

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-408**

**MICROBIOLOGY REVIEW(S)**

**Product Quality Microbiology Review  
Review for HFD-540**

**8 JULY 2002**

**NDA: 21-408**

**Drug Product Name**

**Proprietary: Mentax-TC**

**Non-proprietary: butenafine HCl cream**

**Drug Product Classification: S**

**Review Number: 1**

**Subject of this Review**

**Submission Date: 14 December 2001**

**Receipt Date: 17 December 2001**

**Consult Date: 10 June 2002**

**Date Assigned for Review: 26 June 2002**

**Submission History (for amendments only)**

**Date(s) of Previous Submission(s): N/A**

**Date(s) of Previous Micro Review(s): N/A**

**Applicant/Sponsor**

**Name: Bertek Pharmaceuticals, Inc.**

**Address: PO Box 14149; Research Triangle Park, NC 27709**

**Representative: Sherron P. Wiechert, Director, Regulatory Affairs**

**Telephone: 919-991-9878**

**Name of Reviewer: Bryan S. Riley, Ph.D.**

**Conclusion: Recommended for Approval**

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## Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUPPLEMENT:** N/A
  - 2. SUPPLEMENT PROVIDES FOR:** N/A
  - 3. MANUFACTURING SITE:** DPT Laboratories, Inc.  
307 E. Josephine Street  
San Antonio, TX 78215  
Estab. # 1628114
  - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Cream for topical administration, 1%
  - 5. METHOD(S) OF STERILIZATION:** N/A
  - 6. PHARMACOLOGICAL CATEGORY:** Antimicrobial
- B. SUPPORTING/RELATED DOCUMENTS:** NDAs 20-524 and 20-663
- C. REMARKS:** The drug product is a reformulation of a previously approved product (see NDAs listed in preceding section).

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**Executive Summary**

**I. Recommendations**

- A. Recommendation on Approvability** – This submission is recommended for approval on the basis of product quality microbiology.
- B. Recommendations 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 product has specifications.
- B. Brief Description of Microbiology Deficiencies** – N/A
- C. Assessment of Risk Due to Microbiology Deficiencies** – The product has acceptable specifications that ensure quality of the drug product at release. are adequate to ensure the continued microbiological quality of the drug product during use. Therefore, the drug product presents minimal risk from a microbiological quality standpoint.

**III. Administrative**

- A. Reviewer's Signature** \_\_\_\_\_
- B. Endorsement Block**  
Bryan S. Riley, Ph.D. (Microbiology Reviewer)  
Peter H. Cooney, Ph.D. (Microbiology Supervisor)
- C. CC Block**  
N/A

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2   Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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/s/

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Bryan Riley  
8/12/02 09:51:26 AM  
MICROBIOLOGIST

Peter Cooney  
8/12/02 11:20:51 AM  
MICROBIOLOGIST

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MICROBIOLOGY (HFD-520) NDA FILEABILITY REVIEW

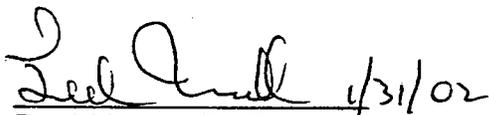
NDA 21-408      Reviewer: Fred Marsik, Ph.D.    Date Review Completed: 31Jan02

- |  | YES | NO |
|--|-----|----|
| 1. Is the microbiology section organized in a manner to allow substantive review to begin?   | X   |    |
| 2. Is the microbiology section indexed and paginated in a manner to allow substantive review to begin?                                 | X   |    |
| 3. Is the microbiology section and other microbiologically pertinent Sections of the NDA legible so that substantive review can begin? | X   |    |

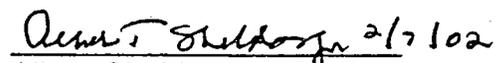
HAS THE APPLICANT SUBMITTED:

- |  |   |                |
|--|---|----------------|
| 1. in vitro data in sufficient quantity, using necessary clinical and non-clinical strains and using necessary numbers of approved laboratories to meet current Divisional standards for approvability of the product based on submitted draft labeling? | X |                |
| 2. any required animal studies necessary for approvability of the product based on the submitted draft labeling?   | X |                |
| 3. draft breakpoints and interpretive criteria in a manner consistent with contemporary standards, in a manner that attempts to correlate criteria with clinical results on NDA studies, and in a manner to allow substantive review to begin?           |   | Not Applicable |
| 4. all special studies/data requested by the Division during pre-submission discussions?   | X |                |
| 5. draft labeling consistent with 201.56 and 201.57, current Divisional policy and the design of the development package.  | X |                |

From a Microbiology perspective, is this NDA fileable? If NO give reasons below. X

  
Fred Marsik, Ph.D.  
Review Microbiologist

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Albert Sheldon, Jr., Ph.D.  
Microbiology Team Leader

**DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)**

**MICROBIOLOGY REVIEW #1**

**DERMATOLOGY (HFD-540) CONSULT**

NDA: 21-408

DATE REVIEW COMPLETED: 14Mar02

Date Company Submitted: 14Dec01

CDER Date Received: 19Dec01

Date Assigned: 30Jan02

Sponsor: Bertek Pharmaceuticals

PO Box 14149

Research Triangle Park, NC 27709-4149

Sherron P Wiechert

Director of Regulatory Affairs

919-991-9878

Established Names/Code Name(s): Butenafine-HCL Cream, 1% / KP 363

Proprietary Name: Mentax<sup>®</sup> – TC-Cream 1%

Chemical Name: N-4-tert-Butylbenz-N-methyl-1-naphthalenemethylamine hydrochloride

Empirical Formula: C<sub>23</sub>H<sub>27</sub>N•HCL

Molecular Weight: 353.93

Drug Category: Antifungal

Proposed Indication: Treatment of tinea versicolor

Dosage Form/Route of Administration: Cream/Topical

Proposed Dosage: 1% Butenafine-HCL used as indicated by physician. Each gram of Mentax<sup>®</sup>-TC Cream, 1% contains 10mg of butenafine-HCL in a white cream base. The Applicant indicates that the proposed duration of treatment is once daily for 7 days (Vol. 1.1 pg. 122).

Supporting Documents: NDA 20-524, NDA 20-663, and IND 60,471

Background and Summary: Butenafine-HCL is a synthetic benzylamine, which is structurally and pharmacologically related to the allylamine agents.

Butenafine-HCL 1% (Mentax<sup>®</sup>) cream has been previously approved for the topical treatment of the following superficial dermatophytoses: interdigital tinea pedis (athlete's foot) tinea corporis (ringworm) and tinea cruris (jock itch) due to *Epidermophyton floccosum*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, and *Trichophyton tonsurans*. Mentax<sup>®</sup> at a later time was also approved for the treatment of tinea versicolor by using it once daily for 14 days. The Sponsor has provided in this current submission data to support their application to market Mentax<sup>®</sup>-TC 1% cream for a 7 day rather than a 14 day treatment course of tinea versicolor due to *Malassezia furfur*.

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**DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)**

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NDA: 21-408

DATE REVIEW COMPLETED: 14Mar02

The Mentax<sup>®</sup>-TC 1% cream that is the subject of this review differs from the Mentax<sup>®</sup> 1% cream which received an approvable letter on 7/27/01 for the topical treatment of interdigital tinea pedis, tinea corporis, and tinea cruris under NDA 21-307 and for a 14 day course of topical treatment of tinea versicolor under NDA 20-524. The difference is that the topical cream (TC) preparation that is the subject of this review contains polyolprepolymer-2 and propylene glycol and trolamine has been substituted for diethanolamine — The concentration of butenafine-HCL is unchanged.

