

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
20-524/S-005**

Correspondence



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Div. 1E
CC: Vaughan
Walker
Wilkin
C. S. S.

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: July 28, 1999 Number of Pages (including cover sheet) - 2

TO: Mary Treuhaft, Ph.D., Vice President, Regulatory Affairs
COMPANY: Penederm Incorporated
FAX #: 650-358-0101

MESSAGE: Clinical comments from our review of your original IND **Mentax**
(butenafine hydrochloride) Cream, 1%, follow:

1. The Sponsor should address, in writing to the IND, implications to human use of DEA and the National Toxicology Program (NTP) study results showing that dermal application of diethanolamine (DEA) in animal studies result in liver neoplasms. The Sponsor should justify continued use of diethanolamine in the cream formulation.
2. The investigator's brochure and the informed consent form should be revised to address this new information concerning the presence of diethanolamine in the cream formulation and implications of the NTP study results.
3. A Pharmacology/Toxicology study, carcinogenicity assay, might be appropriate.
4. The Sponsor should provide the rationale for non-inclusion of yeast forms in the inclusion criteria. Both yeast and hyphal forms should be seen.

IND []

Mentax (butenafine hydrochloride) Cream, 1%

Facsimile of Original IND Clinical Reviewer Comments

Page 2 of 2

5. The descriptive levels of the signs/symptoms scoring scales should be more robust

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone



Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
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Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: March 19, 2001 Number of Pages (including cover sheet) - 1

TO: Paula Mueda, Regulatory Affairs Specialist
COMPANY: Bertek Pharmaceuticals, Inc.
FAX #: 650-524-5969

MESSAGE: Concerning your NDA 20-524/S-005, Mentax® (butenafine hydrochloride cream) Cream, 1%, we have the following requests:

1. Where in the submission does the Applicant address the variation observed in the KOH results that were noted (at the Pre-sNDA teleconference held January 13, 1999) by the Clinical Microbiologist?
2. Please provide CRFs including Baseline Body Diagram (Appendix C) and New Lesion Diagram (Appendix D) for the following patients:

(Study PDC 010-031) - T104, T116, T404, T407, T411, and T416
(Study PDC 010-032) - V102, V111, V401, V424, and V207
3. Please provide CRFs including Baseline Body Diagram (Appendix C) and New Lesion Diagram (Appendix D) for the following patients:

(Study PDC 010-031) - T212, T527, and T529
(Study PDC 010-032) - V122, V210, V213, V218, V321, V402, V436, V505, and V508.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: April 23, 2001 Number of Pages (including cover sheet) - 1

TO: Paula Mueda, Regulatory Affairs Specialist
COMPANY: Bertek Pharmaceuticals, Inc.
FAX #: 650-524-5969

MESSAGE: Concerning your NDA 20-524/S-005, Mentax® (butenafine hydrochloride cream) Cream, 1%, we have the following requests:

1. Please provide the definition of () mentioned in your submission of September 8, 2000, attachment 3, p. 3 and 6.
2. Please provide a rationale for the variable mycology results observed between week 4 and week 8 for the following patients:

(Study PDC 010-031) - T104, T116, T404, T407, T411, and T416
(Study PDC 010-032) - V102, V111, V207, V401 and V424

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: May 4, 2001 Number of Pages (including cover sheet) - 1

TO: Paula Mueda, Regulatory Affairs Specialist
COMPANY: Bertek Pharmaceuticals, Inc.
FAX #: 650-524-5969

MESSAGE: Concerning your NDA 20-524/S-005, Mentax® (butenafine hydrochloride cream) Cream, 1%, we have the following requests:

For your studies PDC 010-031 and PDC 010-032, please provide:

1. A tabular representation of those patients having maximal surface area of involvement of tinea versicolor sorted by study and group (active vs. vehicle) indicating treatment outcome.
2. Please provide an explanation of how patients were recruited into these studies, e.g., patients presenting to clinic for treatment of Tinea versicolor or selected from patients presenting for other indications, etc.
3. Please provide mean amounts of study drug used for each study

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

NDA SUPPL AMENDMENT

SEI-005/BL



BERTEK
PHARMACEUTICALS INC.



