients); a Phase 1 primary irritancy and repeat irritancy study, SERT-9626 (30 patients); a Phase 1 phototoxicity study, SERT-9627 (25 patients); and a Phase 1 photoallergy study, SERT-9628 (30 patients).

Foreign trials include a Phase 2 dose ranging study, CL-3 (20 patients); three Phase 3 safety and efficacy trials that studied multiple dermatomycosis, CL-4 (631 patients), CL-6 (267 patients), and CL-7 (75 patients).

Sponsor includes in the NDA other studies conducted with sertaconazole in other delivery systems and for indications other than tinea pedis interdigitalis, which will not be reviewed here (see Table 3).

Sponsor indicates the total of all patients studied exceeds 3500, and more than 2000 patients have received some form of sertaconazole (page 8-28-7) in US and foreign trials (see Table 3). The primary evidence of the safety of sertaconazole is based upon the 588 patients from the two pivotal US trials, of which 297 were treated with sertaconazole nitrate 2% cream for an average of about 21 days.

2.2 Efficacy

The primary efficacy endpoint for the pivotal trials was **Complete Cure**, defined as Clinical Cure on the Physician's Global Evaluation in combination with Mycological Cure, and the secondary efficacy endpoint was **Effective Treatment**, defined as Effective Clinical Treatment on the Physician's Global Evaluation in combination with Mycological Cure.

In trial SER-960602, the group treated with sertaconazole nitrate 2% cream, twice a day for 4-weeks, demonstrated at the evaluation point of week-6, in the Modified Intent-To-Treat population (MITT), a statistically significant rate of Complete Cure (13.1% vs.3.3% for vehicle, a difference of 10 patients or 9.8%). In trial SER-960603, the group treated with sertaconazole nitrate 2% cream twice daily for 4-weeks demonstrated at the evaluation point of week-6, in the MITT population, a statistically significant rate of Complete Cure (27.2% vs. 4.9% for vehicle, a difference of 23 patients or 22.3%). In these pivotal trials vehicle showed little effect and sertaconazole was statistically superior to vehicle.

There are no US or foreign studies directly comparing sertaconazole to other topical antifungals for the indication interdigital tinea pedis.

2.3 Safety

Sponsor states more than 2000 patients have received some form of sertaconazole (page 8-28-7) in US and foreign trials. Sponsor states the foreign trials were not designed to capture adverse events and will use the US trials as the primary evidence of the safety of sertaconazole, 588 patients, of which 297 received the active treatment for an average of about 21 days. The data from foreign trials will be considered as supportive of the US data. The incidence of adverse events reported for sertaconazole was not significantly different from that reported for the vehicle arm. No pattern of differences was reported on the basis of important demographic features. No significant laboratory abnormalities have been reported that would indicate a potential organ of specific toxicity. Please see the Section 7, Review of Safety, for details.

2.4 Dosing, Regimen, and Administration

The Sponsor is seeking approval for a 4-weeks treatment of interdigital tinea pedis with sertaconazole nitrate 2% cream, applied twice a day. One small study was conducted comparing 1% vs. 2% creams which was largely inconclusive but Sponsor chose to study the 2% drug product based on the safety and possible greater efficacy of the higher concentration preparation.

2.5 Drug-Drug Interactions

No drug-drug interactions have been reported during the trials with sertaconazole nitrate 2% cream.

2.6 Special Populations

Adequate numbers of patients of both genders have been included in the pivotal trials. The participants ranged from 11 to 76 years old, with one patient age 11, fifteen in the 12-15 age group, twelve in the 15-16 age group, and seven age 17. Most study participants have been Caucasian. No significant differences in safety have been reported by the Sponsor related to age, gender, or race. Efficacy has been demonstrated in males, Caucasians, and patients younger than 64. The trials were not powered to detect statistical difference over vehicle for other subgroups.

Sponsor has requested a full waiver from the requirement to conduct studies to satisfy the pediatric rule, based on this drug treatment not representing a significant therapeutic alternative for this age group. This reviewer considers it is reasonable to extrapolate the safety and

efficacy data to the 12-16 year old population for the indication tinea pedis interdigitalis, and to waive the requirement for pediatric studies below the age of 12 years.

Sponsor has not conducted studies in pregnant or nursing women and has not indicated plans for such trials.

Clinical Review

1. INTRODUCTION AND BACKGROUND

1.1 Established and Proposed Trade Name of Drug, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Sertaconazole nitrate is a new molecular entity (see Chemistry Review) and a member of the imidazole antifungal family. It has not been approved in the US but is currently marketed in several countries. The Sponsor proposes to use sertaconazole nitrate 2% cream for the treatment of tinea pedis interdigitalis, twice daily for four weeks, in subjects age —and older who are neither pregnant nor nursing, nor allergic to one of the ingredients in the drug product nor to other imidazole type antifungals. It has demonstrated activity against Tricophyton rubrum.

The Applicant has not proposed a trade name as of this writing.

