# MEDICAL CERTIFICATION REGARDING EUROPEAN REPORT OF HEPATITIS

14 November 2002

To: [redacted]

From: [redacted]

25-year-old patient (woman).

She was admitted to the Digestive Unit of [redacted] Hospital at the end of July 1996 on account of an **acute hepatitis** whose etiology was not determined. The patient was seronegative for HBV HAV, HCV, EBV, and Q fever, and no previous treatment with hepatotoxic drugs was reported. She was discharged from hospital after a good clinical and analytical progress was confirmed.

In November 1996 she was readmitted again because of an important **cholestatic hepatitis** with documented severe liver failure. The etiologic examination did not reveal any data of interest and viral serologic tests remained negative.

Due to the bad clinical course of the disease, the patient was then taken to [redacted] for liver transplant assessment. The etiologic examination in this hospital did not show any intake of hepatotoxic drugs and viral serologic tests were negative. Corticoid therapy was established, and there was an improvement in clinical and analytical data.

In December 1996 the patient was transferred to [redacted] Hospital again for follow-up study. As coagulation had improved, a liver biopsy was performed, and the histological findings were: "a marked modification of the lobular architectonics due to a portal fibrosis that connects to underlying portal structures and centrolobular veins; a marked pericelular sclerosis accompanied by a biliary ductal neoformation with cholestatic complications represented by bile thrombi; parenchyma shows a nodular disposition without complete delimitation due to the fibrosis, and remarkable regenerative and degenerative feathery changes due to the cholestasis.

Final anatomicopathological diagnosis was **precirrhotic-stage heparitis of probable alcohol toxic etiology complicated by a marked cholestasis.**

Data on hepatitis secondary to drug toxicity were never found

1 Page(s) Withheld

9 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: September 10, 2002 Number of Pages (including cover sheet) – 4

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

MESSAGE: Please find attached to this facsimile transmission our minutes of our March 8, 2002, Teleconference regarding your NDA 21-385, ERTACZO™ (sertaconazole nitrate) Cream, 2%

Thank you.

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

Teleconference Date: March 8, 2002 Time: 1200 Location: N225

NDA 21-385, sertaconazole nitrate cream, 2%

Treatment of Interdigital Tinea pedis

Sponsor: Mylan Pharmaceuticals, Inc.

Purpose of Teleconference: Conveyance of Tentative Agency Efficacy Review Results

Meeting Chair: Jonathan K. Wilkin, M.D.,

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Markham Luke, M.D., Ph.D., Acting Clinical Team Leader, DDDDP, HFD-540
Joseph Porres, M.D., Ph.D., Medical Officer, DDDDP, HFd-540
Mohamed Alosh, Ph.D., Biostatistics Team Leader, DOBIII, HFD-725
Kathleen Fritsch, Ph.D., Biostatistician, DOBIII, HFD-725
Frank H. Cross, Jr., M.A., CDR, DDDDP, HFD-540

Applicant Attendees, titles and offices:

Andrea B. Miller, R.Ph., Manager, Regulatory Affairs, Mylan Pharmaceuticals, Inc.
P. Bruce Bottini, Pharm.D., Director, Clinical Research

Agency:

The Agency informed the Applicant that at this point in the review cycle of this NDA, there appears to be insufficient efficacy information to include Trichophyton mentagrophytes in the list of causative organisms in the Indications and Usage Section of the Package Insert.

Applicant:

The Applicant inquired if their submission of supportive in vitro data would assist the Agency in determining the efficacy of sertaconazole nitrate cream, 2%, vs. T. mentagrophytes.

Agency:

The Agency said that in general, in vitro data is not as compelling as clinical information.

Applicant:

The Applicant said that other products have been approved for the indication of T. pedis with the inclusion of the T. mentagrophytes and Epidermophyton floccosum organisms with the same quality and quantity of information as that contained in this NDA 21-385.

Agency:

The Agency thanked the Applicant for its feedback and requested that the Applicant submit this information as well as any additional supportive information to the Agency for its review as soon as possible.

Applicant:

The Applicant thanked the Agency for the teleconference and will make the requested submission in the very near future.

The teleconference ended amicably.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory):_____

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

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/s/
---
Frank Cross
8/13/02 12:48:28 PM
CSO

Jonathan Wilkin
9/5/02 03:12:21 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG 22 2002

Frank E. Dunlap, M.D.
7042 East Broadway
Tucson, Arizona 85710

Dear Dr. Dunlap:

Between May 6 and 9, 2002, Dr. Mathew T. Thomas and Mr. Randall N. Johnson, representing the Food and Drug Administration (FDA), reviewed your conduct of protocol # SER-960602: A Double-Blind, Randomized, Placebo-Controlled, Multicenter, Parallel Group Evaluation of the Efficacy and Safety of Sertaconazole 2% Cream in Patients with Interdigital Tinea Pedis, performed for MYLAN Pharmaceuticals, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to ensure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to pertinent federal regulations governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Dr. Thomas and Investigator Johnson during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

LSI

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 1000150280
Field Classification: NAI
Headquarters Classification:
__X _1)NAI
____ 2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

