CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-385

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration

Rockville MD 20857

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: December 10, 2003 Number of Pages (including cover sheet) – 11

TO: Andrea B. Miller, R. Ph., Esq., Executive Director, Regulatory Affairs
COMPANY: Mylan Pharmaceuticals, Inc.
FAX #: 304-285-6407

MESSAGE: Please find attached to this facsimile transmission our meeting minutes for our December 5, 2003, Teleconferences concerning your NDA 21-385, ERTACZO™ (sertaconazole nitrate) Cream, 2%.

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

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V

FACSIMILE TRANSMITTAL SHEET

DATE: December 10, 2003

To: Andrea B. Miller, R. Ph., Esq., Executive Director, Regulatory Affairs	**From:** Frank H. Cross. Jr., M.A., CDR Senior Regulatory Management Officer
Company: Mylan Pharmaceuticals, Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 304-285-6407	**Fax number:** 301-827-2075/2091
Phone number: 800-848-0461, Ext. 6869	**Phone number:** (301) 827-2063

Subject: Facsimile Transmission of Minutes of Teleconferences for NDA 21-385, ERTACZO™ (sertaconazole nitrate) Cream, 2%

Total no. of pages including cover: 11

Document to be mailed: YES ☑ NO

Document to be mailed: YES ☑ NO

Comments:

Please find attached to this facsimile transmission our minutes for our December 5, 2003, teleconferences concerning your NDA 21-385, ERTACZO™ (sertaconazole nitrate) Cream, 2%.

MEMORANDUM OF TELECON

DATE: 12/4/03, 8:30 A.M. Meeting ID: 11947

APPLICATION NUMBER: NDA 21-385
DRUG PRODUCT: ERTACZO™ (sertaconazole nitrate) Cream, 2%

BETWEEN:

Name: John O'Donnell, Chief Scientific Officer
Frank Sisto, Corporate Vice President, Regulatory Affairs
Andrea B. Miller, Executive Director, Regulatory Affairs
James Sherry, Vice President, Medical Affairs
Peter Bruce Bottini, Executive Director, Clinical Research
Mei-Ying Huang, Executive Director, Pharmacokinetics and Research
[redacted]

Phone: (304) 598-5430 ext. 6869
Representing: Mylan Pharmaceuticals

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
Stanka Kukich, M.D., Deputy Division Director
Jonca Bull, M.D., Office Director, Office of Drug Evaluation V
Markham Luke, M.D., Ph.D., Clinical Team Leader
Joseph Porres, M.D., Clinical Reviewer
Joel S. Hathaway, Ph.D., Chemistry Reviewer
David Allen, Ph.D., Acting Pharmacology/Toxicology Supervisor
Paul Brown, Ph.D., Acting Pharmacology Reviewer
Connie Mahon, M.S., CLS (NCA), Clinical Microbiology Reviewer
Kathleen Fritsch, Ph.D., Biostatistics Reviewer
Dennis Bashaw, Pharm.D., Biopharmaceutics Team Leader
Margo Owens, Regulatory Project Manager

SUBJECT: NDA 21-385

The teleconference was requested by the Agency to discuss proposed labeling and the post-marketing commitments for the submitted NDA.

The following discussion took place:

Post Marketing Commitments
Commitment #1 – 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.")."

Sponsor's Response:
We have agreed to this.

Commitment #2 - Biopharmaceutics:

[redacted]

Applicant's Question 1 from the meeting request dated December 2, 2003:
What is the rationale for this commitment?

Agency's Response:
This commitment will be removed. Since receipt of the applicant's briefing package, we have reviewed this information and determined that since this was not discussed at the EOP2 and Pre-NDA meetings for this application, the Agency would withdraw this request.

Commitment #3 – Clinical Microbiology:

[redacted]

Agency's Response:
This commitment will be removed. We have determined that the data will not have significant meaning because it is not correlated with any clinical outcome.

Applicant's Question 4 from the meeting request dated December 2, 2003:
Mylan is requesting that the Agency only require the protocol submission date and final report submission date as part of the commitment.

Agency's Response:
The study start date is part of a template used by the Agency. If requested, the study start date can be amended as necessary.

Action Item: The Agency will get back to the Applicant on the acceptability of omitting study start dates from Post Marketing Commitments.

Draft Labeling
Agency's Comment:
The Agency has not reached internal agreement on the clinical microbiology section and the clinical pharmacology and indications and usage section regarding *Epidermophyton floccosum (e. floccosum)*. We will contact the Applicant again to discuss after an internal meeting is held.

Chemistry, Manufacturing and Controls:
Applicant's Labeling Question 1 from the meeting request dated December 2, 2003:
Mylan requests that the Agency reconsider its request to rename the product to [redacted]. Since this product is a topical product, the actual drug product at the site of action is sertaconazole nitrate and not sertaconazole. Therefore, we propose that the product retain ERTACZO (sertaconazole nitrate) Cream, 2%.

Agency's Response:
We will consider the Applicant's counter-proposal to retain nitrate. It is recommended that the Applicant immediately apply to the USAN Counsel for the name sertaconazole nitrate.

Applicant's Response:
We will apply to USAN counsel for sertaconazole nitrate.

Applicant's Labeling Question 2 from the meeting request dated December 2, 2003:
CLINICAL PHARMACOLOGY: Pharmacokinetics - (Page 2, line 24): Mylan would like to discuss the removal of the [redacted] and provides meaningful clinical data. Added text is noted in red type in the attached labeling.

Agency's Response:
The proposed [redacted] does not belong in the package insert. [redacted] The question becomes what does this information mean clinical? This information does not mean anything clinically and, therefore, does not belong in the package insert. This [redacted] should be deleted.

Applicant's Response:
We agree to delete this [redacted]

Applicant's Labeling Question 3 from the meeting request dated December 2, 2003:
Activity *In Vitro* - (Page 2, line 38): Mylan is proposing the addition back in to the labeling of [redacted] The information in [redacted] provides useful and meaningful data. The data in the [redacted] are from the [redacted]

Agency's Response:
Regarding the proposed [redacted] Therefore, we recommend that the [redacted] under the [redacted] section be deleted.

Applicant's Response:
We agree to delete the [redacted] under the [redacted] section.

Applicant's Labeling Question 4 from the meeting request dated December 2, 2003:
Mylan re-inserted *Epidermophyton floccosum* as a clinical isolate both in this section and in the INDICATION section (Page 4, line 62). Mylan requests that the Agency reconsider its position on *e. floccosum.*

Agency's Response:
Pending. Internal agreement not yet reached. An additional teleconference to discuss *E. floccosum* with the Applicant will be scheduled.