June 6, 2001

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA 20-524 - Supplement 005: Mentax[®] (butenafine HCl cream) Cream 1%, Clinical Efficacy Supplement for the Treatment of Tinea Versicolor
Response to Proposed Labeling

Dear Dr. Wilkin:

Reference is made to a facsimile transmission from Commander Frank Cross dated June 6, 2001 and received at Bertek Pharmaceuticals Inc. at 10:00 a.m. regarding draft labeling for NDA 20-524/S-005, Mentax[®](butenafine hydrochloride cream) Cream, 1%.

We have reviewed the proposed labeling and agree with the wording of the labeling as stated in the above-referenced facsimile.

This submission is made in duplicate. For any additional information or questions relating to this submission, please contact Paula Mueda at 650-358-0100 (phone) or 650-524-5969 (fax).

Sincerely,

Sherron P. Wiechert, RAC
Director of Regulatory Affairs

SPW/pm
Enclosure (Form FDA 356h)

Copy: Frank Cross, Jr., MA, CDR, Senior Regulatory Management Officer (via facsimile)

ORIGINAL



June 1, 2001

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

SE 1-005

NDA SUPPL AME

Re: **NDA 20-524 - Supplement 005: Mentax[®] (butenafine HCl cream) Cream 1% — Request for Exclusivity**

Dear Dr. Wilkin:

This letter is in reference to Supplement 005, Clinical Efficacy Supplement for the Treatment of Tinea Versicolor, to NDA 20-524, which is currently under review by the Agency.

The application is for the use of 1% Butenafine HCl Cream (Mentax) for the treatment of tinea versicolor. Since this is a new indication for this molecule, the Sponsor would at this time like to request that the Agency grant five-year exclusivity for this product in the treatment of tinea versicolor.

This submission is made in duplicate. For any additional information or questions relating to this submission, please contact Paula Mueda at 650-358-0100 (phone) or 650-524-5969 (fax).

Sincerely,

Sherron P. Wiechert, RAC
Director of Regulatory Affairs

/pm

Enclosure: Form FDA 356h

ORIGIN



May 29, 2001



Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

SE1-005/BM.

NDA SUPPL AMENDME

Re: NDA 20-524 - Supplement 005: Mentax[®] (butenafine HCl cream) Cream 1%, Clinical Efficacy Supplement for the Treatment of Tinea Versicolor

Response to FDA Request of May 23, 2001 — Adverse Events

Dear Dr. Wilkin:

Reference is made to a May 23, 2001 teleconference between FDA representatives Markham Luke, MD, PhD, Acting Dermatology Team Leader; Brenda Vaughn, MD, PhD, Medical Officer, and Frank Cross, Jr., MA, CDR, Senior Regulatory Management Officer and Barbara Brennan, Executive Director of Clinical Research of Bertek Pharmaceuticals Inc. During that telecon, requests for further information from the Sponsor were made on the issues of contact sensitization and adverse events. An initial response to the contact sensitization question was submitted to the Agency on May 25, 2001. This submission contains information on all application-area adverse events that occurred in the Mentax clinical studies covered in the package insert and in the PDC 010-031, PDC 010-032 tinea versicolor studies.

The Sponsor has undertaken a comprehensive review of safety data from the six clinical studies referenced in the Mentax package insert and from the two tinea versicolor studies which are the subject of the Sponsor's submission, Supplement 005 to NDA 20-524. The objective was to identify all adverse events (AEs) of any causality that occurred at the site of application of either Mentax or its vehicle formulation, and to confirm the number of Mentax-treated and vehicle-treated subjects included in the Safety Population of each study. The compiled list of AEs presented herein includes application site adverse events categorized as "not related" to treatment, as well as adverse events whose relationship to treatment was categorized as "possible," "probable," or "definite."