Deficiencies noted: None

cc:
HFA-224
HFD-540 Doc.Rm. NDA# 21-385
HFD-540 Review Div.Dir. Wilkin
HFD-540 MO Porres
HFD-540 PM Cross
HFD-46/47 c/r/s/ GCP File #3882
HFD-47 MTT/GRH
HFR-PA250 DIB Stokke
HFR-PA2565 BIMO Monitor Koller
HFR-PA3540 Investigator Johnson

r/d:GRH:8/15/02
reviewed:aeh:8/16/02
finaled:mrl:8/16/02

**O:\GRH\DUNLAP NAI.DOC**

**Reviewer's Note to Review Division Medical Officer**

This inspection was conducted pursuant to a Request for Consultation from HFD-540 to conduct an audit of protocol SER-960602 at Dr. Dunlap's site. Although no irregularities were apparent, Dr. Dunlap's efficacy results were the most favorable - 36% of the complete cures came from his site, whereas 9.4% complete cures were reported from all other sites, excluding Dr. Dunlap's site.

Of the 42 subjects enrolled, 26 subjects completed the study. Sixteen subjects withdrew or were dropped from the study for a reason other than an adverse event. Informed consent forms and study-related records for all 42 subjects were reviewed. The inspection did not reveal any significant deficiencies or discrepancies that would invalidate the data submitted in support of NDA 21-385. **The data collected from the study site appear acceptable.**

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Rockville, MD 20850

# FACSIMILE TRANSMISSION

DATE: July 26, 2002 Number of Pages (including cover sheet) – 42

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

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

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

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# FACSIMILE TRANSMISSION

DATE: July 22, 2002 Number of Pages (including cover sheet) – 1

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

MESSAGE: Please fax the following information regarding samples which have been withheld for method validation for your NDA 21-385, sertaconazole nitrate cream, 2%:

1. List of items (drug substance samples, drug product units, reference standards, impurity samples, degradant samples, etc.)
2. Quantities (how much, how many)
3. Control Numbers or other identification for each item
4. MSDS (material safety data sheets) for these samples
5. Name and Phone Number of the person responsible for the samples (FDA District Lab personnel will contact this person directly to arrange for the delivery of the samples).

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

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# FACSIMILE TRANSMISSION

DATE: May 29, 2002 Number of Pages (including cover sheet) – 3

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

MESSAGE: Please commit to the following Post Marketing Commitments for your NDA 21-385, sertaconazole nitrate cream, 2%:

[redacted]

1 Page(s) Withheld

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

   Commitment Category: Non-Clinical Toxicology

   | | |
   |---|---|
   | Protocol Submission: | by January 1, 2003 |
   | Study Start: | by July 1, 2003 |
   | Final Report Submission: | by July 1, 2006 |

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

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Rockville, MD 20850

# FACSIMILE TRANSMISSION

DATE: May 23, 2002 Number of Pages (including cover sheet) – 36 ~~37~~

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

MESSAGE: Please find attached to this facsimile transmission our proposed labeling for your NDA 21-385, sertaconazole nitrate cream, 2%.

Thank you.

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

35 Draft Labeling Page(s) Withheld

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Rockville, MD 20850

# FACSIMILE TRANSMISSION

DATE: April 10, 2002 Number of Pages (including cover sheet) - 1

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

MESSAGE: For your NDA 21-385, sertaconazole nitrate cream, 2%, we have the following request from the Pharmacology/Toxicology reviewer:

Please provide as soon as possible the testing lab historical data for teratogenicity studies broken out by the individual types of malformations in rabbits (e.g., arthrogryposis, acaudia, type of rib malformations, and type of vertebral column malformation).

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

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# FACSIMILE TRANSMISSION

DATE: March 15, 2002 Number of Pages (including cover sheet) - 1

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

MESSAGE: For your NDA 21-385, sertaconazole nitrate cream, 2%, we have the following request from the Pharmacology/Toxicology reviewer:

Please provide as soon as possible the historical control data for study titled: "Study of the fertility and embryonic development to implantation in the rat with sertaconazole nitrate via oral administration".

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

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/s/
---
Frank Cross
3/20/02 03:16:38 PM
CSO
Faxed on 3/15/02.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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## Division of Dermatologic and Dental Drug Products

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Rockville, MD 20850

# FACSIMILE TRANSMISSION

DATE: February 26, 2002 Number of Pages (including cover sheet) - 1

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

MESSAGE: For your NDA 21-385, sertaconazole nitrate cream, 2%, we have the following request:

1. Please assist the primary clinical reviewer regarding locating the results of pregnancy tests done at baseline and at study end in the original NDA submission. If this information is not in the original NDA submission, please submit tables regarding pregnancy information as previous as an amendment to the NDA.

2. If any of the pregnancy tests were positive, please identify outcome and study disposition.

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

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# FACSIMILE TRANSMISSION

DATE: February 22, 2002 Number of Pages (including cover sheet) - 1

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

MESSAGE: For your NDA 21-385, sertaconazole nitrate cream, 2%, we have the following request:

To assist the clinical review, the following information would be greatly appreciated:

Please submit a copy of the CRF for patient 9.109.

Your timely response to this information request is greatly appreciated.