**EXECUTIVE SUMMARY:**

Microbiology and clinical data relating to the treatment of the skin disease tinea versicolor caused by a species of the lipophilic fungus *Malassezia furfur* using 1% butenafine-HCL once a day for 7 consecutive days was reviewed. The in vitro and clinical data provided by the Sponsor suggest that Mentax<sup>®</sup>-TC that contains 1% (10 mg/g) of butenafine-HCL will be efficacious in the treatment of tinea versicolor when used once a day for 7 consecutive days. The Microbiology portion of the label is approvable with modifications.

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**DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)**

**MICROBIOLOGY REVIEW #1**

**DERMATOLOGY (HFD-540) CONSULT**

NDA: 21-408

DATE REVIEW COMPLETED: 14Mar02

**INTRODUCTION**

Tinea versicolor, also known as pityriasis versicolor, is a disease of the skin that is found worldwide being most prevalent in tropical and humid climates (1, 2). The disease is currently associated with the organism *Malassezia furfur* a lipophilic fungi. However, recent taxonomic changes now make it unclear as to which species of *Malassezia* is the etiologic agent(s) of tinea versicolor (3, 4). *Malassezia* species normally colonize the stratum corneum, but an imbalance in the host-resident flora relationship allows for invasion into the dermis and subsequent interference with melanin production. This produces characteristic scaly macules and patches of hypo- or hyper-pigmentation, generally on the chest, back, upper arms, and neck, with the face rarely affected. Most eruptions occur in the warmer months. Patients present with affected areas that fail to tan and occasionally with pruritis (1, 2). Young adults, ages 15 –35 years, are primarily affected (1). However, one study demonstrated that nearly 5% of cases have occurred in patients under the age 14 years (2).

The infection received its name from Robert Willan at the beginning of the nineteenth century (5). In 1846, Eichstedt observed fungal elements in the scales of the skin lesions of this disease (6). This fungus received different names and finally *Malassezia furfur* prevailed, as suggested by Baillon in 1889 (7). However, the presence of at least two morphological types of yeast cells was recognized: Bizzozero named them *Saccharomyces ovalis* and *Saccharomyces sphaericus* in 1884 (8). In 1904, Sabourad related the oval form of pityriasis simplex capitis, and called it *Pityrpsporun malassezii* (9). The name was changed to *Pityrosporum ovale* in 1913 (10). The globose form received the name *Pityrosporum obiculare* after Gordon in 1951 (11). These two names coexisted with the old name *Malassezia*, which was considered as the parasitic form of *P. obiculare* (12). Once the lipophilic nature of these yeasts was recognized and culturing of the organisms was possible, different workers observed spontaneous changing from one morphological type to the other. This led to the conclusion that *P. obiculare*, *P. ovale*, and *M. furfur* were only variants of the same species (13). In the taxonomic revision of Yarrow and Ahearn in 1984 (14), *M. furfur* was considered the unique valid name, as it had been described previously. At that time, the genus *Malassezia* also included another species, *M. pachydermatis*, found in the skin of different animals (14). Through the recent years, different workers described stable morphological and serological variants in the unique species, *M. furfur* (15, 16). The use of molecular techniques in the last decade has led to the description of a third lipid-dependent species, *Malassezia sympodialis* (17) and even more recently there has been a description of four additional species: *Malassezia globosa*, *Malassezia restricta*, *Malassezia obtusa* and *Malassezia slooffiae* (18). These taxonomic revisions have led to some uncertainty as to what specie or species of *Malassezia* may actually cause tinea versicolor. A recent paper from a study in Spain suggest that *M. globosa* is the causative agent of tinea versicolor (3). At this time the role that the various species of *Malassezia* may play in tinea versicolor is not known.