Applicant's Labeling Question 5 from the meeting request dated December 2, 2003:
Resistance - (Page 3, line 42): Mylan is proposing the addition back in to the labeling of the [redacted] The information in these paragraphs provides useful and meaningful data. The data in the [redacted] are from the

Agency's Response:
Based on the data submitted, it is not appropriate to include this statement. There are no clinical correlations upon which to base this information. The [redacted] refers to a [redacted]

Applicant's Response:
Pending

Applicant's Labeling Question 6 from the meeting request dated December 2, 2003:
CLINICAL STUDIES – [redacted]: Mylan believes that combining the Treatment Outcomes table and the Outcomes Definition table is not reader friendly and may cause confusion for the physician. Therefore, we are proposing the [redacted] within this section with the same information. This revision is a format change only.

Agency's Response:
It is recommended that this information be included as a footnote as provided in the Agency's draft labeling. In addition, the two columns of the table should be [redacted] so that "sertaconazole" is in the 1st and 3rd column and "vehicle" is in the 2nd and 4th columns. The [redacted] should also be removed from [redacted]

Applicant's Response:
We agree to make the changes.

Applicant's Labeling Question 7 from the meeting request dated December 2, 2003:
CLINICAL STUDIES – ( ): Inserted the complete cure data for *e. floccosum* so that the "N" for this information now matches the table and in accordance with Labeling Comment #4.

Agency's Response:
Pending. Internal agreement not yet reached. An additional teleconference to discuss *E. floccosum* with the Applicant will be scheduled.

Applicant's Labeling Question 8 from the meeting request dated December 2, 2003:
INDICATIONS AND USAGE – : Deleted the reference to Instead a line has been added to noting that

Agency's Response:
" should remain in the Section of Package Insert.

Applicant's Response:
Agree.

Applicant's Labeling Question 9 from the meeting request dated December 2, 2003:
INDICATIONS AND USAGE – . Re-inserted *e. floccosum* in accordance with Labeling Comment #4.

Agency's Response:
Pending. Internal agreement not yet reached. An additional teleconference to discuss *e. floccosum* with the Applicant will be scheduled.

Applicant's Labeling Question 10 from the meeting request dated December 2, 2003:
PRECAUTIONS – Inserted a See Labeling Comment #8.

Agency's Response:
See response to Labeling Comment # 8.

Applicant's Labeling Question 11 from the meeting request dated December 2, 2003:
ADVERSE EVENTS – At the beginning of the section, inserted "In clinical trials.." in order to properly orientate the reader to the source of the data since this section also contains data on irritation studies and non-US data.

Agency's Response:
Delete and keep "In clinical trials..."

Applicant's Response:
Agree.

Applicant's Labeling Question 12 from the meeting request dated December 2, 2003:
ADVERSE EVENTS – [redacted]. Re-inserted the statement that [redacted] This is a factual statement that provides safety data to the prescribing physician.

Agency's Response:
This sentence should be deleted from the label.

Applicant's Response:
Pending

Applicant's Labeling Question 13 from the meeting request dated December 2, 2003:
ADVERSE EVENTS – [redacted] Revised "[redacted] to "slight [redacted] reaction" to more accurately reflect the data.

Agency's Response:
Accept insertion with change to "...a slight erythematous reaction". Also in the 2nd paragraph of the ADVERSE EVENTS section, change "[redacted] to "In a dermal sensitization study".

A teleconference will be scheduled for this afternoon to discuss the following pending items:

- Inclusion of *E. floccosum* in the Package Insert
- Retention of sertaconazole nitrate as the established name and retention of 2% vs. [redacted]
- Deletion of study start dates provided for Phase 4 Post Marketing Commitments

The Agency asked for agreement that there would be no new edits to the labeling. The Applicant agreed.

The conversation ended amicably.

ADDENDUM: A subsequent teleconference was held at 2:30 P.M., December 4, 2003. The participants were as follows:

Mylan Pharmaceuticals and [redacted]

Frank Sisto, Bertek
Andrea B. Miller, Bertek
James Sherry, Bertek
Peter Bruce Bottini. Bertek
[redacted]

Division of Dermatologic and Dental Drug Products, HFD-540
Stanka Kukich, M.D., Deputy Division Director
Markham Luke, M.D., Ph.D., Clinical Team Leader
Joseph Porres, M.D., Clinical Reviewer
Joel S. Hathaway, Ph.D., Chemistry Reviewer
David Allen, Ph.D., Pharmacology/Toxicology Reviewer
Connie Mahon, Ph.D., Clinical Microbiology Reviewer
Margo Owens, Regulatory Project Manager

This teleconference was requested by the FDA to discuss action items from the 8:30 A.M. conference call on December 4, 2003, regarding the draft labeling for the submitted NDA.

The following discussion took place:

Chemistry
Agency's Comment:
We agree to retain sertaconazole nitrate 2% in the labeling. The equivalency statement should be kept in the labeling and be placed on the carton, container and tube labeling.

Applicant's Response:
We will reflect the equivalency statement in the labeling including the carton, container and tube labeling if space provides (i.e., tube label).

Agency's Response:
All required elements should be included on the carton, container and tube. Graphic elements are not required.

Epidermophyton floccosum
Agency's Comment:
We agree to keep *E. floccosum* in the Microbiology, CLINICAL STUDIES, and INDICATIONS AND USAGE Sections of the Package Insert. In the CLINICAL STUDIES section, the Applicant should add "2 of 13 (15%)" to the 3rd paragraph regarding numbers of patients with *E. floccosum.*

Applicant's Response:
Agree.

Post Marketing Commitments
Agency's Comment:
The study start date for Phase 4 Post Marketing Commitments should be included. These dates can be renegotiated, if needed.

Applicant's Response:
Agree.

The Applicant agreed to submit a revised label based on the discussions during today's teleconference. In addition, a new statement regarding acceptance of the one remaining Post Marketing Commitment will be sent to the Project Manager tomorrow morning.

The conversation ended amicably.

ADDENDUM:

An email was received from the Applicant on December 5, 2003, containing the revised labeling and a statement regarding the Applicant's Post Marketing Commitment.

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

/s/

Stanka Kukich
12/10/03 03:03:24 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration

Rockville MD 20857

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: December 10, 2003 Number of Pages (including cover sheet) – 22

TO: Andrea B. Miller, R. Ph., Esq., Executive Director, Regulatory Affairs
COMPANY: Mylan Pharmaceuticals, Inc.
FAX #: 304-285-6407

MESSAGE: Please find attached to this facsimile transmission a copy of our Action Letter for your NDA 21-385, ERTACZO™ (sertaconazole nitrate) Cream, 2%.

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

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration

Rockville MD 20857

Division of Dermatologic and Dental Drug Products

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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: December 10, 2003 Number of Pages (including cover sheet) – 1

TO: Andrea B. Miller, R. Ph., Esq., Executive Director, Regulatory Affairs
COMPANY: Mylan Pharmaceuticals, Inc.
FAX #: 304-285-6407

MESSAGE: A Informational Request from our Clinical review of your NDA 21-385, ERTACZO™ (sertaconazole nitrate) Cream, 2%, follows:

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

Thank you.