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

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# FACSIMILE TRANSMISSION

DATE: February 14, 2002 Number of Pages (including cover sheet) - 1

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

MESSAGE: For your NDA 21-385, sertaconazole nitrate cream, 2%, we have the following Clinical/Biostatistical request:

In our ongoing review of NDA 21-385, sertaconazole nitrate cream, 2%, for the treatment of interdigital tinea pedis, an initial analysis does not appear to have found significant efficacy for the treatment of interdigital tinea pedis when the causative organism is T. mentagrophytes or E. floccosum (apparently attributable to an insufficient number of subjects with these causative organisms). Please provide any additional information that you might have to support efficacy for treatment of interdigital tinea pedis caused by either of these organisms using sertaconazole 2% cream.

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

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Rockville, MD 20850

# FACSIMILE TRANSMISSION

DATE: February 12, 2002 Number of Pages (including cover sheet) - 1

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

MESSAGE: For your NDA 21-385, sertaconazole nitrate cream, 2%, we have the following requests:

To assist the Clinical Microbiology review, please submit the following

1. Summary (studies SER-960602 + SER-960603) of mycological outcome without clinical response by visit and baseline pathogen (Similar to Table 8.7.31 but without clinical response data). Provide summary for both the MITT and per protocol populations.

2. Mycological outcome for studies SER-960602 and SER-960603 individually without clinical response by visit and baseline pathogen. Provide for both the MITT and per protocol populations.

3. Mycological outcome for studies SER-960602 and SER-960603 individually with mycological and clinical response data (similar to Table 8.7.31 but each study presented individually). Provide for both the MITT and per protocol populations.

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

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Rockville, MD 20850

## FACSIMILE TRANSMISSION

DATE: February 8, 2002 Number of Pages (including cover sheet) - 2

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

MESSAGE: For your NDA 21-385, sertaconazole nitrate cream, 2%, we have the following requests:

To assist the clinical review, the following information would be greatly appreciated:

1. Copies of the actual mycology laboratory culture reports for the following patients and visits:

| Patient | Visit # |
|---|---|
| 1.199 | Baseline |
| 1.200 | Baseline |
| 1.202 | Baseline |
| 1.207 | Baseline |
| 1.210 | Baseline |
| 1.385 | Baseline |
| 1.387 | Baseline |
| 1.390 | Baseline |
| 1.421 | Baseline |
| 1.424 | Baseline |
| 3.073 | Baseline |
| 3.076 | 5,6 |
| 3.078 | Baseline |
| 3.080 | Baseline |
| 3.081 | Baseline |
| 3.146 | Baseline |
| 3.147 | Baseline |
| 3.149 | Baseline |
| 3.150 | Baseline |
| 3.151 | Baseline |
| 3.154 | 5,6 |

| | |
|---|---|
| 3.156 | Baseline |
| 3.181 | Baseline |
| 3.183 | 5,6 |
| 3.184 | Baseline |
| 3.186 | 5,6 |
| 3.382 | Baseline |
| 3.384 | Baseline |
| 3.403 | Baseline |
| 3.406 | 1-6 |
| 3.408 | Baseline |
| 4.212 | Baseline |
| 5.062 | Baseline |
| 5.063 | Baseline |
| 5.065 | Baseline |
| 5.066 | Baseline |
| 5.068 | Baseline |
| 5.069 | Baseline |
| 5.070 | Baseline |
| 5.071 | Baseline |
| 5.072 | 5,6 |
| 5.187 | Baseline |

| | |
|---|---|
| 6.097 | Baseline |
| 6.098 | Baseline |
| 6.099 | Baseline |
| 6.100 | Baseline |
| 6.105 | 5,6 |
| 6.292 | Baseline |
| 6.293 | Baseline |
| 7.133 | Baseline |
| 7.134 | Baseline |
| 7.135 | Baseline |
| 7.136 | Baseline |
| 7.137 | Baseline |
| 7.138 | Baseline |
| 7.139 | Baseline |
| 8.085 | Baseline |
| 8.086 | Baseline |
| 9.109 | 6 |
| 9.110 | Baseline |
| 9.111 | Baseline |
| 9.112 | Baseline |
| 9.117 | Baseline |

| | |
|---|---|
| 9.119 | Baseline |
| 9.120 | Baseline |
| 9.158 | Baseline |
| 9.159 | Baseline |
| 9.160 | 6 |
| 9.165 | Baseline |
| 9.166 | Baseline |
| 9.167 | Baseline |
| 9.239 | Baseline |
| 10.037 | 6 |
| 10.039 | Baseline |
| 10.041 | 6 |
| 11.025 | Baseline |
| 11.026 | Baseline |
| 11.027 | Baseline |
| 11.028 | Baseline |
| 11.029 | Baseline |
| 11.036 | 6 |
| 11.169 | Baseline |
| 11.178 | Baseline |
| 11.180 | 5,6 |

| | |
|---|---|
| 11.332 | 6 |
| 11.394 | Baseline |
| 12.254 | Baseline |
| 12.255 | Baseline |
| 12.257 | Baseline |
| 12.258 | Baseline |
| 12.261 | Baseline |
| 12.264 | Baseline |
| 12.368 | Baseline |
| 12.369 | Baseline |
| 13.018 | 5,6 |
| 13.021 | Baseline |

| | |
|---|---|
| 13.024 | 6 |
| 13.243 | Baseline |
| 14.127 | Baseline |
| 14.128 | 6 |
| 14.268 | 6 |
| 14.269 | 6 |
| 15.051 | Baseline |
| 15.052 | Baseline |
| 15.053 | Baseline |
| 15.054 | Baseline |
| 15.057 | Baseline |
| 15.058 | Baseline |