**IN VITRO MICROBIOLOGY**

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**DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)**

**MICROBIOLOGY REVIEW #1**

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NDA: 21-408

DATE REVIEW COMPLETED: 14Mar02

**The organism(s):**

The organism generally associated with tinea versicolor is *Malassezia furfur*. However in recent years a variety of species on *Malassezia* have been identified. The use of molecular techniques in the last decade has led to the description of a third lipid-dependent species, *Malassezia sympodialis* (17) and even more recently there has been a description of four additional species: *Malassezia globosa*, *Malassezia restricta*, *Malassezia obtusa* and *Malassezia slooffiae* (18). Therefore the exact etiology of the disease is uncertain at this time (3). Biochemical methods for the differentiation of the species of *Malassezia* are available (18, 19, 20)

The *Malassezia* group of organisms are lipophilic, saprophytic yeasts. Generally these organisms colonize oily areas of the skin, especially the scalp, back, and chest. Colonization begins when sebaceous glands become active and skin lipids increase. The source of the organisms is unclear. Generally the organisms are recovered from 0% to 10% of newborns and from about 90% of teenagers and adults; however it has been recovered from 30% to 85% of neonates in intensive care units. *Malassezia furfur* causes mild to serious infections, including tinea versicolor in normal hosts, folliculitis in impaired hosts, and line sepsis and major organ infection, which are usually associated with intravascular catheters and lipid infusion (21).

**Mechanism of action of butenafine-HCL:**

The Applicant has provided information from three studies designed to study the mechanism of action of butenafine-HCL against fungi (Vol. 1 pg. 148). Two of the studies used *Sporothrix schenckii* to study the mechanism of action of butenafine-HCL against fungi and one study used *Candida albicans*. There were no studies submitted by the Applicant that used *M. furfur* to study the mechanism of action of butenafine-HCL. Butenafine-HCL (Mentax<sup>®</sup> - TC) is a synthetic benzylamine, which is structurally and pharmacologically related to the allylamine agents. The studies submitted by the Sponsor suggest that like existing allylamines and thiocarbamates, the inhibition of squalene epoxidation is primarily responsible for butenafine's antifungal activity. The inhibition of the epoxidation of squalene results in the accumulation of squalene in the fungal cell. Without epoxidation of squalene ergosterol cannot be synthesized. Without sufficient ergosterol, which is a component of the cell membrane of fungi, the cell membrane becomes leaky and constituents in the cytoplasm important to the fungal cell for metabolism and growth are lost leading first to inhibition of growth and then to the death of the fungal cell. The benzylamine class of antifungals, of which butenafine is a member, have a similar mechanism of action to the azoles. Both classes of antifungals act by inhibiting synthesis of ergosterol. Benzylamines, however, act at an earlier stage in the synthesis of ergosterol than azoles. Depending on the concentration of the drug and the fungal species, the antifungal benzylamines are either fungistatic or fungicidal. It was also suggested in one study with *C. albicans* that butenafine could have a direct damaging effect on the cell membrane of fungi (Vol. 1.7 pg. 2180).

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**Spectrum of activity of butenafine-HCL:**

There is no standardized method for determining the susceptibility of *Malassezia* spp. to antifungal agents. The fact that these organisms are lipophilic makes performing such tests difficult. The Applicant has provided information on the in vitro activity of butenafine-HCL, and several other antifungal agents against *M. furfur*. An agar dilution method using neopeptone, yeast extract glucose, tween containing medium was used to determine the MIC of butenafine-HCL against *M. furfur*. The Applicant tested six isolates of *M. furfur* to determine a MIC range for butenafine (21-408 correspondence dated 21Mar02). While this is a very minimal number of isolates it allows one to have some idea of what concentrations of butenafine inhibit the growth of *M. furfur*. The results of this testing suggests that the MIC of butenafine-HCL against *M. furfur* is in the range of 0.78 to 3.13 µg/mL (Vol. 1.7 pg. 2182).

The Applicant has also provided MIC information for butenafine against

Because these organisms are not pertinent to the indication being requested for the use of butenafine-HCL (treatment of tinea versicolor) the results are not presented here. In addition the applicant has provided data on the activity of butenafine-HCL against the bacteria

Because these organisms are not pertinent to the indication being requested for the use of butenafine-HCL the results are not presented here.