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

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration

Rockville MD 20857

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: December 9, 2003 Number of Pages (including cover sheet) – 18

TO: Andrea B. Miller, R. Ph., Esq., Executive Director, Regulatory Affairs
COMPANY: Mylan Pharmaceuticals, Inc.
FAX #: 304-285-6407

MESSAGE: Please find attached to this facsimile transmission our labeling for your NDA 21-385, ERTACZO™ (sertaconazole nitrate) Cream, 2%.

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

17 Draft Labeling Page(s) Withheld

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration

Rockville MD 20857

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: December 8, 2003 Number of Pages (including cover sheet) – 18

TO: Andrea B. Miller, R. Ph., Esq., Executive Director, Regulatory Affairs
COMPANY: Mylan Pharmaceuticals, Inc.
FAX #: 304-285-6407

MESSAGE: Please find attached to this facsimile transmission our labeling for your NDA 21-385, ERTACZO™ (sertaconazole nitrate) Cream, 2%.

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

17 Draft Labeling Page(s) Withheld

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

FAX COVER

DATE: December 5, 2003

TO: Frank Cross, Senior Regulatory Management Officer
Division of Dermatologic and Dental Drug Products
CDER, FDA

FROM: Andrea B. Miller, R.Ph., Esq.
Director, Regulatory Affairs
Mylan Pharmaceuticals Inc.

RE: NDA 21-385, Sertaconazole Nitrate Cream

Dear Frank:

Please find attached Mylan's request for final approval dated December 5, 2003, to the Agency. A hard copy of this correspondence will be provided via overnight courier.

If you have any questions or comments, please contact the undersigned at the numbers listed below

Regards,

Andrea

PHONE - (800) 826-9526 Ext 6869

FAX - (304) 285-6407

Number of pages including this sheet 34

CONFIDENTIALITY NOTICE

THIS FACSIMILE TRANSMISSION COVER SHEET, AND ANY DOCUMENTS WHICH MAY ACCOMPANY IT, CONTAIN INFORMATION WHICH IS INTENDED ONLY FOR THE USE OF THE INDIVIDUAL OR ENTITY TO WHICH IT IS ADDRESSED, AND WHICH MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND/OR OTHERWISE EXEMPT FROM DISCLOSURE UNDER APPLICABLE LAW. IF THE READER OF THIS MESSAGE IS NOT THE INTENDED RECIPIENT OF THE EMPLOYEE OR AGENT RESPONSIBLE FOR DELIVERING THE MESSAGE TO THE INTENDED RECIPIENT, ANY DISCLOSURE, DISSEMINATION, DISTRIBUTION, COPYING OR OTHER USE OF THIS COMMUNICATION OR ITS SUBSTANCE IS PROHIBITED. IF YOU HAVE RECEIVED THIS COMMUNICATION IN ERROR, PLEASE CALL US COLLECT TO ARRANGE FOR THE DESTRUCTION OF THE COMMUNICATION OR ITS RETURN TO US AT OUR EXPENSE. THANK YOU.

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

December 5, 2003

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products, HFD 540
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
ATTENTION: Central Document Room
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 21-385; SERTACONAZOLE NITRATE CREAM, 2%
Request for Final Approval
(Labeling and Phase IV Commitment Enclosed)

Dear Dr. Wilkin:

Reference is made to the New Drug Application (NDA) identified above that is currently pending final approval, to the Agency's November 25, 2003 facsimile transmissions providing a Phase IV commitments request and proposed final printed labeling, and to Mylan's December 02, 2003 response to the Agency's November 25 correspondence. Reference is also made to telephone conferences between the Agency and Mylan on December 04, 2003. During these telephone conferences the Phase IV requirements and labeling were discussed and agreement was reached regarding these items. Pursuant to these telephone conferences:

1. Mylan commits to the post approval conduct of a dermal carcinogenicity study.

2. Mylan revised the prescribing information and container/carton labeling to reflect the agreements reached between the Agency and Mylan regarding the labeling during the telephone conferences. A draft copy of the labeling is attached.

Based upon the finalization of the labeling and the Phase IV commitment, Mylan respectively respects the consideration of this application for Final Approval of this application. Should you require additional information or have any questions regarding this meeting request, please contact the undersigned at (304) 599-2595, ext. 6869 or via facsimile at (304) 285-6407.

Sincerely,

Andrea B. Miller, R.Ph., Esq.
Executive Director, Regulatory Affairs

Department—Fax Numbers

Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 599-6401
Administration	(304) 599-7284	Legal Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5406	Quality Control	(304) 598-5409
Corporate Services	(304) 598-5404	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 599-5445	Research & Development	(304) 285-6409
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-5232

TABLE OF CONTENTS

SIGNED FDA FORM 356h

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
21-385

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
MYLAN PHARMACEUTICALS INC.	**December 5, 2003**
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(304) 599-2595	**(304) 285-6407**
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
781 Chestnut Ridge Road **P.O. Box 4310** **Morgantown, WV 26504-4310**	**N/A**

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
Sertaconazole Nitrate	**Not Assigned**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)
(±)-1-[2,4-Dichloro-β-[(7-chlorobenzo[b]thien-3yl)methoxy]phenethyl]imidazole nitrate

CODE NAME (*If any*)
TX

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Cream	**2%**	**Topical**

(PROPOSED) INDICATION(S) FOR USE:
The treatment of interdigital tinea pedis caused by dermatophytes.

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER OF DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Submission of Negotiated Labeling and Phase IV Commitment

PROPOSED MARKETING STATUS *(check one)* ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED **1** THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

ATTACHMENT 1

FINAL DRAFT PRESCRIBING INFORMATION, CARTON LABELING AND TUBE LABELING

29 Draft Labeling Page(s) Withheld

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

December 2, 2003

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products, HFD 540
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
ATTENTION: Central Document Room
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 21-385; SERTACONAZOLE NITRATE CREAM, 2%
REQUEST FOR A TELEPHONE CONFERENCE

Dear Dr. Wilkin:

Reference is made to the New Drug Application (NDA) identified above that is currently pending final approval and to the Agency's November 25, 2003 facsimile transmissions providing a Phase IV commitments request and proposed final printed labeling. Pursuant to these correspondences, Mylan would like to request a telephone conference with the Division to discuss the Phase IV commitments and proposed labeling. In preparation for this telephone conference, please find attached the specific items Mylan would like to discuss during the telephone conference.