1.2 State of Armamentarium for the Indication Tinea Pedis interdigitalis.

Tinea pedis may involve the interdigital (between the toes) area predominantly, tinea pedis interdigitalis, or the plantar surface, tinea pedis plantaris. Commonly, both are present in some combination. They differ in their response to treatment, with the plantar type often being more difficult to cure. The layman's term **athlete's foot** tends to be used to cover both. The treatment of tinea pedis interdigitalis usually focuses on topical therapy. Topical antifungals are available as cream, gel, solution, lotion, spray and powder. Cream formulations of topical antifungal agents currently marketed in the US include: clotrimazole 1%, econazole 1%, ketoconazole 2%, miconazole 2%, oxiconazole 1%, sulconazole 1%, naftifine 1%, terbinafine 1%, butenafine 1%, and ciclopirox olamine 1%.

1.3 Important Milestones in Product Development

1.3.1. Communications between Sponsor and Agency:

This section summarizes the salient commitments made in communications between the Agency and the applicant:

1.3.1.1 RECORD OF TELECON. Minutes of the End-of-Phase 2 Meeting, Meeting #1073, Date: June 23, 1997

BIOPHARMACEUTICS:
Agency: Scarified skin may not mimic the diseased skin in that the former usually affects only the top layer of the skin.

CLINICAL:
The Agency requested a rationale for choosing the 2% formulation for Phase 3 trials
Sponsor: The Sponsor presented graphs demonstrating time to clinical cure. Discussion of these graphs ensued, with comments from the Agency concerning the apparent end of treatment results at which time the 1% cream appeared to have increased efficacy over the 2% cream. The Sponsor will present additional dose ranging information to the Agency that addresses concentration, duration, and frequency.
Reviewer comment: The data originally presented is discussed on page 60. No additional information has been presented to the Agency in support of the 2% formulation.

BIOSTATISTICS:
Agency recommended a Modified Intent-to-Treat analysis to include all patients with a positive baseline KOH and culture that were dispensed study treatment. The Agency stated that the clinical trial outcomes of interest should fall into 3 groups: completely cured, effectively treated, and mycological cure at the **Proof of Cure (POC) time point**. Patients judged completely cured (1^0 efficacy endpoint) will be called **treatment successes** for statistical purposes. Completely Cured should be patients in whom all signs and symptoms have completely resolved. The KOH and culture should be negative, and physician's global assessment should be "cleared" - i.e., skin normal, and no evidence of dermatophyte infection. Clinical signs and symptoms should be absent (i.e., 0 in scale, erythema, and pruritus). Effectively Treated (2^0 efficacy endpoint) should be patients in whom the drug is determined to be therapeutically effective, although all clinical signs and symptoms have not completely resolved. This category is intended to include patients who have minimal residual clinical signs, but are essentially normal. The KOH and culture should be negative; global assessment should indicate at least 90% of interdigital area is clear; there should be no greater than minimal erythema, minimal scale; there should be no vesicles, papules, or pruritus. Mycological Cure (2^0 efficacy endpoint) should be patients with both negative KOH and negative culture at the point of cure.

It was agreed tc [redacted] inclusion age [redacted] to 12 years, provided that there are no preclinical concerns.

The Agency advised a rationale should be presented for the inclusion/exclusion criteria, such as pregnancy, because labeling may be based upon information obtained in the pivotal trials, and items in the inclusion/exclusion criteria could impact the label. The Sponsor's protocol excludes women of child bearing potential. If all the pharmacology/toxicology data has been collected, the rationale for this exclusion should be presented to the Agency.
Reviewer comment: A rationale for the exclusion of pregnant and nursing women has not been presented.

The Agency did not recommend measurement of a target lesion but preferred that all web spaces be evaluated. The Sponsor should score the worst web space at baseline, and each subsequent evaluation should be of the worst web space, even if this is not the original lesion.

The Sponsor agreed with all of the above-mentioned points.

1.3.1.2 PRE-NDA MEETING, Meeting ID# 6259, Date: October 18, 2000

BIOPHARMACEUTICS:
For PK studies, the analytical method should be sensitive for the purpose, i.e., the method should be able to detect at the NOEL level in animals studies. The sampling scheme should be such that it can capture the full PK profile. Collecting only trough samples is not acceptable.

CLINICAL MICROBIOLOGY:
Proposed labeling for Clinical Microbiology should annotate the microbiology claims and indicate exactly the portion of the reference(s) that supports each claim.

CLINICAL:
The Sponsor should present a rationale/demonstration that the addition of [redacted] does not have an effect upon the drug product performance, efficacy or safety.
Reviewer comment: Sponsor has submitted a report in the chemistry section of this NDA suggesting that batches of the clinical and to-be-marketed formulations had equivalent in vitro release rates in Franz Cell diffusion studies. Sponsor hypothesizes there should be no difference clinically in safety or effectiveness, but no study has been presented to substantiate these claims. As per the Guidance document on Non sterile Semisolid Dosage forms, the addition of — would represent a Level 3 Change, and Sponsor is required to supply documentation to support that the addition of — does not have an effect on efficacy or safety of the to be marketed drug product as compared to the drug product studied in the pivotal trials.

1.4 Important Issues with Pharmacologically Related Agents

Hypersensitivity to imidazoles has not been reported often but the potential for cross sensitivity with other imidazole type antifungals exists. A publication included in the MEDLINE search reported by the Sponsor identifies a patient who had not previously used an antifungal, and who developed an allergic contact dermatitis after having used sertaconazole nitrate 2% cream. Upon patch testing, it was shown the patient had a positive test to sertaconazole, miconazole and econazole, but not to clotrimazole, itraconazole or ketoconazole (Goday JJ et al. Allergic contact dermatitis from sertaconazole with cross-sensitivity to miconazole and econazole. Contact Dermatitis 1995:32:370-371)

2. SIGNIFICANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, AND/OR MICROBIOLOGY

The chemistry review was not available at the time this review was finalized.