**Mechanism(s) of resistance to butenafine-HCL:**

The Applicant presents information from a study that suggests strains of fungi that are defective in the activity of their squalene epoxidase are resistant to butenafine HCL (Vol. 1.7 pg. 2180). Results of experiments submitted by the Applicant (Vol. 1.7 pg. 2187) that were done to induce resistance to butenafine by repeated exposure of both *T. mentagrophytes* and *C. neoformans* to increasing concentrations of butenafine showed that the original MIC of these organisms to butenafine increased by only one dilution. The increase of one dilution in the MIC did not cause the organisms to be classified as resistant to butenafine.

**Epidemiology of tinea versicolor:**

While tinea versicolor is found worldwide, its prevalence in tropical and humid climates suggests environmental factors play a role in its pathogenesis. Organisms of the genera *Malassezia* colonize the stratum corneum, but an imbalance in the host-resident flora relationship allows for invasion into the dermis and subsequent interference with melanin production. This produces characteristic scaly macules and patches of hypo- or hyper-pigmentation, generally on the chest, back, upper arms, and neck, with the face rarely affected.

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Generally *Malassezia* are recovered from 0% to 10% of newborns and from about 90% of teenagers and adults; however it has been recovered from 30% to 85% of neonates in intensive care units. *Malassezia furfur* causes mild to serious infections, including tinea versicolor in normal hosts, folliculitis in impaired hosts, and line sepsis and major organ infection, which are usually associated with intravascular catheters and lipid infusion (18).

**IN VIVO**

**Pharmacokinetics/Pharmacodynamics of butenafine-HCL:**

No pharmacodynamic study results were submitted with this application.

The pharmacokinetic studies submitted were the studies done to support the Applicant's NDA submission 20-524 (Vol. 1.1 pg. 135). These studies were in vitro percutaneous absorption studies. In the study 5mg/cm<sup>2</sup> of the butenafine cream was applied to dermatome skin. After a 24-hour exposure period, the amount of radiolabel applied as <sup>14</sup>C-butenafine contained in the receptor fluid and skin samples was measured. Ninety-five +/- 8.8% was recovered from the skin. Five milligrams of butenafine cream represents approximately 0.5 mg of butenafine HCL/cm<sup>2</sup>. Assuming that the MIC range for *M. furfur* is 0.78 to 3.13 µg/mL the concentration of butenafine-HCL applied and remaining on the dermatome skin after 24 hours would be sufficient to inhibit the growth of *M. furfur*. In two similar studies (Vol. 1.1 pg. 137) that used different procedures for recovery of the butenafine it was found that >82% of the butenafine could be recovered. Here again based on the MIC range of *M. furfur* presented in this application there would be a sufficient amount of butenafine on the skin to inhibit the growth of *M. furfur*.

**Animal models of infection:**

No in vivo animal experiments were performed by the Applicant to test the efficacy of butenafine against *M. furfur* (Vol. 1.1 pg. 123).

**Clinical studies:**

The Applicant has submitted the results of two studies (PDC 010-033 and PDC 010-036) done to test the efficacy of butenafine-HCL 1% cream to treat tinea versicolor (Vol. 1.1 pg. 154). Both studies were multicenter, randomized, double blind parallel group, and vehicle controlled studies. Thirteen geographically distributed sites provided subjects from the northern, eastern, western and southern parts of the United States. The following information comes from Volume 1.8 pg. 2286. Study 010-033 had 51.9% males and 48.1% females with an age range of 12-65 years old while study 010-036 had 53.9% males and 46.1% females with an age range of 12-65 years old. Eleven of the participants in study 033 were black with 87 being white and 31 were of other races. For study 036 17 participants were black, 178 were white 22 were of other races. In study 033 eighty-six participants were treated with butenafine and 43 with vehicle while

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**DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)**  
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NDA: 21-408

DATE REVIEW COMPLETED: 14Mar02

in study 036 143 participants were treated with butenafine and 74 were treated with vehicle.