Phase IV Commitments:

1. Mylan would like to seek the Agency's rationale for the request for a Phase IV commitment to

We believe that the current application has sufficient information to describe the potential systemic absorption of sertaconazole. As noted in our October 9, 2003 amendment, Mylan conducted and submitted a bioavailability study of sertaconazole nitrate in patients with tinea pedis and tinea cruris. The total lesion areas in this study ranged from 42-140 cm^2 for the interdigital *tinea pedis* patients and cm^2 for *tinea cruris* patients. Even with the skin area as large as no detectable plasma sertaconazole concentration was found in any of the patients studied with the exception of patient No. 002, who had only one measurable concentration of ng/mL on the 6th day of the drug application. The results indicated that the sertaconazole cream was not absorbed. In addition to the larger surface area in patients with tinea cruris, absorption of drugs is greatest from the groin area.

Mylan designed and conducted the bioavailability study in tinea pedis and tinea cruris after such a study was requested by the Division at the June 23, 1997 End of Phase II Meeting between Mylan and the Agency. During that meeting, the Agency noted that: "...tinea corporis or tinea versicolor can involve much greater body surface area, a PK study for tinea corporis or tinea versicolor may support the indication of interdigital tinea pedis." A copy of the Agency's minutes from this meeting is attached. The bioavailability study in tinea pedis and tinea cruris that was submitted in the NDA mets the requirements of study requested by the Agency in the EOPII meeting and adequately describes the

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Business Development	(304) 598-5419	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Corporate Services	(304) 598-5404	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6409
Human Resources	(304) 598-5406	Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

systemic absorption of sertaconazole under maximal use. Accordingly, Mylan does not believe an additional bioavailability study is necessary.

[redacted]

3. Mylan commits to the conduct of a dermal carcinogenicity study.

4. Regarding the commitment dates provided for each commitment, Mylan questions the requirement for a commitment for a study start date. Generally, Phase IV commitments only contain a protocol submission date and final report submission date as part of the commitment since the study start may be delayed while the Agency and the sponsor finalizes and approves the protocol. The protocol submission and final report submission dates are the two most critical date in meeting the commitment. Accordingly, Mylan is requesting that the Agency only require the protocol submission date and final report submission date as part of the commitment.

Labeling:

Revised labeling is attached. The additions are noted in blue text and the deleted text is noted in a box in the margin.

1. Mylan requests that the Agency reconsider its request to rename the product to ERTACZO [redacted] Since this product is a topical product, the actual drug product at the site of action is sertaconazole nitrate and not sertaconazole. Therefore, we propose that the product retain ERTACZO (sertaconazole nitrate) Cream, 2%.

2. **CLINICAL PHARMACOLOGY: Pharmacokinetics -** [redacted] Mylan would like to discuss the removal of the first paragraph regarding the [redacted] While this study was not on diseased skin, it does reflect absorption in diseased skin and provides meaningful clinical data. Added text is noted in red type in the attached labeling.

3. **Activity *In Vitro* -** [redacted]): Mylan is proposing the addition back in to the labeling of the two paragraphs regarding the *in vitro* activity of sertaconazole. The information in these paragraphs provides useful and meaningful data. The data in the first paragraph are from the recently conducted study on the clinical isolates. These studies were previously requested by the Agency [redacted]

4. **Activity *In Vivo* –** [redacted] Mylan re-inserted *Epidermophyton floccosum* as a clinical isolate both in this section and in the INDICATION section ([redacted] Mylan requests that the Agency reconsider its position on *e. floccosum*. While the numbers of patients with *e. floccosum* tinea pedis exposed to sertaconazole in the clinical program is small (13), it is representative of the general population and the populations studied in prior antifungal application. As presented in Mylan's April 19, 2002 amendment, Mylan believes the Agency is providing a different review standard to this application than previously approved antifungals that included *e. floccosum* in their labeling despite have similarly low numbers of patients with *e. floccosum* tinea pedis. The data support this position presented in our April 19, 2002 amendment is extracted below:

This request is inconsistent with previous discussions between the Division and Mylan and is inconsistent with the Division's previous labeling/approval requirements for recently approved treatments for tinea pedis.

The primary etiologic agent of tinea pedis is *Trichophyton rubrum*, typically 70% or more of isolates from culturally confirmed tinea pedis are *T. rubrum*. Two other dermatophytes are responsible for the balance of tinea pedis infections, *T. mentagrophytes*, which typically is isolated 20-25% of the time, and *Epidermophyton floccosum*, which is isolated at a rate of 1-9%. Randomized clinical trials of antifungals in the treatment of tinea pedis typically reflect the epidemiology described above.

Since the majority of tinea pedis patients are infected by *T. rubrum*, statistical analysis of subsets defined by infectious organism would not be adequately powered without conduction of studies that were unreasonably overpowered for the primary organism. Subset analyses by causative organism were not included in the statistical plans discussed with the Division prior to initiation of Phase III trials. Furthermore, the meeting minutes of the End-of-Phase II meeting and subsequent IND correspondence supports the conclusion that analysis of a single cohort including all causative organisms was envisioned both by Mylan and the Division. The fact that the Agency did not plan subanalysis by organism as a requirement is evident through correspondence showing that the Division noted that only 100 patients per treatment arm be included based on its original power analyses. The Agency recommended number of patients was less than that proposed by Mylan and much less than that needed to support the statistical analysis of subsets defined by infectious organism.

Assuming a Complete Cure rate (all signs and symptoms resolved plus negative KOH and negative culture) of 30% in the active group and 10% in the vehicle group, (a cure rate equal to or better than that achieved by approved topical antifungal products), in order to achieve statistical significance with 80% power in a subset of subjects with *E. floccosum*, 72 subjects per group would be required *(nQuery Advisor, version 4.0)*. Achieving 72 subjects per group for an organism that may be the etiologic agent in only 6% of cases of tinea pedis requires 2400 subjects in the MITT population. An even larger number of subjects would need to be enrolled in the study to assure 2400 subjects with culturally confirmed tinea pedis in the MITT population.

As with other anti-infectives, demonstration of efficacy against less common pathogens that occur in a clinical study with approximately the same frequency as they occur in the general population has been sufficient to allow the organism to be included in product labeling for antifungal products. This analytical technique has been accepted by the Division for the approvals of Mentax® (butenafine HCl) Cream, 1% for the treatment of interdigital tinea pedis and Lamisil® (terbinafine HCl) Cream, 1% for the treatment of interdigital tinea pedis and plantar type tinea pedis. Thus the sponsor is requesting the same analytical technique be accepted for this NDA.

As shown in Table 1, both Sertaconazole Nitrate Cream, 2% studies (SER-960602 and SER-960603) included patients with positive dermatophyte cultures in a prevalence that was consistent with that described in literature and with that included in the primary efficacy trials of the products described above.