| | |
|---|---|
| 16.224 | Baseline |
| 16.225 | 6 |
| 16.229 | Baseline |
| 16.230 | Baseline |
| 16.231 | Baseline |
| 16.233 | 6 |
| 16.307 | Baseline |
| 16.311 | Baseline |
| 16.312 | Baseline |
| 16.315 | 4,4,5,6 |
| 17.277 | Baseline |
| 17.285 | Baseline |

| | |
|---|---|
| 17.286 | Baseline |
| 18.321 | 5,6 |
| 18.322 | Baseline |
| 18.325 | Baseline |
| 18.326 | Baseline |
| 19.349 | Baseline |
| 19.350 | Baseline |
| 20.295 | 5,6 |
| 21.338 | Baseline |
| 21.340 | Baseline |
| 21.343 | 5,6 |

2. Copies of the CRF for these patients:

| |
|---|
| 1.208 |
| 3.084 |
| 3.145 |
| 5.061 |
| 9.160 |
| 12.126 |

| |
|---|
| 13.245 |
| 14.126 |
| 14.130 |
| 14.268 |
| 16.233 |
| 16.315 |

Your timely response to this information request is greatly appreciated.

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

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# FACSIMILE TRANSMISSION

DATE: January 15, 2002 Number of Pages (including cover sheet) - 1

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

MESSAGE: Per yesterday's phone conversation:

For your NDA 21-385, sertaconazole nitrate cream, 2%, please submit a copy of the actual mycology culture reports from the mycology lab for Study SER-960602.

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

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# FACSIMILE TRANSMISSION

DATE: November 29, 2001 Number of Pages (including cover sheet) - 5

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

MESSAGE: Please find enclosed our minutes of our November 19, 2001, teleconference.

Thank you.

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

Teleconference Date: November 19, 2001 Time: 1530 Location: N225

NDA 21-385, sertaconazole nitrate cream, 2%

Treatment of Interdigital Tinea pedis

Sponsor: Mylan Pharmaceuticals, Inc.

Purpose of Teleconference: Convey Information Requests from Fileability Meeting

Meeting Chair: Mohamed Alosh, Ph.D.

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Mohamed Alosh, Ph.D., Biostatistics Team Leader, DOBIII, HFD-725
Kathleen Fritsch, Ph.D., Biostatistician, DOBIII, HFD-725
Frank H. Cross, Jr., M.A., CDR, DDDDP, HFD-540

Applicant Attendees, titles and offices:

Andrea B. Miller, R.Ph., Manager, Regulatory Affairs, Mylan Pharmaceuticals, Inc.

Agency:

The following informational items should be submitted by the Applicant:

Chemistry, Manufacturing, and Controls:

A statement that all manufacturing sites are ready for inspection at the time of the NDA submission.

Clinical:

1. We note that the Applicant has already supplied data for the treatment by center interaction. However, the Applicant should also submit Complete Cure and Effective Treatment data per center, for the MITT population, defined as all randomized patients with positive mycology at baseline, for each of the two studies.

Applicant:

The Applicant asked how to handle missing data in the by center analysis.

Agency:

The Agency stated that LOCF would be acceptable.

2. Mycology:

   Please identify MIC studies for E. floccosum.

3. Dosage studies:

   At the End of Phase 2 Meeting the Applicant agreed to supply further information on dosage studies that justify selecting the following dose regimen (2%, twice a day, and one month of treatment) for the study. Please provide such material.

4. Please also supply:

   a. a comprehensive list of references quoted throughout the NDA.

      i. If these references are for studies included within the NDA, indicate the pages in the NDA where the quoted studies are to be found. The NDA includes several lists of references which do not seem to agree with each other and which point to page numbers where the expected studies are not found.

      ii. If these references are published articles, indicate where in the NDA can they be found or supply a copy of the quoted article.

   b. translations of foreign studies included in the NDA only in a foreign language.

Biostatistics:

To aid in the review, please provide the following variables electronically in SAS transport format. For each patient in Studies 960602 and 960603 please provide:

1. MITT population status

2. Per protocol population status

3. Complete cure status at Week 6 (with Missing values treated as failures)

4. Complete cure status at Week 6 (with Missing values handled with LOCF)

5. Effective treatment status at Week 6 (with Missing values treated as failures)

6. Effective treatment status at Week 6 (with Missing values handled with LOCF)

We note that the numbers on the flow chart on page 8-25-17 (of the Applicant's original NDA submission) do not appear to add up. The submission of these variables will assist the Agency in determining the status of each subject.

Applicant:

The Applicant said that it would submit the requested items during the week of November 26, 2001. The translations of the Spanish protocols will be submitted by mid December 2001.

The teleconference ended amicably.

Addendum:

In addition to the above information requests, the Agency also requests the following:

Clinical:

1. Regarding Clinical Information Request # 1 (above), the Applicant should submit all efficacy data per center, for MITT population, defined as randomized with positive mycology at baseline, for each of the two studies.

2. Pediatric Waiver:

   Please specify the age group for which are you requesting a waiver from performing pediatric studies.

3. Mycology:

   a. Please explain whether any micro-organisms were recovered for those patient visits which are reported as "unknown/not recorded" and identify which visits actually had mycology not recorded and which ones had "unknown" and what "unknown" actually means.

   b. Please identify any fungus recovered during the study which were identified as "other" than T. rubrum, T. mentagrophytes and E. floccosum.

   c. Please identify studies addressing possible resistance of dermatophytes to sertaconazole as well as cross-resistance with other antifungals.

   d. Please identify MIC studies conducted with fungi isolated during the two U.S. pivotal studies.