The following studies were reviewed by the Sponsor; numbers 1 through 6 comprise the studies described in the current package insert, numbers 7 and 8 are from Supplement 005, NDA 20-524.

ORIGIN

BEST POSSIBLE COPY

1. PDC 010-001: A Double-Blind Evaluation of Butenafine HCl 1% Cream and Vehicle in the Treatment of Tinea Pedis
2. PDC 010-002: A Double-Blind Evaluation of Butenafine HCl 1% Cream and Vehicle in the Treatment of Tinea Pedis
3. PDC 010-004: A Multicenter, Double-Blind Study to Evaluate Butenafine HCl 1% Cream and Vehicle in the Treatment of Tinea Corporis
4. PDC 010-005: A Multicenter, Double-Blind Study to Evaluate Butenafine HCl 1% Cream and Vehicle in the Treatment of Tinea Cruris
5. PDC 010-014: A Multicenter, Double-Blind Study to Evaluate Butenafine HCl 1% Cream and Vehicle in the One-Week Treatment of Tinea Pedis
6. PDC 010-015: A Multicenter, Double-Blind Study to Evaluate Butenafine HCl 1% Cream and Vehicle in the One-Week Treatment of Tinea Pedis
7. PDC 010-031: A Multicenter, Double-Blind, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of Butenafine HCl 1% Cream in the Treatment of Tinea Versicolor
8. PDC 010-032: A Multicenter, Double-Blind, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of Butenafine HCl 1% Cream in the Treatment of Tinea Versicolor

During the Sponsor's review of the adverse event tables for the above studies, it became apparent that not all adverse events which occurred at the application site were coded to "Skin." For example, "stinging," reported by vehicle group Subject #2326 in study PI 010-002, was coded to "parasthesia" under body system NER/PNS; however, the event described in the package insert as having occurred at the application site. Additionally not all adverse events coded to "Skin" occurred at the application site. For example, in tinea versicolor study PDC 010-032, Subject #V315 contracted poison ivy which was coded as "contact dermatitis" under body system "Skin," and Subject #V508 had a rash on the arms and legs which was remote from the tinea versicolor site and coded as "dermatitis" under "Skin." Both these subjects were in the Mentax-treated group. Therefore, the Sponsor has reviewed all adverse events coded to any body system, not just those coded to body system, "Skin." Additionally, the Sponsor has reviewed the Adverse Event line listings for every subject enrolled in each study listed above, as well as any other line listing that could provide helpful information, e.g., Comments, Medical History, Physical Exam, Concomitant Medication.

The Sponsor's review of study data has confirmed the following adverse event information. For the Mentax-treated subjects in the Safety Population for the six studies shown in the current package insert, the total number of subjects who experienced an adverse event at the treatment site has not changed from the 8 reported in the insert (one AE/subject); however, the total number of subjects exposed to Mentax in the studies has been changed from 644 to 651. For vehicle-treated subjects, the package insert currently only reports information on the two subjects who discontinued the studies due to an adverse event at the application area. A total of 16 subjects from the vehicle groups in the six studies covered by the package insert reported a total of 18 application site adverse events. The total number of subjects in the Safety Population for the vehicle group/combined studies has been changed from the 624 shown in the insert to 638.

The two tinea versicolor studies, PDC 010-031 and PDC 010-032, contribute to the safety data as follows. For study PDC 010-031, the total number of Mentax-treated subjects in the Safety Population is 83, the total number of vehicle-treated subjects is 39. There were no application site adverse events reported for either treatment group. In study PDC 010-032, the total number of Mentax-treated subjects in the Safety Population is 81, the total number of vehicle-treated subjects is 41. One subject in the Mentax group reported an adverse event at the application site (mild itching), no subject in the vehicle group reported any application site adverse events.