2.1 Animal Pharmacology

The Sponsor has provided a spectrum of *in vitro* and *in vivo* non-clinical studies in multiple species. The systemic absorption via topical route never exceeded 18% of the administered dose. The rapidly metabolized parent drug was excreted through bile. In comparison, only 0.5% of the administered dose was absorbed through human skin. In a number of animal studies conducted at fairly large proportionate drug dose levels using different routes in several species, no significant incidence of severe adverse events was reported. In addition, such events

disappeared during the recovery period. In primary assays, the cream formulation produced slight irritation.

In rat croton oil model, sertaconazole nitrate exhibited reduction in edema.

Reviewer comment: a putative anti inflammatory effect could theoretically contribute to a beneficial effect of this drug product if it is additive to the antifungal effect.

Mutagenicity tests failed to detect cellular cytotoxicity or induction of sister chromatid exchange.

Sertaconazole nitrate did not produce any maternal toxicity, embryotoxicity, or teratogenicity in rats and rabbits. It also did not affect indices for fertility, implantation, and embryonic development. 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).

2.2 Microbiology

The Sponsor has provided in vitro susceptibility data for sertaconazole against a variety of fungi, including the three pathogens related to this application: T. rubrum, T. mentagrophytes, and E. floccosum. Only one isolate of E. floccosum was studied.

Table 1. Antimicrobial Testing of Dermatophytes to Sertaconazole

Pathogen	Number tested	MIC (μg/mL) 24-48 hr	MIC (μg/mL) 7-10 day	MLC ('mg/mL)24-48 hr
E. floccosum	1		4	
T. mentagrophytes	5		2	
	1		0.5	
	2	0.125/0.125		
	30		2.6	16/64
	7		2	
	12		4	
	3		8	
	2	0.09/50		>50/>50
T. rubrum	7	0.125/0.125		0.125-0.5/1-64
	8	0.125/0.125		0.25-16/2->64
	3	0.25/0.25		0.25-32/0.25->64
	3	0.5/0.5		0.5-16/0/5->64
	10			
	2		0.4	
	1		2	
			4	

These studies show that minimum inhibitory concentrations (MIC) tend to be lower at 24 hours than at 48 hours or at 7-10 days. The new NCCLS standardized method calls for a reading at 46-50 hours. The minimum lethal concentration (MLC) which could be a better indicator of the efficacy of sertaconazole is a log higher than the MIC.

The MIC's for the three dermatophytes range from 0.125-0.5 μg/mL when assessed at 24 hours, and from 0.5-8 when assessed at 7-10 days. The MLC's for the three dermatophytes range from 0.5->64 mg/mL.

Although Sponsor is supplying in vitro susceptibility data against many other microorganisms, this information will not be reviewed here because it is not germane to this application.

Reviewer comment: Testing for MIC's was conducted using a variety of different methods, and prior to the development of a standardized technique. Therefore, comparing results is not possible. Comparison of MIC's and MLC's with the reported skin levels of ——— ng/mL suggest that the amount of sertaconazole one can expect on the skin following treatment as per the indication, might not always suffice for microbicidal action. However no studies are available to correlate tissue levels, MIC's, MLC's and actual therapeutic results. MLC's for T. mentagrophytes were generally higher than for T. rubrum, which might account for the lower clinical effect demonstrated for T. mentagrophytes in the pivotal trials. It would be appropriate to request a postmarketing study of a larger number of recent isolates of each of the species of dermatophyte often recovered from interdigital tinea pedis.

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

Sponsor supplies reports of 10 pharmacokinetic studies. SERT-9758, conducted in patients with tinea pedis and patients with ——— is the only one with relevant information on the systemic absorption of sertaconazole nitrate 2% cream. Following application as per the indication, systemic absorption of sertaconazole nitrate from 2% cream through the diseased and surrounding skin was below the detectable level of ——— In healthy volunteers 6-7% of the applied dose was found to stay in the stratum corneum, with saturation between 3 and 48

hours, producing a concentration in the epidermis of [redacted]ng/ml, as measured by tape stripping. Approximately 31% of sertaconazole dose penetrated into deep layers of the skin. In study THE/SER/91003 with radioactively marked sertaconazole, no radioactivity was found in blood or plasma and only traces in urine and feces. Sertaconazole levels in the skin seem to be higher than the reported MIC but lower than some MLC's of dermatophytes isolated from tinea pedis.

Reviewer comment: These results suggest a limited exposure to absorbed drug. However, the analytical procedure seemed to be unable to detect amounts below [redacted] rather than [redacted] The absorption in healthy skin cannot be extrapolated to diseased skin. Tape stripping is not a validated method to measure tissue levels and results obtained with such method are difficult to interpret and offer little regulatory utility.

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1 Sources of Clinical Data

Sponsor has conducted two vehicle-controlled, randomized trials specifically for the indication tinea pedis interdigitalis, as shown in the following table:

Table 2. Pivotal Trials for sertaconazole nitrate 2% cream.