Table 1
Frequency Distribution of Pathogens in Tinea Pedis Studies

	T. rubrum	*T. mentographytes*	*E. floccosum*	Other
Literature [1,2,3]	≥ 70%	20-25%	1 – 9%	
Sertaconazole Nitrate Cream, 2% (NDA #21-385) for the treatment of interdigital tinea pedis				
ISE Table 8.7.9 Combined Studies SER-960602 & SER-960603	154 (79%) SER 148 (79%) vehicle 302 (79%) total	27 (14%) SER 27 (15%) vehicle 54 (14%) total	13 (7%) SER 13 (7%) vehicle 26 (11%) total	1 (1%) SER 0 (0%) vehicle 1 (<1%) total
Mentax®[7] 4 week qd (NDA #20-524) for the treatment of interdigital tinea pedis				
PDC 010-001	42 (79%) BUT 47 (89%) vehicle 89 (84%) total	7 (13%) BUT 5 (9%) vehicle 12 (11%) total	4 (8%) BUT 1 (2%) vehicle 5 (5%) total	N/A
PDC 010-002	38 (95%) BUT 36 (88%) vehicle 74 (91%) total	1 (3%) BUT 3 (7%) vehicle 4 (5%) total	1 (3%) BUT 0 (0%) vehicle 1 (1%) total	0 (0%) BUT 2 (2%) vehicle 2 (2%) total
Mentax®[8] 1 week bid (NDA #20-524) for the treatment of interdigital tinea pedis				
PDC 010-014	107 (88%) BUT 109 (87%) vehicle 216 (88%) total	9 (7%) BUT 14 (11%) vehicle 23 (9%) total	4 (3%) BUT 3 (2%) vehicle 7 (3%) total	1 (<1%) BUT 0 (0%) vehicle 1 (<1%) total
PDC 010-015	102 (77%) BUT 118 (85%) vehicle 220 (81%) total	20 (15%) BUT 12 (9%) vehicle 33 (12%) total	8 (6%) BUT 4 (3%) vehicle 12 (4%) total	2 (2%) BUT 4 (3%) vehicle 6 (2%) total
Lamisil®[*9] (NDA #20-192) 1 week bid for the treatment of interdigital tinea pedis				
Study 2-1	26 (79%) TER 29 (85%) vehicle 55 (82%) total	3 (9%) TER 4 (12%) vehicle 7 (10%) total	3 (9%) TER 1 (3%) vehicle 4 (6%) total	0 (0%) TER 1 (3%) vehicle 1 (1%) total
Study 2-2	32 (68%) TER 35 (78%) vehicle 67 (73%) total	8 (18%) TER 11 (23%) vehicle 19 (21%) total	4 (9%) TER 2 (4%) vehicle 6 (7%) total	0 (0%) TER 1 (1%) vehicle 1 (1%) total
Lamisil®[*9] (NDA #20-192) 2 week bid for the treatment of plantar type tinea pedis				
Study 2509-01	47 (96%) TER 44 (94%) vehicle 91 (95%) total	1(2%) TER 2 (4%) vehicle 3 (3%) total	1(1%) TER 1 (1%) vehicle 2 (2%) total	N/A
Study 2509-02	39 (81%) TER 39 (80%) vehicle 78 (80%) total	9 (19%) TER 9 (19%) vehicle 18(19%) total	0 (0%) TER 1 (2%) vehicle 1 (2%) total	N/A

SER: sertaconazole nitrate
BUT: butenafine HCl
TER: terbinafine HCl
*Lamisil® is a registered trademark of Novartis.

As demonstrated in Tables 2, 3 and 4, mycological cure rates for the less common organisms are generally comparable to those of *T. rubrum*. Mycological cure is defined as a negative KOH and negative cultures.

Table 2
Mycological Cure Rates of Tinea Pedis Pathogens at the End of Study
MITT Population

	T. rubrum		T. mentagrophytes		E. floccosum	
	BUT	*Vehicle*	*BUT*	*Vehicle*	*BUT*	*Vehicle*
Mentax®[10] 4 week qd (NDA #20-524)						
PDC 010-001	36/42 (86%)	18/47 (38%)	5/7 (71%)	2/5 (40%)	3/4 (75%)	0/1 (0%)
PDC 010-002	31/38 (82%)	11/36 (31%)	1/1 (100%)	2/3 (66%)	1/1 (100%)	0/0 (0%)
Mentax®[11] 1 week bid (NDA #20-524)						
PDC 010-014	91/107 (85%)	18/109 (17%)	8/9 (89%)	5/14 (36%)	3/4 (75%)	0/3 (0%)
PDC 010-015	78/102 (76%)	23/118 (19%)	15/20 (75%)	7/13 (54%)	4/8 (50%)	0/4 (0%)

BUT: butenafine HCl

Table 3
Mycological Cure Rates of Tinea Pedis Pathogens at the End of Study
MITT (FDA) Last Observation Carried Forward

	T. rubrum		T. mentagrophytes		E. floccosum	
	SER	*Vehicle*	*SER*	*Vehicle*	*SER*	*Vehicle*
Sertaconazole Nitrate Cream, 2% (NDA #21-385)						
SER 960602	44/76 (58%)	16/77 (21%)	5/10 (50%)	2/7 (29%)	6/10 (60%)	2/8 (25%)
SER 960603	63/80 (79%)	15/77 (20%)	10/18 (56%)	5/20 (25%)	1/3 (33%)	0/5 (0%)
Combined SER 960602 & SER 960603	107/156 (69%)	31/154 (20%	15/28 (54%)	7/27 (26%)	7/13 (54%)	2/13 (15%)

Source: SER-960602 Table EFF.10.7, SER-960603 Table EFF.10.7, SER-960602 and SER-960603 Table EFF.10.7, submitted in an amendment dated March 7, 2002 per FDA request of February 12, 2002
SER: sertaconazole nitrate

Table 4
Mycological Cure Rates of Tinea Pedis Pathogens at the End of Study
MITT (FDA) Missing Value = Failure

	T. rubrum		T. mentagrophytes		E. floccosum	
	SER	Vehicle	SER	Vehicle	SER	Vehicle
Sertaconazole Nitrate Cream, 2% (NDA #21-385)						
SER 960602	37/76 (49%)	15/77 (20%)	5/10 (50%)	2/7 (29%)	6/10 (60%)	1/8 (13%)
SER 960603	60/80 (75%)	15/77 (20%)	10/18 (56%)	5/20 (25%)	1/3 (33%)	0/5 (0%)
Combined SER 960602 & SER 960603	97/156 (62%)	30/154 (20%)	15/28 (54%)	7/27 (26%)	7/13 (54%)	1/13 (8%)

Source: SER-960602 Table EFF.10.8, SER-960603 Table EFF.10.8, SER-960602 and SER-960603 Table EFF.10.8, submitted in an amendment dated March 7, 2002 per FDA request of February 12, 2002
SER: sertaconazole nitrate

5. [redacted]. Mylan is proposing the addition back in to the labeling of the [redacted] The information in [redacted] provides useful and meaningful data. The data in the [redacted] are from the recently conducted study on the clinical isolates.