Listing of Application Site Adverse Events of Mentax-Treated Subjects

Study	Subject Number	Adverse Event
PDC 010-001	1608	Worsening of condition
PDC 010-002	2222	Mild burning at application site
PDC 010-005	5111	Moderate burning upon application
PDC 010-005	5321	Possible bacterial infection of crural area due to scratching
PDC 010-014	A0111	Mild burning in treated area
PDC 010-014	A0305	Mild erythema on the soles of the feet
PDC 010-014	A0606	Moderate maceration
PDC 010-015	B0707	Moderate burning/stinging
PDC 010-032*	V318	Mild itching

*All adverse events listed are from studies covered in the Mentax package insert except this one (tinea versicolor study, PDC 010-032)

Listing of Application Site Adverse Events of Vehicle-Treated Subjects

Study	Subject Number	Adverse Event
PDC 010-002	2326	Severe stinging of both feet
PDC 010-002	2326	Severe burning of both feet
PDC 010-002	2326	Severe itching of both feet
PDC 010-002	2330	Severe itching s/p each application
PDC 010-002	2331	Mild red streak (rash) s/p scraping for mycology sample
PDC 010-004	4308	Mild new ringworm lesion on back
PDC 010-005	5322	Possible bacterial infection of crural area due to scratching
PDC 010-014	A0102	Mild burning s/p first dose
PDC 010-014	A0105	Moderate irritation to target area
PDC 010-014	A0129	Mild burning on feet
PDC 010-014	A0647	Moderate increased itching
PDC 010-014	A0734	Mild stinging on application
PDC 010-014	A1122	Moderate burning in toe webs
PDC 010-015	B0311	Mild burning between toes
PDC 010-015	B0325	Mild bleeding in cracks and fissures of target lesion
PDC 010-015	B0519	Mild eczematous patches bilateral dorsal feet
PDC 010-015	B0622	Moderate burning on application
PDC 010-015	B0626	Mild tingling sensation on first application

This submission is made in duplicate. For any additional information or questions relating to this submission, please contact me at 650-358-0100 (phone) or 650-524-5969 (fax).

Sincerely,



Bhaskar Chaudhuri, PhD
Executive Vice President Scientific Affairs

/pm

Enclosures

Copy via facsimile: Frank Cross, Jr., MA, CDR, Senior Project Manager



May 25, 2001

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

SEI-0051

NDA SUPPL AMEN

Re: NDA 20-524 - Supplement 005: Mentax[®] (butenafine HCl cream) Cream 1%, Clinical Efficacy Supplement for the Treatment of Tinea Versicolor
Response to FDA Request of May 23, 2001 — Contact Sensitization

Dear Dr. Wilkin:

Reference is made to a May 23, 2001 teleconference between Bertek Pharmaceuticals Inc. and FDA representatives Markham Luke, MD, PhD, Acting Dermatology Team Leader, Brenda Vaughn, MD, PhD, Medical Officer, and Frank Cross, Jr., MA, CDR, Senior Regulatory Management Officer. As requested during the teleconference, the following information is provided for the contact sensitization issue discussed:

- The text of the study report for study PDC 010-006, Human Repeat Insult Patch Test for Butenafine HCl Cream, 1% (Mentax[®]) and its vehicle formulation (9 pages).
- Also included are two summary tables showing the group reaction scores following the application of the two test materials. Butenafine HCl Cream 1% (butenafine) is test article A; results are shown in Table 1A. The vehicle formulation is test article B, and results are shown in Table 1B. Over 200 subjects completed the HRIPT study.

As is shown in the tables, there were no skin reactions at butenafine-treated sites in either the induction or challenge phases of the study. There were a total of four skin reactions in skin treated with vehicle during the induction phase of the study, one each after applications #5, 6, 7, and 8. All of the reactions were scored as 1: mild reaction - macular erythema (faint, but definite pink). All subjects had scores of zero for both test articles following the challenge application, indicating contact sensitization was not induced.

ORIGINA

This HRIPT report was previously submitted in the original NDA 20-524 on April 4, 1995. It may be found in Volume 1.22 of that submission, beginning with page 6-3058.