		Number of patients		
US Protocols	Phase	Total	Vehicle	Sertaconazole
SER-960602 (pivotal)	3	299	148	151
SER-960603 (pivotal)	3	289	143	146
TOTAL PATIENTS		588	281	297

The review of efficacy is based on these two studies.

The Applicant submitted electronic data sets for the Phase 3 efficacy and safety studies. In the initial submission for the NDA, the Sponsor included the efficacy results for KOH, culture, physician's global evaluation, and signs and symptoms scores in separate data sets. These efficacy results are used to define primary and secondary endpoints of complete cure, effective treatment and mycological cure, but no overall classification of participants as complete cure, effective treatment or mycological cure was supplied in the data sets. These were supplied later upon request by the Agency.

4.2 Overview of Clinical Trials

The Sponsor includes other US and foreign studies that are reviewed here for safety. The following table indicates these studies, the study Phase, whether Case Report Forms are available, and the number of patients.

Table 3. Overall Exposure to Sertaconazole During US and Foreign Studies

			Number of patients		
Foreign Protocols	CRF available	Phase	Total	Vehicle	Sertaconazole
THE/SER 91003	Yes	1	5[1]	-	5
THE/SER 91002	Yes	1	4	-	4
PAZ 3018/295	Yes	1	12	-	12
CL-PH-1	No	1	8	-	8
CL-PH-2	No	1	12	-	12
93-TX-15338-2-RD	Yes	1	12	-	(12)
93-TX-15338-3-RD	Yes	1	7[1]	-	(7)
94-TX-15338/21338-1-RD	Yes**	1	4	-	(4)
93-TX-19338-1-RD	Yes	1	13	-	(13)
CL-1	Yes	2	21	-	10/(11)
CL-2	Yes	2	21	-	10/(10)
CL-3	Yes	2	20	-	10/(10)
CL-5/93	Yes	2	59	-	(59)
92-TX-338-1-RD	Yes	3	26[1]	-	26
CL-4	Yes**	3	631	314	317
CL-SOL-1*	Yes	3	60	31	29
91-TX-1338-6-C-IIIA-33	Yes	3	251	122	129
CL-6	Yes**	3	267	134	133
CL-7	Yes**	3	75	38	37
93-TX-15338-1-RD	Yes	3	369	186	(183)
SER(III)1	Yes**	3	582	294	(288)
96-TX-1338-1-RD	Yes	3	191	96	95
Total foreign CRFs					541
US Protocols					
SERT-9758 (pK)		1	10	-	10
SERT-9625 (dermal safety)		1	221	-	221
SERT-9626 (dermal safety)		1	30	-	30
SERT-9627 (dermal safety)		1	25	-	25
SERT-9628 (dermal safety)		1	30	-	30
SER-960602 (pivotal)		3	299	148	151
SER-960603 (pivotal)		3	289	143	146
Total US			904		613
TOTAL PATIENTS			3553		2047[2] 1450[3] (597)[4]

[1] Sponsor indicates the study reports indicated a number of patients but number of individual patient reports available differed slightly.
[2] These are patients who were treated with any form of sertaconazole drug product
[3] These are patients who were treated with sertaconazole nitrate 2% cream
[4] Numbers within brackets indicate the patients who were treated with sertaconazole nitrate cream other than 2%.
* This was the only vehicle controlled study in the list, but CRF were not available (page 8-28-29) and it was not for a cream based product but for a solution.
**Randomization code not available.

4.3 Postmarketing Experience

Sertaconazole is not yet approved in the US. Sponsor states that Sertaconazole nitrate is currently marketed in 48 countries as sertaconazole cream, gel, powder, solution, vaginal cream, and vaginal suppositories under the brand names Dermofix, Zalain, Sertaconazole, and others. The indications for which it is being marketed include: superficial mycosis, tinea pedis,

tinea cruris, tinea corporis, tinea barbae, tinea manuum, candidiasis, and pityriasis versicolor, and it is to be used variously from once to twice a day for unspecified periods of time. The English translations of foreign labeling provided by the Sponsor make no reference as to whether these products are available with or without prescription.

The safety data available from post-marketing experience in foreign countries is limited and will be discussed in the review of safety.

4.4 Literature Review

A MEDLINE search reported by the applicant contains a list of publications. One contains an adverse event and will be detailed in the Review of Safety section. The other publications comprise a series of small studies for indications other than interdigital tinea pedis, are not germane to this application, and will not be reviewed here.

5. Clinical Review Methods

Sponsor has conducted two pivotal trials in the US in support of this application: SER-960602 and SER-960603. Both trials were of identical design and protocol, and were conducted at the same time, but included different sites, investigators, and patients.

Sponsor states none of the foreign trials were designed specifically to assess sertaconazole for the treatment of interdigital tinea pedis under protocol criteria complying with those currently required by the US FDA (page 8-28-29). Therefore, they will not be reviewed here.
For review of safety, studies conducted in the US for reasons other than efficacy will also be reviewed. The Sponsor states the foreign studies will only be used as supportive of the US studies because in these foreign studies laboratory testing was not standardized and was limited, and because of the expected under reporting of adverse events in foreign studies.

5.1 Materials Consulted for Review

The Applicant originally submitted IND 50,726 on 6/3/1996, for the indications tinea pedis, [redacted]. This application has been active since then.