Patients in both studies were treated with Mentax-TC (butenafine HCL) cream 1% or vehicle once daily for 7 days. Clinical and mycological assessments of the subjects were made at baseline and repeated at the end of treatment (Day 8) and Days 28 and 49. "Effective Treatment" was defined a priori by the Sponsor as "Negative Mycology" plus a "Total signs and Symptoms Score of  $\leq 1$ ". The Agency's definition for "Effective Treatment" for this submission was "Negative Mycology" plus "Total Signs and Symptoms" of  $\leq 1$  with a score of 0 for scaling and results using this definition are referred to as "Effective Treatment post hoc" in this submission (Vol. 1.8 pg. 2283).

Mycological assessment of patients was done at baseline by using a Wood's lamp to aid in the identification of any lesions that were not obvious by visual examination. The lesions fluoresce yellow under the Wood's light. Because the pigments that fluoresce yellow are water-soluble the subjects were asked not to bath for 12 hours prior to the examination. A map of the location of the lesions was made for each patient (Vol. 1.9 pg. 3173). Skin scrapings of the lesion(s) were obtained and a KOH wet mount prepared. Microscopic KOH assessment was performed at baseline and at each subsequent study visit. The following description of what mycological evidence was required for a patient to be enrolled in the study and what constituted a clinical cure was provided by the Sponsor (Vol. 1.9 pg. 3173). Because *M. furfur* is part of the normal cutaneous flora, the yeast (blastospore) form can be observed in KOH preparations from the skin scrapings in the absence of disease: therefore, the presence of yeast cells alone is not confirmatory for diagnosis of tinea versicolor. The characteristic microscopic presentation of *M. furfur* in tinea versicolor is the appearance of short septate hyphae and round or budding yeast cells. Since the pathogenic form of the organism is the mycelial phase, the observation of hyphae at Baseline was necessary to confirm the diagnosis and qualify the subject for entry into the study. At weeks 1, 4, and 7 the absence of hyphae in the microscopic preparation made from the lesion ("Negative Mycology") was the criteria for confirmation of "Mycological Cure", even if many yeast forms were observed in the KOH preparation. Cultures of the lesions were not performed.

Table 1 is shows the results of each study individually and the results for both studies combined. As seen in Table 1 butenafine showed a higher rate of cure in each study in both the "Effective Treatment post hoc" and "Effective Treatment a priori" groups. The results, however, were not significant in either study. Using the Sponsor's analysis of the data a significant result was shown for the "Effective Treatment a priori" when the results of studies 033 and 036 were combined. In the case of the "Negative Mycology" results again the results for each individual study were not significant but when the studies were combined the results for "Negative Mycology" were significant.

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Table 1. Results of studies PDC 010-033 and PDC 010-036 at day 49 for the ITT population (Vol. 1.13 pg. 4839)

| <u>Criterion</u>             | Study 33          |                |                 | Study 36          |                |                 | Studies 33 and 36 Combined |                 |                 |
|------------------------------|-------------------|----------------|-----------------|-------------------|----------------|-----------------|----------------------------|-----------------|-----------------|
|                              | <u>Butenafine</u> | <u>Vehicle</u> | <u>p-value*</u> | <u>Butenafine</u> | <u>Vehicle</u> | <u>p-value*</u> | <u>Butenafine</u>          | <u>Vehicle</u>  | <u>p-value*</u> |
| Effective Treatment post hoc | 37/86<br>(43%)    | 10/43<br>(23%) | 0.0176          | 77/143<br>(54%)   | 25/74<br>(34%) | 0.0033          | 114/229<br>(50%)           | 35/117<br>(30%) | 0.0002          |
| Effective Treatment a priori | 40/86<br>(47%)    | 10/43<br>(23%) | 0.0065          | 83/143<br>(58%)   | 25/74<br>(34%) | 0.0005          | 123/229<br>(54%)           | 35/117<br>(30%) | <0.0001         |
| Negative Mycology            | 44/86<br>(51%)    | 10/43<br>(23%) | 0.001           | 87/143<br>(61%)   | 25/74<br>(34%) | 0.0001          | 131/229<br>(57%)           | 35/117<br>(30%) | <0.0001         |
| Complete Cure                | 34/86<br>(40%)    | 8/43<br>(19%)  | 0.011           | 74/143<br>(52%)   | 23/74<br>(31%) | 0.0021          | 108/229<br>(47%)           | 31/117<br>(26%) | 0.0001          |

