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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-524/S-005

Microbiology Review(s)

NOV 9 8 2000

Consultative Review for HFD-540
Division of Dermatologic and Dental Drug Products
Clinical Microbiology Review

Requester:	Frank Cross
Date of Request:	8-28-00
Date Received by DAIDP:	9-11-00
Reason for Request:	Clinical Microbiology Review of an NDA efficacy supplement
NDA Number:	20524-ES1-005
Review Date:	10-27-00
Submission/Type:	Original NDA, Efficacy Supplement
Document Date:	8-4-00
Assigned Date:	9-25-00
Applicant:	Bertek Pharmaceuticals Inc. Research & Development Division
320 Lakeside Drive. Suite A	Foster City, CA 94404
Contact Person:	Mary W. Treuhaft, Ph.D., Vice President Regulatory & Clinical Affairs Bertek Pharmaceuticals Inc. Research & Development Division 320 Lakeside Drive. Suite A Foster City, CA 94404 Phone: (650) 358-0100

Drug Product Name:

Proprietary:	Mentax
Nonproprietary/USAN:	Butenafine HCl 1% cream
Code Names/#'s:	KP-363
Therapeutic Class:	Antifungal

Pharmacological Category/Indication:

Butenafine HCl 1% cream is an antifungal agent for treatment of tinea pedis, tinea cruris, and tinea

corporis. Under this application the sponsor is requesting addition of tinea versicolor as an indication.

Dosage Form: Topical cream

Strength(s): 1% Butenafine HCl

Route of Administration: Topical

Dispensed: ___X__RX _____OTC

Related Documents (if applicable): None

REMARKS/COMMENTS

Butenafine HCl 1% cream is an FDA approved product for treatment of tinea pedis, tinea cruris, and tinea corporis. Under this submission the sponsor is requesting addition of tinea versicolor as an indication for this product.

The sponsor has conducted two phase III studies under identical protocols to demonstrate the efficacy and safety of butenafine HCl 1% cream in treatment of tinea versicolor. The primary efficacy variable was proportion of subjects attaining "Effective Treatment" at Day 56 (week 8), i.e. 6 weeks post treatment. The secondary efficacy variable was proportion of subjects attaining "Complete Cure" and proportion of subjects attaining " Negative Mycology" at day 56 (8 weeks). The "Effective Treatment" was defined as "Negative Mycology" plus "Total Sign and Symptoms Score" of ≤ 1. **The "Negative Mycology" was defined as the absence of hyphae in a potassium hydroxide (KOH) preparation of skin scrapings, i.e.; no fungal forms seen or the presence of yeast cells (blastospores) only in the KOH preparation**. The "Total Signs and Symptoms Score" was defined as the sum of individual scores for signs and symptoms of tinea versicolor (erythema, scaling, and pruritis) graded on a four-point scale (0-3) corresponding to absent, mild, moderate and severe. The "Complete Cure" was defined as "Negative Mycology" plus "Total Signs and Symptom Score" of zero.

Microbiologically the definition of "Negative Mycology" as defined by the sponsor in the absence of culture is problematic and will overestimate the efficacy of the product. *Malassezia furfur* the causative agent of tinea versicolor is known to go in to yeast forms when exposed to oil and/or ointment. The product is an oily formulation and the sponsor is considering the presence of yeast on the KOH prep from a treated lesion as a "Negative Mycology" result. This reviewer would like to caution the clinical reviewer to pay a special attention to the number of the patients with presence of yeast on the KOH who were declared as successes in the clinical trial. If the Clinical reviewer approves the product then the following changes must be made in the label before the product is proved for marketing in the US.

1. Move the Mechanism of Action subsection under the CLINICAL PHARMACOLOGY section of the label to the MICROBIOLOGY section of the label.
2. Rewrite the Tinea (pityriasis) versicolor subsection under the CLINICAL STUDY section of the label in the same format and content as the other two subsections, namely the Tinea Corporis and Tinea Cruris and Tinea Pedis.

CONCLUSION & RECOMMENDATIONS:

Microbiologically the definition of "Negative Mycology" as defined by the sponsor in the absence of culture is problematic and will overestimate the efficacy of the product. *Malassezia furfur* the causative agent of tinea versicolor is known to go in to yeast forms when exposed to oil and/or ointment. The product is an oily formulation and the sponsor is considering the presence of yeast on the KOH prep from a treated lesion as a "Negative Mycology" result. This reviewer would like to caution the clinical reviewer to pay a special attention to the number of the patients with presence of yeast on the KOH who were declared as successes in the clinical trial. If the Clinical reviewer approves the product then changes must be made to the MICROBIOLOGY section of the label to read as follows.

MICROBIOLOGY

Butenafine HCl is a benzylamine derivative with a mode of action similar to that of the allylamine class of antifungal drugs. Butenafine HCl is hypothesized to act by inhibiting the epoxidation of squalene, thus blocking the biosynthesis of ergosterol, an essential component of fungal cell membranes. The benzylamine derivatives, like the allylamines, act at an earlier step in the ergosterol biosynthesis pathway than the azole class of antifungal drugs. Depending on the concentration of the drug and the fungal species tested, butenafine HCl may be fungicidal or fungistatic in vitro. However, the clinical significance of these in vitro data is unknown.

Butenafine HCl has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in the IINDICATIONS AND USAGE section:

Epidermophyton floccosum
Malassezia furfur
Trichophyton mentagrophytes
Trichophyton rubrum
Trichophyton tonsurans

/S/

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