This review is based on the following volumes: 1 (overall summary), 26-62 (clinical section). The following amendments for NDA 21-21-385 were reviewed:

Amendment	Date of Submission
000 BI	11/15/2001
000 BZ	11/23/2001
000 BZ	1/07/2002
000 BZ	1/22/2002
000 BM	2/06/2002
000 BM	3/04/2002
000 BM	3/08/2002
000 BI	3/08/2002
000 BM	4/08/2002
000 BZ	4/22/2002
000 WC	4/25/2002

5.2 Overview of Methods Used to Evaluate Data Quality and Integrity

An investigation by the Division of Scientific Investigations (DSI) was conducted of site #003 of study SER-960602, which revealed no improprieties.

5.3 Were Trials Conducted in Accordance with Accepted Ethical Standards

Sponsor claims the US studies were conducted in conformance with the regulations on Protection of Human Subjects as outlined in US CFR 21, Part 50; Investigational Review Boards as outlined in US CFR 21, Part 56; and the Declaration of Helsinki as amended in Venice (1983).
Reviewer comment: The Sponsor states these studies were conducted in accordance with accepted ethical standards.

5.4 Evaluation of Financial Disclosure

Sponsor states all of the investigational sites provided MYLAN Pharmaceuticals, Inc. with written evidence that the following statements were correct:

- No financial agreement with MYLAN Pharmaceuticals, Inc. or with the [redacted] was entered into with any of the investigators, whereby the value of compensation for the clinical study was influenced by the outcome of the study.
- With the exclusion of study conduct costs, neither MYLAN Pharmaceuticals, Inc. nor [redacted] made significant payments of more than $25,000 during the course of the study. Such payments could have included a grant to fund ongoing research, compensation in the form of equipment, or a retainer for ongoing consultation or honoraria.
- None of the investigators had a proprietary interest in the product being tested or an equity interest greater than $50,000 in MYLAN Pharmaceutical, Inc.

Form 3454 has been included in the NDA for both studies SER-960602 and SER-960603 jointly.
Reviewer comment: It would appear the financial disclosure requirements have been met for this application.

6. INTEGRATED REVIEW OF EFFICACY

6.1 Brief Statement of Conclusions

The Applicant is proposing labeling including three dermatophyte species: T. rubrum, T. mentagrophytes and E. floccosum, but the data presented only shows statistically significant efficacy for T. rubrum. Therefore, this reviewer recommends that labeling reflects there is insufficient data to demonstrate efficacy for E. floccosum and for T. mentagrophytes, particularly since there is no in vitro data supporting susceptibility of these two species to sertaconazole.

6.2 General Approach to Review of the Efficacy of the Drug

Only the two US Phase 3 trials will be reviewed here for efficacy since none of the other trials included in the application directly address the indication claimed.

6.3 Detailed Review of Trials for the Indication Tinea Pedis Interdigitalis.

6.3.1 Protocol #SER-960602. 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. It was conducted from September 25, 1997 to May 13, 1998.

6.3.1.1 Objective/Rationale

Primary Objectives: To compare the efficacy and safety of sertaconazole 2% cream versus a vehicle cream, applied twice daily for 4 weeks, in the treatment of patients with potassium hydroxide (KOH)-positive and culture-positive symptomatic interdigital tinea pedis.

Secondary Objectives: To compare the time to successful clinical and mycological treatment outcomes for sertaconazole 2% cream versus vehicle cream, applied twice daily for 4 weeks, in the treatment of patients with KOH-positive and culture-positive symptomatic interdigital tinea pedis.

6.3.1.2 Overall Design

This was a 6-week, Phase 3, multicenter, randomized, double-blind, parallel group, vehicle-controlled study of sertaconazole nitrate 2% cream in patients with interdigital tinea pedis.

6.3.1.3 Population and Procedures

Eligible patients had a clinical diagnosis of interdigital tinea pedis and met the inclusion/ exclusion criteria.

Inclusion Criteria:

- At least 12 years of age
- Males or non-pregnant, non-nursing females
- Negative urine pregnancy test (EPT® pregnancy tests, distributed by Warner Lambert Consumer Healthcare) at Day 0 (Visit 1) [a second test was done at Day 42 (Visit 6) or at the discontinuation visit] for females of childbearing potential
- Presence of interdigital tinea pedis on one or both feet characterized by **clinical evidence** of a tinea infection between the toes (at least moderate erythema and moderate scaling plus at least mild pruritus).
- A confirmatory microscopic demonstration of fungal elements and growth of fungus using baseline skin scrapings obtained from the interdigital site most severely affected.
- Chronic diseases were clinically stable for at least 1 month and acute illnesses were stabilized prior to enrollment
- Understanding of the requirements and restrictions of the study.
- Ability and willingness to sign a written informed consent by patient or legal guardian.

Exclusion criteria:

- Failure to meet inclusion criteria.