6. **CLINICAL STUDIES** – : : Mylan believes that combining the Treatment Outcomes table and the Outcomes Definition table is not reader friendly and may cause confusion for the physician. Therefore, we are proposing the

7. **CLINICAL STUDIES** – : Inserted the complete cure data for *e. floccosum* so that the "N" for this information now matches the table and in accordance with Labeling Comment #4.

8. **INDICATIONS AND USAGE** – . . Deleted the reference to Instead a has been added to

9. **INDICATIONS AND USAGE** – ' Re-inserted *e. floccosum* in accordance with Labeling Comment #4.

10. **PRECAUTIONS** – (Page 4, line 82): Inserted a See Labeling Comment #8.

11. **ADVERSE EVENTS** – (Page 7, line 139): At the beginning of the section, inserted "In clinical trials.." in order to properly orientate the reader to the source of the data since this section also contains data on irritation studies and non-US data.

12. **ADVERSE EVENTS** – (Page 7, line 144): Re-inserted the statement that This is a factual statement that provides safety data to the prescribing physician.

13. **ADVERSE EVENTS** – (Page 7, line 145): Revised ' to "slight erythema reaction" to more accurately reflect the data.

It is our understanding that a tentative telephone conference time has been scheduled for Thursday, December 4, 2003 at 8:00 am. Please advise if the meeting time has changed. A toll free call in number will be forwarded to you. Should you require additional information or have any questions regarding this meeting request, please contact the undersigned at (304) 599-2595, ext. 6869 or via facsimile at (304) 285-6407.

Sincerely,

Andrea B. Miller, R.Ph., Esq.
Executive Director, Regulatory Affairs

TABLE OF CONTENTS

SIGNED FDA FORM 356h

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY
APPLICATION NUMBER
21-385

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
MYLAN PHARMACEUTICALS INC.	**December 4, 2003**
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(304) 599-2595	**(304) 285-6407**
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
781 Chestnut Ridge Road **P.O. Box 4310** **Morgantown, WV 26504-4310**	**N/A**

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
Sertaconazole Nitrate	**Not Assigned**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)
(±)-1-[2,4-Dichloro-β-[(7-chlorobenzo[b]thien-3yl)methoxy]phenethyl]imidazole nitrate

CODE NAME (*If any*)
TX

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Cream	**2%**	**Topical**

(PROPOSED) INDICATION(S) FOR USE:
The treatment of interdigital tinea pedis caused by _____

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER OF DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Request for Telephone Conference

PROPOSED MARKETING STATUS *(check one)* ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED_____ THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

ATTACHMENT 1

END OF PHASE 2 MEETING MINUTES
JUNE 23, 1997

MINUTES FOR END OF PHASE 2 MEETING FOR IND 50,726 ARE PROVIDED ELSEWHERE IN CORRESPONDENCE SECTION OF THIS REVIEW

ATTACHMENT 2

SERTACONAZOLE REVISED LABELING

11 Draft Labeling Page(s) Withheld

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration

Rockville MD 20857

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: November 25, 2003 Number of Pages (including cover sheet) – 19

TO: Andrea B. Miller, R. Ph., Esq., Executive Director, Regulatory Affairs
COMPANY: Mylan Pharmaceuticals, Inc.
FAX #: 304-285-6407

MESSAGE: Please find attached to this facsimile transmission our labeling for your NDA 21-385, ERTACZO™ (sertaconazole) Cream,

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

16 Draft Labeling Page(s) Withheld

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration

Rockville MD 20857

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: November 25, 2003 Number of Pages (including cover sheet) – 2

TO: Andrea B. Miller, R. Ph., Esq., Executive Director, Regulatory Affairs
COMPANY: Mylan Pharmaceuticals, Inc.
FAX #: 304-285-6407

MESSAGE: Please commit to the following Post Marketing Commitments for your NDA 21-385, ERTACZO™ (sertaconazole) Cream,

1. Commitment/Study Description: 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.").

   Commitment Category: Non-Clinical Toxicology:

Protocol Submission:	by March 10, 2004.
Study start:	by December 10, 2004
Final report submission:	by December 10, 2007

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

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

October 24, 2003

RECEIVED
OCT 27 2003
MEGA/CDER

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products, HFD 540
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
ATTENTION: Central Document Room
9201 Corporate Boulevard
Rockville, MD 20850

ELECTRONIC LABELING
ORIG AMENDMENT

RE: NDA 21-385; ERTACZO™ (sertaconazole nitrate) CREAM, 2%
RESPONSE TO AGENCY'S TELEPHONE REQUEST OF OCTOBER 17, 2003
Electronic Labeling

Dear Dr. Wilkin:

Reference is made to the New Drug Application (NDA) cited above that was submitted to the Agency on September 28, 2001 and to the Mylan's Amendment on October 9, 2003. Reference is also made to the Agency's October 17, 2003 telephone request for an electronic copy of the labeling submitted in the October 09, 2003 Amendment. Accordingly, the electronic copy of the tube labeling, carton labeling and prescribing information is provided with this amendment. In addition, an electronic copy of the annotated labeling is also provided. The electronic copies of the labeling provided with this amendment are exact versions of the draft labeling submitted in the October 09, 2003 amendment.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6869 or via facsimile at (304) 285-6407.

Sincerely,

Andrea B. Miller, R.Ph., Esq.
Executive Director, Regulatory Affairs

Enclosures

ORIGINAL

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 598-5411
Corporate Services (304) 598-5404
Human Resources (304) 598-5406
Information Systems (304) 285-6404
Label Control (800) 848-0463
Legal Services (304) 598-5408
Marketing (304) 598-5411
Medical Unit (304) 598-5445
Product Development (304) 285-6411
Purchasing (304) 598-5401
Quality Assurance (304) 598-5407
Quality Control (304) 598-5409
Regulatory Affairs (304) 285-6407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

19 Draft Labeling Page(s) Withheld

MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

October 9, 2003

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products, HFD 540
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
ATTENTION: Central Document Room
9201 Corporate Boulevard
Rockville, MD 20850

NDA AMENDMENT
— FORMULATION
CLASS 1 RESUBMISSION

RE: NDA 21-385; ERTACZO™ (sertaconazole nitrate) CREAM, 2%
RESPONSE TO AGENCY'S JULY 26, 2002 APPROVABLE LETTER

Dear Dr. Wilkin:

Reference is made to the New Drug Application (NDA) cited above that was submitted to the Agency on September 28, 2001 and to the Agency's July 26, 2002 approvable letter. A copy of the Agency's July 26, 2002 approvable letter is provided in Attachment 1 for the reviewer's reference. At this time Mylan is amending the application to provide for the — Free formulation. Accordingly and in response to the Agency's approvable letter, Mylan wishes to amend this application as described in this correspondence.