4. Please also supply:

   a. Data or rationale for expecting that [redacted] will not affect either efficacy or safety.

   b. Data indicating current usage, broken down by age and by indication.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory):_____

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

/s/
---
Frank Cross
11/28/01 11:26:17 AM
CSO

Kathleen Fritsch
11/28/01 12:44:31 PM
BIOMETRICS

Joseph Porres
11/28/01 12:50:51 PM
MEDICAL OFFICER

Mohamed Alosh
11/29/01 11:48:36 AM
BIOMETRICS
Concur with Telecon minutes

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 3, 2000 Number of Pages (including cover sheet) - 12

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

MESSAGE: Please find enclosed our minutes of the pre-NDA Meeting of October 18, 2000.

Thank you.

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

Meeting Date: October 18, 2000 Time: 0930 Location: S400
Meeting ID# 6259

IND 50,726, Sertaconazole Nitrate Cream, 2%

Interdigital Tinea pedis

Sponsor: Mylan Pharmaceuticals, Inc.

Pre-NDA Meeting

Meeting Chair: Jonathan K. Wilkin, M.D.

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Bonnie Dunn, Ph.D., Deputy Division Director, DNDCIII, HFD-830
Tony DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-830
Steve Hathaway, Ph.D., Chemist, DNDCIII, HFD-830
Abby Jacobs, Ph.D., Pharmacology/Toxicology Team Leader, DDDDP, HFD-540
Kumar Mainigi, Ph.D., M.P.H., D.A.B.T., Toxicologist, DDDDP, HFD-540
Sue-Chih Lee, Ph.D., Biopharmaceuticist, DPEIII, HFD-880
Harold Silver, Ph.D., Clinical Microbiologist, DAIDP, HFD-520
Susan Walker, M.D., Dermatology Team Leader, DDDDP, HFD-540
M. Atiar Rahman, Ph.D., Biostatistician, DOBIII, HFD-725
Frank H. Cross, Jr., M.A., CDR, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

Mylan Pharmaceuticals, Inc.:

James H. Sherry, M.D., Ph.D., Vice President, Clinical Research
P. Bruce Bottini, Pharm.D., Director, Clinical Research
Frank Sisto, Vice President, Regulatory Affairs
Mei-Ying Huang, Ph.D., Executive Director, Pharmacokinetics
Timothy Irby, Senior Scientist, Analytical Laboratory
Patrick McGrath, Ph.D., Director, Clinical Research
Andrea B. Miller, R.Ph., Esq., Associate Director, Regulatory Affairs
Bhaskar Chauduri, Ph.D., Vice President and General Manager, Research, Bertek
Barbara Brennan, Pharm.D., Director, Clinical Research, Bertek

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With reference to the August 24, 2000, pre-NDA Meeting Request, the September 29, 2000, Pre-NDA Meeting Briefing Package, and to the October 17, 2000, Pre-NDA Meeting Discussion Points, the following discussion took place:

Agency:

**Chemistry, Manufacturing and Controls:**

1. Drug Substance Description:

   a. The Sponsor should provide UV-Vis spectra [redacted] of drug substance.

   b. The Sponsor should provide [redacted]

2. Drug Substance Specifications:

   a. The Sponsor should provide copies of the European Pharmacopeia and British Pharmacopeia monographs for sertaconazole nitrate.

   b. The Sponsor should describe the preparation and purification of the Reference Standard lot(s) of sertaconazole nitrate.

3. Drug Substance [redacted]

   a. The Sponsor should provide descriptions of test methods and results used to confirm that [redacted] can be detected and quantitated in the drug substance.

   b. The Sponsor should propose specifications for the [redacted]

4. Drug Product:

   The Sponsor should provide a summary that shows the lot number and quantitative component's composition of all investigational formulations used for each pre-clinical and clinical trial.

5. Drug Product Specifications and Stability:

   a. A specification for the component [redacted] should be incorporated into the regulatory specifications. [redacted] should begin as soon as possible for future lots.

   b. The Sponsor may perform [redacted] testing, rather than [redacted] testing, on primary stability and production lots ONLY IF there is a validated correlation between [redacted] for a developmental batch which has a formulation identical to (except in the level of preservatives) the to-be-marketed formulation.

   c. The Sponsor has proposed separate release and stability specifications. FDA does not accept variable regulatory specifications and the Sponsor is advised that regulatory specifications must be revised to be the same at release and at end of shelf-life.

The tentative specification acceptance criteria must be based on the results obtained from the developmental lots, and not on desired maximum limits.

d. Because the to-be-marketed formulation contains — only those lots of this formulation will be considered primary stability lots. The lots manufactured by — will be considered as supportive stability lots.

e. The Sponsor is advised that submitting insufficient or inadequate stability data may result in a shortened expiration dating period.