- Received no non-approved treatments, foot or shoe powders, topical anti-fungal therapy to the feet within 14 days of study entry (30 days for terbinafine, butenafine, and naftifine), oral anti-fungal therapies within 3 months of study entry (8 months for oral terbinafine), systemic antibiotic or corticosteroid treatment, topically corticosteroids within 30 days of study entry, radiation therapy and/or anti-neoplastic agents within 1 year of study entry
- A known sensitivity to any components of the test medications or hypersensitivity to imidazoles.
- Immunosuppression.
- A disease or condition that compromised the evaluation of the therapeutic response of interdigital tinea pedis to treatment
- A life-threatening condition (for example: autoimmune deficiency syndrome, cancer, unstable angina, or myocardial infarction) within the last 6 months
- A history of drug or alcohol dependency within the last 6 months
- Foot psoriasis, corns and/or callus involving any interdigital web spaces, atopic or contact dermatitis.
- Unstable diabetes mellitus [glycosylated hemoglobin $A1_c$ ($HgA1_c$) level of $\geq$ 10% at study entry]
- Laboratory test abnormalities of serum creatinine > 2.5 mg/dL, serum albumin < 3.0 g/dL, total protein < 5 g/dL, or abnormal liver function tests [aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT), or alkaline phosphatase] > 2 times the upper normal limit)
- Received an investigational drug within 30 days prior to study enrollment
- Hemodialysis or chronic ambulatory peritoneal dialysis therapy
- Infected with tinea pedis of such severity that entry into this study would not have been appropriate (such as extremely severe, incapacitating cases)
- Widespread dermatophytoses, moccasin type interdigital tinea pedis, onychomycosis (on the evaluated foot), mucocutaneous candidiasis, or bacterial skin infection.

Sponsor states the primary basis for the exclusion of widespread dermatophytoses was the need for unblinded treatment with an antifungal agent, and that dermatophytosis complex is a clinical presentation associated with bacterial infection and maceration of the skin, which cannot be treated effectively with an antifungal alone. The concomitant therapy needed for treatment of this complex would have complicated this study. Exclusion of patients with onychomycosis referred to the treated foot/feet only because it was unlikely that the skin of the onychomycosis patient's treated foot would ever regain the appearance of normal skin. If a patient had interdigital tinea pedis (without onychomycosis) on one foot and onychomycosis (without interdigital tinea pedis) on the other foot, that patient was not excluded. Only the foot with interdigital tinea pedis was clinically tracked.

Removal of Patients From Therapy or Assessment

Patients could have been prematurely discontinued for any of the following reasons:

- A serious adverse event.
- The patient requested withdrawal.

- A need for a prohibited concomitant medication.
- The baseline fungal culture remaining negative for fungal pathogens by Day 14.
- If the study's continuation could no longer be justified for medical reasons.

Patients who were prematurely discontinued due to a serious adverse event were followed until resolution of the serious adverse event; all other patients were followed for 14 days following the last application of the study medication.

6.3.1.4 Treatments

Patients were instructed to apply study cream twice daily to all affected interdigital web spaces of the affected foot (feet) the affected area(s) including a half-inch margin of healthy skin adjacent to the affected area(s) and to withhold use of study medication on the morning of the weekly clinic visits.

Foot areas affected at baseline were clinically tracked. At Visit-5 or at study discontinuation, the remaining drug supply was collected from the patient and retained by the site (total treatment duration was to have been 4 weeks).

All study personnel as well as patients were blinded to treatment and randomization codes. Patients were randomized in balanced blocks of six. The randomization codes were held by an independent statistician until after database lock.

Medication

A vehicle cream and sertaconazole nitrate 2% cream were manufactured by [redacted] The formulation of sertaconazole nitrate 2% cream to be marketed (page 3-1-84) is as follows:

Table 4. Sertaconazole Nitrate 2% Cream Ingredients.

Ingredients	% (w/w)
Sertaconazole Nitrate	2.0
Purified Water, USP	[redacted]
Methylparaben, NF	[redacted]
Ethylene Glycol and Polyethylene Glycol Palmitostearate	[redacted]
Polyoxyethylene and Glycolyzed Saturated Glycerides ([redacted])	[redacted]
Glyceryl Isostearate	[redacted]
Sorbic Acid, NF	[redacted]
Light Mineral Oil, NF	[redacted]
[redacted]	[redacted]
Total	100.0

The formulation used in the pivotal studies is the same except for [redacted] The vehicle cream was the same except it contained no sertaconazole nitrate. The creams were supplied in appropriately labeled 30-gram tubes. The drug product used for the trial was part of production batch K4. The vehicle cream had a similar appearance and was part of production batch PLC2.

Prior and Concomitant Therapy
A description of all concomitant medications and the indication for use was recorded on the CRF. Non-study medications not specifically excluded by this protocol were permitted to continue with stable doses for all required concomitant medications maintained by the investigator.

Treatment Compliance
Treatment compliance was assessed using a diary record maintained by the patient.

6.3.1.5 Schedule of Visits

Efficacy, safety, and clinical laboratory evaluations were performed, following treatment with vehicle or sertaconazole nitrate 2% cream, at screening and/or baseline, and at the end of study (Visit-6), or at early discontinuation. Efficacy evaluations were also performed at Visits 2 through 5. The schedule of study assessments is illustrated in:

Table 5. SER-960602. Schedule of Study Assessments

Phase	Screening/ Enrollment	Interim (Treatment)			End of Treatment	2-Week follow-up
Assessments / Visit: Day	V1; 0[a]	V2; 7[b]	V3; 14[b]	V4; 21[b]	V5; 28[b]	V6; 42[b]
Consent, Inclusion/Exclusion[d], Med Hx	x					
Physical Examination/Vital Signs, Pregnancy test	x					x[c]
Review and Document Use of Concomitant Medications		x	x	x	x	x
Dispense Study Medication	x	x	x	x		
Efficacy Mycology Evaluations[e]						
KOH Wet Mount Preparation by Site	x	x	x	x	x	
KOH Wet Mount Prepared by Fungal Laboratory						x
Skin Scrapings for Central Laboratory Mycology	x	x	x	x	x	x
Clinical Evaluation of Signs/Symptoms of Disease Severity[f]	x	x	x	x	x	x
Physician's Global Evaluation, Adverse events		x	x	x	x	x
Patient Evaluation of Treatment					x	
Clinical Laboratory Tests	x					x[c]
Retrieve all Study Medication[g]					x[c]	

[a] Baseline. [b] ± 3 days. [c] Or at the time of premature study discontinuation. [d] at least moderate erythema and scaling + at least mild pruritus.
[e] Using an interdigital area of most extensive scaling or the previous site if not determinable.
[f] Using a four point scale of 0 = absent; 1 = mild; 2 = moderate; and 3 = marked, at the interdigital area most clinically affected at this visit.
[g] The used medication tube was retrieved from the patient at Visits 2, 3, 4, and 5 with a new medication tube dispensed at Visits 1, 2, 3, and 4.
Data Source: Protocol, Appendix 16.1.1.

Clinical laboratory tests consisted of Complete blood count, Liver and Clinical Chemistries, and Urinalysis. Blood and urine samples were obtained on Day 0 (Visit-1) and at the 2-Week follow-up (Visit-6) or at the last study visit/early termination.

Clinical Laboratory Tests	Fungus Testing Laboratory
[redacted]	[redacted]

6.3.1.6 Mycology methods:

Skin scrapings were obtained from the diseased toe web with the most extensive scaling at baseline on Day 0 (Visit-1), during treatment on Days 7, 14, 21, and 28 (Visits 2 through 5), and at the Week-6 visit. For any visit in which all interdigital web spaces appeared normal, the skin scrapings were obtained from the interdigital web spaces used at the preceding visit. A KOH wet mount was used to confirm the presence of fungal elements and two fungal cultures to identify the dermatophyte.

The KOH (enhanced with [redacted] preparation was prepared and read within 72 hours of sample collection. Once the stain was applied, the reading had to be performed within 30 minutes. The KOH wet mount preparations for Visits 1 through 5 were read at clinical sites. The KOH wet mount evaluation at the Week-6 was performed by the central mycology laboratory. All fungal culture evaluations were performed by the central mycology laboratory.

If the Baseline KOH was negative for fungal elements, the patient was discontinued from the study. If the Baseline KOH was positive, a portion of the skin scraping was placed onto agar slants ([redacted]) and the specimens sent to the central mycology laboratory.

Patients with negative (i.e., no growth) baseline fungal cultures by Day 14 (Visit-3) were discontinued and the study exit procedures were performed for that patient on Day 21 (Visit-4).

Sponsor states a videotape demonstrating proper techniques was shown and discussed at the investigator's meeting, and a copy of the videotape was provided to study personnel to ensure consistency of training but this videotape has not been provided with the NDA for review.

6.3.1.7 Evaluations/Endpoints

Efficacy assessments included: Mycology, clinical evaluation of signs/symptoms of disease severity; and Physician's Global Evaluation of response to treatment.

The affected interdigital web spaces, providing **clinical evidence** of interdigital tinea pedis (at least moderate erythema and scaling and at least mild pruritus), and the most clinically affected area were noted in the CRF. If both feet were infected, the investigator evaluated both feet. All web spaces were treated; however, only the web space most clinically affected by the disease process **at the time of the visit** was used for tracking of signs and symptoms, which were assessed using the following four-point scale:

Signs and Symptoms Grading Scale:

0 = absent (normal appearing skin)
1 = mild (barely abnormal)
2 = moderate (distinctly present abnormality)
3 = marked (intense involvement or marked abnormality).

Erythema, scaling, pruritus, cracking, fissures, maceration, and burning were assessed at Baseline. At all subsequent visits erythema, scaling, and pruritus of the interdigital web space most clinically affected during that visit (could vary from visit-to-visit) were assessed.

Physician's Global Evaluation of Clinical Response to Treatment

The Physician's Global Evaluation (based on the clinical status of interdigital tinea pedis and on information provided by the patient) occurred on Days 7, 14, 21, 28, and at the 2-Week follow-up (Visit 6) and used the following scale:

Table 6. Physician's Global Evaluation Scale

1	Clinical Cure: Physician's Global Evaluation referring to normal appearance of the skin in all treated interdigital web spaces. Signs and symptoms associated with interdigital tinea pedis have completely resolved.
2	Effective Clinical Treatment: Physician's 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.
3	Moderate Clinical Improvement: Most baseline signs and symptoms of interdigital tinea pedis have shown a definite decrease.
4	Mild Clinical Improvement or No Change: Some baseline signs and symptoms of interdigital tinea pedis have decreased. Significant evidence of disease remains.
5	Worsening of Clinical Status: Some baseline signs and symptoms of interdigital tinea pedis are more severe and/or new signs and symptoms are present.

Efficacy Variables

The Applicant used the proportion of subjects reaching "effective treatment" at week-6 as the primary efficacy endpoint. At the End of Phase 2 meeting, the Agency had recommended the primary endpoint be defined as patients reaching "complete cure" and this will be used in the Agency's review for efficacy.