This submission is made in duplicate. For any additional information or questions relating to this submission, please contact me at 650-358-0100 (phone) or 650-524-5969 (fax).

Sincerely,



Bhaskar Chaudhuri, PhD
Executive Vice President Scientific Affairs

/pm

Enclosures



May 8, 2001

Jonathan Wilkin, MD, Director
Division of Dental and Dermatological Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

**Re: NDA #20-524/S-005 — Mentax® (butenafine HCl) Cream, 1%
Request for Information**

Dear Dr. Wilkin:

This letter is in response to a facsimile message from Commander Frank Cross dated May 4, 2001 requesting information on clinical studies PDC 010-031 and PDC 010-032 for NDA 20-524/Supplement 005 for Mentax (butenafine HCl cream).

Requests for information from the Agency were for Bertek to provide the following information for studies PDC 010-031 and PDC 010-032:

- (1) A tabular presentation of those patients having maximal surface area of involvement of tinea versicolor sorted by study and group (active vs. vehicle) indicating treatment outcome.

Response:

Recording area of involvement of tinea versicolor was not stipulated in the protocols. The investigators did not capture this information in the case report form or in the source records. The Agency did not request that this be incorporated into the protocol at the End of Phase II meeting or at any time during the conduct of the studies. We cannot provide the Agency with these data.

- (2) Please provide an explanation of how patients were recruited into these studies, e.g., patients presenting to clinic for treatment of tinea versicolor or selected from patients presenting for other indications, etc.

ORIGINAL

Response:

In addition to recruiting from their practices, 8 out of 10 sites in the PDC 010-031 and PDC 010-032 studies used IRB-approved advertisements in local newspapers to recruit subjects for the trial. Dr. Kaminester (Site T2) and Dr. Shavin (Site V2) did not use paid advertising. They only recruited subjects from their practices, either from reviewing patient charts for a history of tinea versicolor or from patients presenting for other dermatological complaints.

- (3) Please provide mean amounts of study drug used for each study.

In study PDC 010-031, more than three quarters of all subjects applied all 14 doses of medication. In the Mentax group, a mean of 42.8 grams of study drug was applied by each subject (3.1 grams per day). The vehicle group used a mean of 42.9 grams (3.1 grams per day) of study drug per subject.

The mean drug usage in the PDC 010-032 study was similar. The Mentax group used an average of 44.7 grams per subject (3.2 grams per day), and the vehicle group used an average of 46.8 grams per subject (3.3 grams per day) over the 14 days of dosing.

If there are further questions, please contact me at 650-358-0100.

Sincerely,



Bhaskar Chaudhuri, PhD
Executive Vice President, Scientific Affairs

Copy (via facsimile): Frank H. Cross, Jr., MA, CDR, Senior Regulatory Management Officer



BERTEK
PHARMACEUTICALS INC.

April 6, 2001

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

SE 1 005 BM
NDA SUPPL AMEN

**Re: NDA 20-524/S-005 Mentax (butenafine HCl cream) Cream, 1%
Response to Agency Facsimile Dated March 19, 2001**

Dear Dr. Wilkin:

This submission to NDA 20-524/S-005, represents a response to the Agency's Facsimile Transmission of March 19, 2001 (provided in Attachment 1) and a subsequent clarifying telephone conversation on March 29, 2001 with Commander Frank H. Cross. There were three requests from the Agency:

1. **Where in the submission does the Applicant address the variation observed in the KOH results that were noted (at the Pre-sNDA teleconference held January 13, 1999) by the Clinical Microbiologist.**

The Sponsor's response to this question is provided in Attachment 2 of this submission.

2. **Please provide CRFs including Baseline Body Diagram (Appendix C) and New Lesion Diagram (Appendix D) for the following patients:**

(Study PDC 010-031) - T104, T116, T404, T407, T411, and T416
(Study PDC 010-032) - V102, V111, V401, V424, and V207

All requested CRFs, Baseline Body Diagrams and New Lesion Diagrams are supplied in Attachment 3 of this submission, with the exception of a New Lesion Body Diagram for Subject V102. A faxed message from the study site

confirming that Subject V102 had no new lesions and stating that the site could not locate a New Lesion Diagram for the subject is included in Subject V102's CRFs/Baseline Body Diagram.