\*p-value from Cochran-Mantel-Haenzel test adjusted for centers

## CONCLUSION

The in vitro microbiology data and the results of the clinical trials suggests that Mentax<sup>®</sup>-TC will be efficacious in the treatment of tinea versicolor due to *Malassezia furfur* when used once a day for 7 consecutive days. The Microbiology portion of the label is approvable with modifications.

## REFERENCES

1. Rogers, CJ, TF Cook, and DA Glaser. 2000. Diagnosing tinea versicolor: Don't scrape, just tape. *Pediatric Dermatol* 17:68-69.
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4. Guillot J, E Gueho, M Lesourd, et al. 1996. Identification of *Malassezia* species, a practical approach. *J Myco Med* 6:103-110.
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7. Baillon H. 1889. *Traite de Botanique Medicale Cryptogamique*. Paris: Octave Douin 234-238.
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DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)

MICROBIOLOGY REVIEW #1

DERMATOLOGY (HFD-540) CONSULT

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DATE REVIEW COMPLETED: 14Mar02

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DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)

MICROBIOLOGY REVIEW #1

DERMATOLOGY (HFD-540) CONSULT

NDA: 21-408

DATE REVIEW COMPLETED: 14Mar02

AGENCY PROPOSED MICROBIOLOGY PORTION OF PACKAGE LABEL

The following is the Microbiology portion of the label as proposed by the Sponsor with modifications made by this Reviewer indicated by strikeouts or highlighting.

Microbiology

It is hypothesized that Butenafine-HCL inhibits the growth of fungi — by inhibiting the epoxidation of squalene, thus blocking the biosynthesis of ergosterol, an essential component of the fungal cell membrane. Lack of or diminished quantities of ergosterol in the fungal cell membrane injures the cell causing inhibition of growth.

Results of non-standardized in vitro susceptibility tests suggest that Butenafine HCL has activity against *Malassezia furfur*.

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DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)

MICROBIOLOGY REVIEW #1

DERMATOLOGY (HFD-540) CONSULT

NDA: 21-408

DATE REVIEW COMPLETED: 14Mar02

Microbiology Comments on Applicant's Proposed Label:

\_\_\_\_\_ have been taken out of the label because their relevance to the sought indication ("...topical treatment of tinea (pityriasis) versicolor due to *Malassezia furfur*...") has not been substantially proven.

\_\_\_\_\_ Date: \_\_\_\_\_  
Frederic J Marsik, Ph.D.  
Microbiology Reviewer

CONCURRENCE ONLY:

\_\_\_\_\_ Date \_\_\_\_\_  
HFD-520/DepDir/L Garvilovich

\_\_\_\_\_ Albert T. Sheldon, Jr. Ph.D. \_\_\_\_\_ Date Rd#1 and Final Initialed 3/15/02  
HFD-520/TLMicro/ A T Sheldon, Jr.

cc:  
Original NDA 21-408  
HFD-540 Divisional File  
HFD-520/Micro/F Marsik  
HFD-540/PMF/ F Cross

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/s/

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Frederic Marsik  
6/4/02 09:35:46 AM  
MICROBIOLOGIST

Albert Sheldon  
6/10/02 10:42:29 AM  
MICROBIOLOGIST

Lillian Gavrilovich  
6/10/02 10:57:44 AM  
MEDICAL OFFICER

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