- Complete Cure (absent clinical signs and symptoms, Global = 1) is defined here at the 6-week "Point of Cure" (i.e., the Final Treatment Visit plus 2 weeks). The physician's Global Evaluation of Complete Cure needs to be supported by a complete absence of clinical signs and symptoms.

The secondary efficacy variables used to assess the antifungal efficacy of sertaconazole nitrate 2% cream applied twice daily for 4 weeks versus vehicle cream were the proportion of patients who demonstrated

- Effective Treatment (minimal residual clinical signs and symptoms, Global = 1 or 2) at the Week-6 "Point of Cure" (i.e., the Final Treatment Visit plus 2 weeks)

- Mycological Cure (negative KOH and negative culture) at the 6-week "Point of Cure" (i.e., the Final Treatment Visit plus 2 weeks)

Reviewer comment: The efficacy variables applied here are those commonly applied for this type of application. There are no data to suggest that blinding of patients and study personnel was not adequate.

Additional Efficacy Variables
Additional efficacy variables included:

- Time point analyses of the following variables at Visits 2 to 5: proportion of patients who demonstrated Successful Treatment Outcomes, Physician's Global Evaluation, mycological cure rate, and clinical signs and symptoms by item.
- Subgroup analyses were conducted for study center, pathogen, gender, race, and age.

Sponsor states the patient's evaluation of treatment effectiveness and cosmetic acceptability was done for [redacted].
Reviewer comment: The patient's own evaluation of treatment effectiveness has not been validated and offers little regulatory utility and will not be reviewed here.

Statistical Plan
In the protocol, the sponsor defined the primary analysis population (MITT) as all subjects randomized and dispensed treatment who return for at least one post-baseline treatment, have positive baseline culture, and have no major protocol violations. Missing data was to be imputed by Last observation carried forward. The Agency had recommended at the End of Phase 2 meeting that a "Modified Intent-to-Treat analysis should include patients with a positive baseline culture regardless of whether a post-baseline evaluation took place. The sponsor was again advised of this definition of the MITT at the Pre-NDA meeting held on October 18, 2000. Subsequent to this meeting, the sponsor re-analyzed the data defining the MITT population as all subjects randomized, who had positive baseline KOH and culture, and who were dispensed treatment.

The sponsor's protocol-defined per protocol population was the same as the protocol-defined MITT (randomized, dispensed treatment, returned for a post-baseline evaluation, and had no major protocol violations) except that it only included subject visits falling within a ± 3 day window. Various methods to impute missing data were used in the per protocol analyses, including last observation carried forward (LOCF), missing values treated as failures, and observed cases only.

Details of the results from the Sponsor's various analysis will be presented in section 6.3.3 Overview of Efficacy for the Indication Interdigital Tinea Pedis (page 42). For the analysis of success rates, the sponsor proposed either chi-square tests or Fisher's exact test in the protocol. This proposal was updated in the Statistical Analysis Plan (dated February 3, 1998, finalized while the studies were ongoing) to specify that the Cochran-Mantel-Haenszel (CMH) test stratified by investigator would be used. Centers with fewer than 7 enrolled

patients would be pooled for the analysis. The CMH analysis proposal from the Statistical Analysis Plan was followed in the study report.

See biostatistics review for further details.

6.3.1.8 Results. Efficacy Endpoint Outcomes.

The reviewer will include in this section the results of the analysis conducted by the Agency. Patients who dropped from the study and were not a protocol violation were treated as follows: their last observation was carried forward (LOCF) and any missing values were treated as failures (MVTF).

Randomization was described in the protocol as in blocks of 4 but in the NDA as done in blocks of 6. This change does not appear to be a cause for concern and appears to have been done prior to conducting the trials and to have been applied adequately.

Subject Disposition

This trial included 21 study sites but only 20 sites were used to enroll patients. Study Site 02 was closed due to lack of eligible patients and Sponsor states no study medication was dispensed at this site. The following table presents the site numbers, the investigators, and the number of patients randomized, and who completed the study for each center.

Table 7. SER-960602. 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]
01	Debra Breneman, M.D.	12/12	6/8
03	Frank Dunlap, M.D.	21/21	12/14
04	Boni Elewski, M.D.	3/2	2/2
05	John Estess, M.D.	7/6	1/3
06	Michael Gold, M.D.	9/8	6/5
07	Guy F. Webster, M.D.	¾	
08	Edward Kitces, M.D.	2/0	
09	Stephen Kraus, M.D.	14/15	8/9
10	Toivo Rist, M.D.	3/3	2 /3
11	Ronald Savin, M.D.	19/20	14/17
12	Matthew Stiller	7/9	5/3
13	John L. Buker, M.D.	8/9	8/7
14	Daniel Stewart, D.O.	11/10	10/9
15	James Swinehart, M.D.	4/6	1/3
16	Michael T. Jarratt, M.D.	10/11	7/7
17	Thomas Littlejohn, M.D.	5/5	2 /4
18	Lewis Kaminester, M.D.	5/4	4/2
19	Ronald Rapini, M.D.	1/1	
20	Kim Butterwick, M.D.	0/1	0/1
21	Janet Hickman, M.D.	4/4	4/2

[1] from page 8-2-235
[2] modified by the Agency
[3] P = vehicle; S = sertaconazole