3. Please provide CRFs including Baseline Body Diagram (Appendix C) and New Lesion Diagram (Appendix D) for the following patients:

(Study PDC 010-031) - T212, T527, and T529
(Study PDC 010-032) - V122, V210, V213, V218, V321, V402, V436, V505, and V508

All requested CRFs, Baseline Body Diagrams, and New Lesion Body Diagrams are supplied in Attachment 4 of this submission. In addition, further information regarding the New Lesion Body Diagram for Subjects T529, V210 and V218 is included in this submission. When the New Lesion Body Diagrams for Subjects T529 and V210 were received by the Sponsor from the study sites, missing or apparently discrepant information was noted, and the Sponsor requested clarification from the sites. Dr. David Tashjian confirmed that the New Lesion Body Diagram for Subject T529 was incomplete, and that documentation is included with the Subject's CRFs/Diagrams. Dr. Donald Greer confirmed that the statement "no new lesions" on the New Lesion Diagram for Subject V210 was incorrect, and supplied a revised Diagram to the Sponsor which is included with the Subject's CRFs/Diagrams. Dr. Greer also forwarded additional unsolicited information on Subject V218's New Lesion Body Diagram, and that revised Diagram is also included to assure that documents supplied to the Agency in this submission are identical to those documents at the study sites.

We trust that this material will handle the requests. This submission is submitted in duplicate. If there are any questions, or if additional information needed, please contact me at 650-638-3017.

Sincerely,



Bhaskar Chaudhuri, PhD
Executive Vice President, Scientific Affairs

Copy: Cmdr. Frank Cross
Senior Regulatory Management Officer



November 1, 2000

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: Mentax® (butenafine HCl cream) Cream 1%
NDA 20-524 - Supplement 005
Clinical Efficacy Supplement for the Treatment of Tinea Versicolor

Dear Dr. Wilkin:

In response to a request from Lt. Commander Frank Cross, we are enclosing an electronic copy in Word 97 of proposed labeling for Mentax® (butenafine HCl cream) Cream, 1%, as submitted in Supplement 005 to NDA 20-524 on August 4, 2000. A desk copy is also being provided under separate cover for Lt. Commander Cross.

This is a strike-out version of the proposed labeling with identical text to that submitted in paper format on August 4, 2000.

For any additional information or questions relating to this submission, please contact me at 650-356-6434 (phone) or 650-524-5969 (fax).

Sincerely,

Mary W. Treuhhaft, PhD
Vice President Regulatory and Clinical Affairs

Enclosures

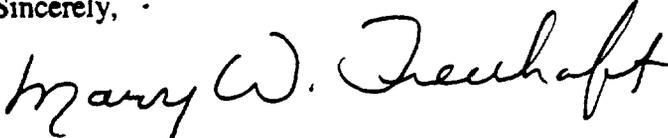
Desk Copy: Lt. Commander Frank Cross

- Annotated Casebook is enclosed as **Attachment 5**.
- PROC CONTENTS and sample PROC PRINT of each dataset (10 observations for each) are enclosed as **Attachment 6**.

During the October 24 teleconference, Dr. Freidlin also requested additional statistical analyses for clinical studies PDC 010-031 and PDC 010-032. These will be submitted when available.

This submission is made in duplicate. For any additional information or questions relating to this submission, please contact me at 650-356-6434 (phone) or 650-524-5969 (fax).