This amendment provides a complete response to the deficiencies/comments outlined in the Agency's July 26, 2002 approvable letter. Thereby, this response constitutes a resubmission. Pursuant to the Agency's Guidance for Industry entitled "*Classifying Resubmissions in Response to Action Letters (April 1998)*", Mylan is requesting that this response be designated as a Class 1 Resubmission. This amendment provides revised labeling, a safety update, responses to the Agency's proposed Phase IV studies, updated stability data and other minor information clarifying the revision to the —-free formulation. All the items provided in this amendment are described in the Guidance as the type of items permitted in a Class 1 Resubmission. This response does not contain items that would change the designation to a Class 2 Resubmission; no clinical studies, no item that would warrant presentation to an advisory committee nor no new information that would require re-inspection is provided in this response.

A. APPROVAL ISSUES:

FDA COMMENT 1. [redacted]

MYLAN RESPONSE: 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 formulation) is the same as that used to dose the pivotal clinical trials submitted in support of the referenced application, the need for a [redacted] is no longer necessary.

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

MYLAN RESPONSE: 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.

B. PROPOSED PHASE IV COMMITMENTS:

Pharmacology/Toxicology:

FDA COMMENT 1. A dermal carcinogenicity study is needed.

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.")

MYLAN RESPONSE: Based on the reasons elaborated below, Mylan does not believe that a dermal carcinogenicity study is required for sertaconazole nitrate cream, 2% and thereby is seeking clarification from the Agency as to why the Agency is requesting that Mylan conduct a dermal carcinogenicity study with sertaconazole nitrate cream, 2%:

1. The duration of administration of sertaconazole nitrate cream, 2% in the treatment of the proposed indication, tinea pedis, is for a relatively short period (4-weeks). This treatment period is considerably less than the treatment period of 3 to 6 months identified in the ICH guidelines that would prompt the need for carcinogenicity testing.

2. Sertaconazole nitrate cream, 2% is not expected to be used frequently in the intermittent treatment of tinea pedis. Although tinea pedis may recur in some patients throughout the patient's lifetime, the recurrence rate and frequency of treatment is much less than the frequent, intermittent treatment of recurrent depression, anxiety, and allergic rhinitis described in the guidance. Furthermore, sertaconazole's use pattern is not likely to be more frequent than other imidazole antifungals that have been approved for topical use. Based upon the approved labeling, most of the other antifungals appear to have not been required to be tested for their carcinogenic potential.

3. There is no significant reason to consider that sertaconazole has a potential for causing tumors. The imidazole class of topical antifungals have not been associated with tumor formation nor is there is any indication that this class has a potential for causing genetic damage. Furthermore, there is no indication that sertaconazole itself causes genetic damage. Testing of sertaconazole in rats and dogs by the topical route for approximately 90 days did not reveal local or systemic changes that are considered precancerous. Changes at the site of application were typical of those associated with mild irritation. The changes in the skin were not progressive and appeared to decrease with time. Similarly, in six-month oral studies in the rat and dog relatively high levels of

systemic exposure (approximately 46% absorption after oral dosing as compared to 18% absorption after dermal dosing) did not cause systemic changes that could be considered precancerous.

Accordingly, Mylan does not believe that a dermal carcinogenicity is warranted and respectfully requests that the Agency reconsider its request for a Phase IV dermal carcinogenicity study. If necessary, Mylan would like to request a telephone conference with the appropriate FDA staff members to further discuss this request.

2 Page(s) Withheld

C. OTHER RECOMMENDATIONS:

Mylan acknowledges that the cover letter should unambiguously identify the proposed to-be-marketed formulations (i.e., — -containing or — -free). As noted in the introductory paragraph, Mylan has chosen to proceed with the — -free formulation as the proposed market formulation.

Mylan also acknowledges that while not approvability issues for the — containing formulation, the following issues have been identified and, if the — free formulation is chosen, should be addressed in future submissions for the — free formulation of ERTACZO™ Cream, 2%. Since Mylan has chosen to proceed with the — free formulation, the following items are addressed in this amendment.

Chemistry, Manufacturing and Controls Issues:

FDA COMMENT 1. The drug substance specification contains a — which does not conform to the recommendation in ICH Q3A, Impurities in New Drug Substances.

Since — impurities — (assuming a maximum daily dose of 100 mg of sertaconazole nitrate) have been identified as — the specification should be revised to specify these impurities individually, as well as to include an acceptance criterion of — for any unspecified impurity.

MYLAN RESPONSE: Mylan acknowledges the Agency's comments and have updated our specifications to include the individual impurities. The [redacted] impurity [redacted] will be controlled for as a known impurity in the drug substance specifications and not in the drug product since it is only a [redacted] impurity. The impurities [redacted] will be controlled for as known impurities in the drug substance and drug product sections since they are [redacted]. The updated drug substance specifications are as follows and are provided in Attachment 7:

[redacted]	NMT [redacted]
[redacted]	NMT [redacted]
[redacted]	NMT [redacted]
Any Unspecified Impurity	NMT [redacted]
Total Impurities	NMT [redacted]

In addition, Mylan is amending the application to provide for DPT as the testing laboratory responsible for releasing drug substance.

FDA COMMENT 2. The drug product regulatory and stability specifications contain a quality test for " [redacted] which does not conform to the recommendation in ICH Q3B, Impurities in New Drug Products. Since [redacted] impurities [redacted] (assuming a maximum daily dose of 100 mg of sertaconazole nitrate) have been identified as [redacted], the specification should be revised to specify these impurities individually, as well as to include an acceptance criterion of [redacted] for any unspecified impurity. The recommended section is shown here:

Test	Acceptance Criterion	Procedure
[redacted]		73.5126
[redacted]	NMT [redacted]	
[redacted]	NMT [redacted]	
[redacted]	NMT [redacted]	
Any Individual Unspecified Impurity	NMT [redacted]	
Total	NMT [redacted]	

MYLAN RESPONSE: Mylan acknowledges the Agency's request to include specified impurities for the drug product. As requested, the drug product specifications have been updated to include limits for the known impurities and specified impurities that Mylan has seen throughout the primary stability program. It is important to note that the drug product lots used as the primary stability data are the same lots which were used in Mylan's pivotal clinical studies. An expert report has been prepared by [redacted] to characterize the specified impurities that are seen in the drug product. A copy of the report "Identification of Impurities in Sertaconazole Nitrate Cream 2%" is included in Attachment 8. The proposed specifications for the drug product are as follows and are provided in Attachment 9:

—		NMT —
—		NMT —
Any Specified Impurity	—	NMT —
Any Specified Impurity	—	NMT —
Any Unspecified Impurity		NMT —
Total Impurities		NMT —

In addition, the method for the Assay of ... — method has been provided in Attachment 10. The specifications were established based upon the observed stability data. A copy of the updated stability data is contained in Attachment 11.