6. Methods Validation Package:

a. The Sponsor should submit with the proposed NDA one Methods Validation Package for review and, in addition, two identical Methods Validation Packages for FDA's internal use.

b. The Sponsor should ensure that, at the time of submission of the NDA, all referenced Drug Master Files are up-to-date, and that the NDA contains CURRENT letters of authorization to refer to the DMF's.

c. The Sponsor should provide a statement at the time of submission of the NDA that all listed manufacturing and testing facilities are ready for inspection at the time of submission of the NDA.

d. The Sponsor is advised that submitting insufficient or inadequate stability data may result in an expiration-dating period, which may be as short as —

e. The Methods Validation package should be complete in and of itself.

f. Please separately paginate each volume of the Method Validations Package.

g. The Sponsor is advised to consult the MV guidance at if there are any additional questions.

7. If the details of other investigational formulations are located in other volumes of the IND, please cross-reference the location.

8. CMC Question 1 of Sponsor's October 17, 2000, Pre-NDA Meeting Discussion Points, "1. — information and specifications were presented in the Briefing Package, Attachment 4, Part 2 (pp. 41-44). Does the Agency agree with the information and specifications established?"

Agency:

a. The evaluation of specifications for — is a review issue

b. The Sponsor is requested to submit IR Spectra to demonstrate that the —

9. CMC Question 2 of Sponsor's October 17, 2000, Pre-NDA Meeting Discussion Points, "Does the Agency concur with the drug substance and drug product impurity specifications presented in the Pre-NDA Meeting Briefing Package, Attachment 4, Part 2 (pp. 37,43) and Part 4 (p. 82)?

Agency:

The evaluation of the impurity specifications is a review issue. Acceptance criteria are based on actual observed limits.

10. CMC Question 3 of Sponsor's October 17, 2000, Pre-NDA Meeting Discussion Points, "The Phase III clinical supplies of Sertaconazole Nitrate Cream, 2%, were manufactured by ——— Mylan plans to use DPT Laboratories of San Antonio, Texas to manufacture future drug supplies for both clinical trials use and commercial marketing...Does the Agency agree that, for the reasons summarized above and described in the Pre-NDA Meeting Briefing Package, Attachment 4, Part 1 (pp. 30-33), no additional studies are necessary to demonstrate the equivalence between the formulations with respect to product performance, efficacy and safety?

Agency:

No additional CMC studies are needed for CMC purposes (note: chemists do not evaluate safety and efficacy). However, the Sponsor should provide in the NDA a table of the impurity profile physical and chemical testing results for the formulation containing — and the formulation not containing —

11. CMC Question 3 of Sponsor's October 17, 2000, Pre-NDA Meeting Discussion Points, "The proposed contents of the Chemistry, Manufacturing and Controls section of the NDA were described in Attachment 4 of the Briefing Package. The proposed table of contents for this section was provided in Attachment 3 of the Briefing Package. Does the Agency agree that the proposed CMC section is sufficient to support the filing of a New Drug Application for Sertaconazole Nitrate Cream, 2%.

Agency:

The CMC information presented in the Briefing Package appears to be adequate.

12. A separate CMC Teleconference can be scheduled if the Sponsor desires clarification of the guidance/recommendations given above.

**Pharmacology/Toxicology:**

Information submitted is sufficient. No comments.

**Biopharmaceutics:**

The Sponsor conducted a PK study in patients with Tinea pedis and Tinea cruris but no measurable plasma sertoconazole concentrations were detected. The Sponsor should note the following:

1. The analytical method should be sensitive for the purpose, i.e., the method should be able to detect at the NOEL level in animals studies.

2. The sampling scheme should be such that it can capture the full PK profile. Collecting only trough samples is not acceptable.

**Clinical Microbiology:**

1. The proposed table of contents for the NDA is acceptable.

2. Please provide the Clinical Microbiology information on CDROM in MS Word.

3. Regarding the proposed labeling for Clinical Microbiology:

   a. Annotate the microbiology claims.

   b. Indicate exactly the portion of the reference(s) that supports each claim.

   c. Sequentially number each reference.

   d. Tab each reference.

4. Speciate all targeted fungi.

5. Please format the Clinical Microbiology portion of the labeling as follows:

   **MICROBIOLOGY**

   **Mechanism of Action:**

   **Activity *In Vivo*:**

   **Activity *In Vitro*:**

   **Drug Resistance:**

6. Microbiology Question 1 of Sponsor's letter dated October 18, 2000, i.e.,"Mylan believes that the microbiology information outlined in Attachment 5 of the Briefing Package that will be submitted in the NDA supports the submission of a New Drug Application for Sertaconazole nitrate Cream, 2%. Does the Agency agree?

Agency:

Agreed.

7. Please identify in the Clinical Microbiology portion of the NDA when the old drug product information is used and when the new drug product information is used.

**Clinical:**

1. The Sponsor generally appears to be presenting the endpoints suggested by the Agency. These include mycologic cure (negative KOH and culture); effectively treated (negative KOH and culture with no score greater than one in erythema and scale and no score greater than 0 in other clinical signs) and clinical cure (negative KOH and culture and all clinical signs equal to 0). The Sponsor's minutes of the June 23, 1997, End of Phase 2 Meeting (briefing package, page 7) and the Agency minutes (briefing package, page 16) appear to be in agreement.

2. The Sponsor has identified a "relapse" group at week 6, consisting of patients whose clinical condition worsened from End of Treatment (4 wks) to week 6.