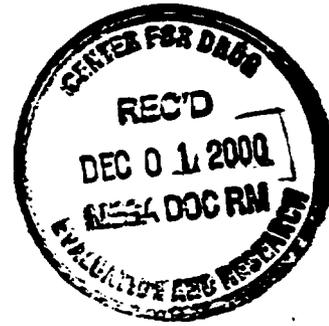
Sincerely,



Mary W. Treuhaft, PhD
Vice President Regulatory and Clinical Affairs

Enclosures

November 30, 2000



Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
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9201 Corporate Blvd., HFD-540
Rockville, MD 20850

NDA 20-524-005
SEI-005/BS

**Re: NDA 20-524 - Supplement 005
Mentax® (butenafine HCl cream) Cream 1%
Clinical Efficacy Supplement for the Treatment of Tinea Versicolor
Response to FDA Requests of October 24, 2000**

Dear Dr. Wilkin:

Reference is made to an October 24, 2000 teleconference between Bertek Pharmaceuticals Inc. and your representatives Valeria Freidlin, PhD, Biostatistics Reviewer and Frank Cross, Senior Regulatory Management Officer. As requested by Dr. Freidlin, we are providing:

- Additional new efficacy analyses for clinical studies PDC 010-031 and PDC 010-032, which were requested by Dr. Freidlin, are enclosed in **Attachment 1**.
- Analysis Programming Specifications for PDC 010-031, which describes the methodology and data extraction for the new analyses for PDC 010-031 is enclosed as **Attachment 2**.
- Analysis Programming Specifications for PDC 010-032, which describes the methodology and data extraction for the new analyses for PDC 010-032 is enclosed as **Attachment 3**.

This submission is made in duplicate. For any additional information or questions relating to this submission, please contact me at 650-356-6434 (phone) or 650-524-5969 (fax).

Sincerely,

A handwritten signature in cursive script that reads 'Mary W. Treuhaft'.

Mary W. Treuhaft, PhD
Vice President Regulatory and Clinical Affairs

Enclosures

ORIGINAL

September 8, 2000

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850



NEW CORRESP

NC

581-005

Re: NDA 20-524 - Supplement 005
Mentax® (butenafine HCl cream) Cream 1%
Clinical Efficacy Supplement for the Treatment of Tinea Versicolor
Response to FDA Requests of August 17, 2000

Dear Dr. Wilkin:

Bertek Pharmaceuticals Inc is providing the following information in support of the above referenced Clinical Efficacy Supplement for NDA 20-524. This information was requested by Lt. Comdr. Frank Cross by telephone on August 17, 2000.

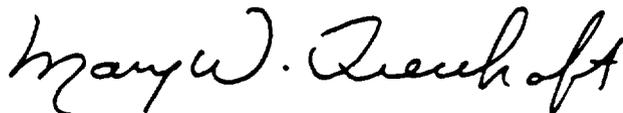
1. To be consistent with the Agency's records, the Sponsor agrees that the above referenced Supplement will be numbered as Supplement 005.
2. The Sponsor confirms that data sets have been provided for the ISS and ISE. These are the PDC 010-031 and PDC 010-032 clinical study data sets. A diskette has been provided which contains the ISS and ISE programs. In order to produce the ISS and ISE results, the statistician should follow the instructions provided in the file on the ISS and ISE diskette. Following these instructions the data for PDC 010-031 and PDC 010-032 are pooled automatically and the ISS and ISE results are generated.
3. The data cut-off date for the ISS is December 31, 1999. This includes all data for which the Sponsor is aware from all sources domestic and foreign.
4. The Sponsor wishes to update the Foreign Marketing History presented in Section 3. Application Summary, Volume 1, page 1-056. The updated Foreign Marketing History is enclosed as Attachment 1.

ORIGINAL

5. As requested, copies of Product Information from all countries where the product is marketed are being provided. The product information for Canada is enclosed as Attachment 2. The Product Information for Japan, South Korea and Indonesia is provided on pages 8-9 of Kaken Pharmaceutical's Periodic Safety Update Report on Butenafine Hydrochloride, April 4, 2000, which is enclosed as Attachment 3.
6. The Sponsor does not have nor does not intend to have any Patient Information for this product.
7. Confirmation that the clinical studies were conducted in compliance with the Declaration of Helsinki and FDA regulations set forth in Part 56 of Title 21 of the Code of Federal Regulations is provided in each clinical study report:
 - PDC 010-031 Volume 2, Page 2-093,
 - PDC 010-032 Volume 5, Page 5-058.