FDA COMMENT 3. The "Description" test acceptance criterion for drug product is listed as — This should be revised to declare the actual observation, i.e., — This is required to allow detection of changes during storage. The corresponding metho — should be revised accordingly.

MYLAN RESPONSE: The test acceptance criterion for the drug product Description has been revised to record the actual observation. Revised drug product specifications are provided in Attachment 9.

FDA COMMENT 4. The "Identification" test acceptance criterion for drug product is listed as — This should be revised to declare the actual observation, i.e., the — This is necessary to allow detection of changes during storage. The corresponding method — should be revised accordingly.

MYLAN RESPONSE: The test acceptance criterion for the drug product Identification has been revised to record the actual observation. Identification testing is —

Revised drug product specifications are provided in Attachment 9.

FDA COMMENT 5. Updated stability data for the drug product's primary stability lots submitted in the NDA should be provided. The data from the stability studies performed at — which reportedly showed incompatibility of the drug product with these conditions, should be provided to justify your decision to study the drug product only under the intermediate conditions.

MYLAN RESPONSE: With this amendment, the primary stability lots are the lots manufactured without — Updated stability for these primary stability lots are provided in Attachment 11. — of real time stability data at room temperature and — of accelerated (30°C/60%RH) are provided on the primary stability lots to support the proposed expiration date of 24 months.

In the initial development work conducted by — on sertaconazole nitrate cream 2%, they determined that sertaconazole nitrate cream 2% losses consistency and increases fluidity when maintained at — Data obtained from — from a — batch manufactured in 1986 is shown in the following table.

		Data			
Time (months)	Appearance	Purity HPLC (%)	Viscosity (cps)	pH	Density (g/mL)

Based upon information, Mylan discontinued studies at conditions (at) in lieu of the intermediate conditions at 30°C and 60% RH that were presented in the NDA.

FDA COMMENT 6. The protocol for selection of units of the finished drug product for release testing should be described in the master batch record.

MYLAN RESPONSE: The proposed master batch record details the , of the bulk material. The packaging module defines the packaging of the finished product. Samples for finished drug product release testing will be selected the finished drug product. Provided in Attachment 12 are Sampling Logs for the 2 gm, 15 gm and 30 gm tubes that will be provided with each completed packaging module. The Sampling Log notes

FDA COMMENT 7. The UV-Visible absorption spectrum of sertaconazole nitrate drug substance should be submitted for reference.

MYLAN RESPONSE: A full page UV-Visible scan of sertaconazole nitrate drug substance from Interquim is provided in Attachment 13.

FDA COMMENT 8. A revised master batch manufacturing procedure, deleting the from the formulation is needed.

MYLAN RESPONSE: Pursuant to Mylan's decision to proceed with the free formulation, DPT, the contract manufacturing site, has revised the representative master batch record to delete and associated references from the master batch record. A copy of the revised representative master batch record is provided in Attachment 14.

FDA COMMENT 9. A revised finished drug product specification, which omits the is needed.

MYLAN RESPONSE: The finished drug product specifications have been revised to delete the A copy of the revised finished drug product specifications is provided in Attachment 9.

FDA COMMENT 10. Revisions to the carton, container, and package insert labeling to remove the reference to [redacted] in the list of ingredients should be addressed in the revised draft labeling.

MYLAN RESPONSE: References to the inactive ingredient [redacted] has been delete from all product labeling: carton, tube and prescribing information. Four draft copies of the carton labeling, tube labeling and prescribing information is provided in Attachment 2.

FDA COMMENT 11. Revised qualitative and quantitative statements of composition are needed.

MYLAN RESPONSE: The revised qualitative and quantitative statements of composition deleting reference to [redacted] are provided in Attachment 15.

FDA COMMENT 12. A revision to indicate that the supporting stability data submitted in the NDA would be considered as the primary data, and the data derived from [redacted] containing lots would be considered supporting lots.

MYLAN RESPONSE: As previously noted, Mylan requests that the application be amended to designate Lots K4, L1 and L3 (these lots did not contain [redacted] in the formulation) as the primary stability data. In addition, Mylan requests that the lots previously identified as primary stability data that contained [redacted], in the formulation as noted below, now be considered as supportive stability data.

Lot No.	Date of Manufacture	Batch Size	Packaging
NGB	6/29/99	[redacted]	2 gram
NGB-1			15 gram
NGB-2			30 gram
NGC	6/29/99	[redacted]	2 gram
NGC-1			15 gram
NGC-2			30 gram
NHIN	8/18/99	[redacted]	2 gram
NHIN-1			15 gram
NHIN-2			30 gram

A post approval stability protocol is provided in Attachment 16.

Safety Issues:

FDA COMMENT 1. Describe in detail any significant changes or findings in the safety profile.

MYLAN RESPONSE: As described in the May 22, 2002 NDA Safety Update, no new studies have been conducted or initiated in the United States 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 pharmacovigilance survey conducted by Ferrer Internacional since that submitted on May 22, 2002 and in the review of published literature. Ferrer's most current Periodic Safety

Update Report for sertaconazole (January 1, 1998 to January 1, 2003) is provided in Attachment 17.

FDA COMMENT 2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

MYLAN RESPONSE: Since the May 22, 2002 NDA Safety Update there is no new safety data to incorporate and no additional clinical studies have been conducted.

FDA COMMENT 3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

MYLAN RESPONSE: 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.

FDA COMMENT 4. Provide 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. In addition, provide narrative summaries for serious adverse events.

MYLAN RESPONSE: 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 a study or withdrew from a study due to an adverse event.

FDA COMMENT 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

MYLAN RESPONSE: Subsequent to the filing of the NDA safety update in May 2002 no new safety data has been obtained.

FDA COMMENT 6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

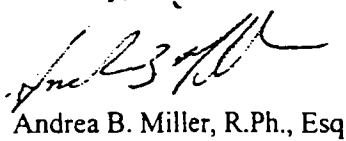
MYLAN RESPONSE: Ferrer's Periodic Safety Update Report summarizing the worldwide experience with sertaconazole is provided in Attachment 17.

FDA COMMENT 7. Provide English translations of current approved foreign labeling not previously submitted.

MYLAN RESPONSE: The Ferrer's current Core Safety Data Sheet is provided in their Periodic Safety Update Report in Attachment 17.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6869 or via facsimile at (304) 285-6407.

Sincerely,



Andrea B. Miller, R.Ph., Esq.
Executive Director, Regulatory Affairs

Enclosures

ATTACHMENT 3

REDLINED, ANNOTATED PRESCRIBING INFORMATION

17 Draft Labeling Page(s) Withheld