   As the *a priori* timepoint for evaluation is 6 weeks, each patient should be classified at that time based upon the originally described efficacy endpoints (above). Patients who are not classified as clinical cures or effectively treated at 6 weeks should be classified as treatment failures. (briefing package, page 7, of the Sponsor's minutes of the June 23, 1997, End of Phase 2 Meeting).

3. The Sponsor uses the physician's global evaluation (page 192 of the Sponsor's September 29, 2000, Meeting Briefing Package) to determine clinical cure/effective treatment. The global must be directedly supported by the individual clinical sign scores.

4. The Sponsor has an analysis of time to treatment outcome (page 213 of the Sponsor's September 29, 2000, Meeting Briefing Package). If the Sponsor intends to pursue claims for efficacy prior to the originally established single endpoint (6 weeks), then statistical adjustments for multiplicity may be necessary. Please refer to the Sponsor and agency EP2 comments (in the briefing jacket) which appear to be convergent.

5. The Sponsor should include a complete description of the outcome categories (clinical cure, successfully treated, mycologic cure, treatment failure) in the study reports and summaries.

6. The Sponsor should present a rationale/demonstration that the addition of ← (see chemistry comments) does not have an effect upon the drug product performance, efficacy or safety.

7. The NDA submission should include the complete individual study reports for SER 960602 and SER 960603. The complete study protocol (not a summary or synopsis) should be included at the beginning of each study report.

8. It would be helpful to the clinical reviewer if line listings were presented in a format similar to Appendices A and B (attached).

9. It would be helpful to receive the protocol and study reports for SER 960602 and 603 in Word 7.0.

**Biostatistics:**

1. The Sponsor submitted efficacy analysis results using their own definition of MITT (page 193 of the September 29, 2000, Meeting Briefing Package). The Sponsor is requested to analyze the efficacy data following the definitions of MITT proposed by the Division.

However, if the Sponsor desires, they may submit efficacy analysis results following their definition of MITT as additional analysis. The Sponsor is further advised to conduct sub-group analysis by gender, race, age, and possibly by baseline severity.

2. The Sponsor proposes a test of homogeneity of the results across centers before the performance of the CMH test. The Sponsor should state the alternative methods they are going to adopt in case the homogeneity is not achieved.

3. The Sponsor should provide demographic, baseline, efficacy, and safety data sets by patient. All data sets should be in SAS transport file and submitted at the time of the NDA submission.

**Project Management:**

1. Pediatric Rule:

   The Sponsor was reminded of the following:

   The Food and Drug Administration Modernization Act [FDAMA] of 1997, Section 111, Pediatric Studies of Drugs, effective April 1, 1999, requires the following:

   Per 21CFR 314.50(d)(7), NDA applications are required to contain "A section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications, a reference to the full descriptions of such studies provided under paragraphs (d)(3) and (d)(5) of this section, and information required to be submitted under Section 314.55."

   Waivers are requested in accordance with 21CFR 314.55(c)

2. Financial Disclosure:

   For applications submitted after February 2, 1999, per 21CFR 54.3 and 21CFR 54.4, an NDA applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests.

3. Labeling:

   If the Sponsor has an Information for Patients leaflet/labeling, please submit it with the NDA.

4. Please submit the proposed annotated labeling and unannotated labeling with the NDA. A copy of the proposed labeling on diskette in MS Word should also be submitted with the NDA.

5. Comments are based upon the pre-NDA Briefing Package, which is an unofficial briefing document submitted as information. Please submit the requested information with the proposed NDA.

Signature, minutes preparer: _ /S/ _____

Concurrence Chair (or designated signatory) /S/

Attachment/Handout/Appendices:

1. Meeting Request dated August 24, 2000
2. Meeting Briefing Package, dated September 29, 2000
3. Pre-NDA Meeting Discussion Points, dated October 17, 2000.
4. Appendices:

   a. Appendix A: Line Listings: All visit data for patients grouped by outcome categories

   b. Appendix B: Line Listing Examples: Patients grouped by outcome categories; showing Baseline and 6-week (efficacy endpoint) data

Appendix A
Line Listings: All visit data for patients grouped by outcome categories



| Individual Patient Data: Clinically cured patients | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient #1 | | | | | | | | | | | |
| | Date | KOH | Culture | Erythema | Scale | Pruritus | Cracking | Fissuring | Maceration | Burning | Global |
| Visit 1 | | | | | | | | | | | |
| Visit 2 | | | | | | | | | | | |
| Visit 3 | | | | | | | | | | | |
| Visit 4 | | | | | | | | | | | |
| Visit 5 | | | | | | | | | | | |
| Visit 6 | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| Patient #2 | | | | | | | | | | | |
| | Date | KOH | Culture | Erythema | Scale | Pruritus | Cracking | Fissuring | Maceration | Burning | Global |
| Visit 1 | | | | | | | | | | | |
| Visit 2 | | | | | | | | | | | |
| Visit 3 | | | | | | | | | | | |
| Visit 4 | | | | | | | | | | | |
| Visit 5 | | | | | | | | | | | |
| Visit 6 | | | | | | | | | | | |
| | | | | | | | | | | | |
| Patient #3 | | | | | | | | | | | |
| | Date | KOH | Culture | Erythema | Scale | Pruritus | Cracking | Fissuring | Maceration | Burning | Global |
| Visit 1 | | | | | | | | | | | |
| Visit 2 | | | | | | | | | | | |
| Visit 3 | | | | | | | | | | | |
| Visit 4 | | | | | | | | | | | |
| Visit 5 | | | | | | | | | | | |
| Visit 6 | | | | | | | | | | | |
| | | | | | | | | | | | |