For any additional information or questions relating to this submission, please contact me at 650-356-6434 (phone) or 650-524-5969 (fax).

Sincerely,



Mary W. Treuhaft, PhD
Vice President Regulatory and Clinical Affairs

Desk copies: Lt. Comdr. Frank Cross (20)



August 4, 2000

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

NDA NO 20-524 REF NO. 005
NDA SUPPL FOR 531

Re: Mentax® (butenafine HCl cream) Cream 1%
NDA 20-524 - Supplement 006
Clinical Efficacy Supplement for the Treatment of Tinea Versicolor

Dear Dr. Wilkin:

Pursuant to section 505(b) of the Federal food, Drug and Cosmetic Act and in accordance with CFR 21 Parts 314.70 and 314.71, Bertek Pharmaceuticals Inc. herewith submits a Clinical Efficacy Supplement to the above referenced NDA for the once daily, two week treatment of tinea versicolor.

The Phase III clinical studies conducted in support of this supplemental application were conducted under IND [redacted] and utilized the currently approved formulation of butenafine HCl cream, 1%. No changes to the formulation have been made. Reference is made to a Pre-IND/End of Phase 2 Meeting held with the Agency on January 11, 1999 and to a pre-SNA Teleconference held April 17, 2000.

Please be advised that the information contained in this application is proprietary and confidential. Confidentiality of all enclosed information is provided for under 18 USC, section 1905 and/ or 21 USC, section 331j.

This supplemental application is submitted in 16 volumes as follows:

Section	Archival Copy	Review Copy
1. Index	Volume 1 (1 copy)	Volume 1 (6 copies)
Form FDA 356h - Application to Market		
Form FDA 3397 - User Fee		
Form FDA 3454 and 3455- Financial Interests of Clinical Investigators		

1. Index, Forms and
A. Form FDA 356h
B. Form FDA 3397
C. Forms FDA 3454
D. Index to the

1. Index, Forms and
 Attachments
 A. Form FDA 356h
 B. Form FDA 3397
 C. Forms FDA 3454
 D. Index to the

Section	Archival Copy	Review Copy
Debarment Certification Statement		
Environmental Impact - Request for Categorical Exclusion		
Pediatric Studies - Request for Waiver		
2. Labeling		
3. Application Summary		
4. Chemistry, Manufacturing, and Controls		
5. Nonclinical Pharmacology and Toxicology		
6. Human Pharmacokinetics and Bioavailability		
7. Clinical Microbiology	Volumes 2-8 (1 copy)	Volumes 2-8 (1 copy)
8. Clinical Data Section		
9. Statistical Section		
10. Case Report Forms	Volume 15 (1 copy)	Volume 15 (1 copy)

The following electronic files on diskette are being provided in the indicated volumes:

Electronic files on diskette	Archival Copy	Review Copy
Draft Package Insert in MS Word	Volume 1	Volume 1
PDC 010-031 Protocol in MS Word	Volume 2	Volume 2
PDC 010-031 Final Report in MS Word	Volume 2	Volume 2
PDC 010-032 Protocol in MS Word	Volume 5	Volume 5
PDC 010-032 Final Report in MS Word	Volume 5	Volume 5
PDC 010-031 SAS Data Sets and Programs	Volume 14	Volume 14
PDC 010-032 SAS Data Sets and Programs	Volume 14	Volume 14
ISS and ISE Data Sets and Programs	Volume 14	Volume 14

For any additional information or questions relating to this submission, please contact me at 650-356-6434 (phone) or 650-524-5969 (fax).

Sincerely,



Mary W. Treuhaft, PhD
 Vice President Regulatory and Clinical Affairs