| Individual Patient Data: Effectively Treated patients | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient #1 | | | | | | | | | | | |
| | Date | KOH | Culture | Erythema | Scale | Pruritus | Cracking | Fissuring | Maceration | Burning | Global |
| Visit 1 | | | | | | | | | | | |
| Visit 2 | | | | | | | | | | | |
| Visit 3 | | | | | | | | | | | |
| Visit 4 | | | | | | | | | | | |
| Visit 5 | | | | | | | | | | | |
| Visit 6 | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| Patient #2 | | | | | | | | | | | |
| | Date | KOH | Culture | Erythema | Scale | Pruritus | Cracking | Fissuring | Maceration | Burning | Global |
| Visit 1 | | | | | | | | | | | |
| Visit 2 | | | | | | | | | | | |
| Visit 3 | | | | | | | | | | | |
| Visit 4 | | | | | | | | | | | |
| Visit 5 | | | | | | | | | | | |
| Visit 6 | | | | | | | | | | | |
| | | | | | | | | | | | |
| Patient #3 | | | | | | | | | | | |
| | Date | KOH | Culture | Erythema | Scale | Pruritus | Cracking | Fissuring | Maceration | Burning | Global |
| Visit 1 | | | | | | | | | | | |
| Visit 2 | | | | | | | | | | | |
| Visit 3 | | | | | | | | | | | |
| Visit 4 | | | | | | | | | | | |
| Visit 5 | | | | | | | | | | | |
| Visit 6 | | | | | | | | | | | |
| | | | | | | | | | | | |

| Individual Patient Data: Mycologic Cure | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient #1 | | | | | | | | | | | |
| | Date | KOH | Culture | Erythema | Scale | Pruritus | Cracking | Fissuring | Maceration | Burning | Global |
| Visit 1 | | | | | | | | | | | |
| Visit 2 | | | | | | | | | | | |
| Visit 3 | | | | | | | | | | | |
| Visit 4 | | | | | | | | | | | |
| Visit 5 | | | | | | | | | | | |
| Visit 6 | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| Patient #2 | | | | | | | | | | | |
| | Date | KOH | Culture | Erythema | Scale | Pruritus | Cracking | Fissuring | Maceration | Burning | Global |
| Visit 1 | | | | | | | | | | | |
| Visit 2 | | | | | | | | | | | |
| Visit 3 | | | | | | | | | | | |
| Visit 4 | | | | | | | | | | | |
| Visit 5 | | | | | | | | | | | |
| Visit 6 | | | | | | | | | | | |
| | | | | | | | | | | | |
| Patient #3 | | | | | | | | | | | |
| | Date | KOH | Culture | Erythema | Scale | Pruritus | Cracking | Fissuring | Maceration | Burning | Global |
| Visit 1 | | | | | | | | | | | |
| Visit 2 | | | | | | | | | | | |
| Visit 3 | | | | | | | | | | | |
| Visit 4 | | | | | | | | | | | |
| Visit 5 | | | | | | | | | | | |
| Visit 6 | | | | | | | | | | | |
| | | | | | | | | | | | |

Appendix B:
Line Listing Examples: Patients grouped by outcome categories; showing Baseline and 6-week (efficacy endpoint) data

**Table: Clinical Cure**

| | Baseline | | | | | | | | | 6 weeks | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | KOH | Cult | Erythema | Scale | Pruritus | Crack | Fiss | Mace | Burn | KOH | Cult | Erythema | Scale | Pruritus | Crack | Fiss | Mace | Burn | Global |
| Pt. 1 | | | | | | | | | | | | | | | | | | | |
| Pt. 2 | Neg | Neg | 0 | 0 | 0 | 1 | 0 | 3 | 1 | Neg | Neg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Cure |
| Pt 3 | | | | | | | | | | | | | | | | | | | |
| etc | | | | | | | | | | | | | | | | | | | |

**Table: Effectively Treated**

| | Baseline | | | | | | | | | 6 weeks | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | KOH | Cult | Erythema | Scale | Pruritus | Crack | Fiss | Mace | Burn | KOH | Cult | Erythema | Scale | Pruritus | Crack | Fiss | Mace | Burn | Global |
| Pt. 1 | | | | | | | | | | | | | | | | | | | |
| Pt. 2 | Neg | Neg | 0 | 0 | 0 | 1 | 0 | 3 | 1 | Neg | Neg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Cure |
| Pt 3 | | | | | | | | | | | | | | | | | | | |
| etc | | | | | | | | | | | | | | | | | | | |

**Table: Mycology Negative**

| | Baseline | | | | | | | | | 6 weeks | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | KOH | Cult | Erythema | Scale | Pruritus | Crack | Fiss | Mace | Burn | KOH | Cult | Erythema | Scale | Pruritus | Crack | Fiss | Mace | Burn | Global |
| Pt. 1 | | | | | | | | | | | | | | | | | | | |
| Pt. 2 | Neg | Neg | 0 | 0 | 0 | 1 | 0 | 3 | 1 | Neg | Neg | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Cure |
| Pt 3 | | | | | | | | | | | | | | | | | | | |
| etc | | | | | | | | | | | | | | | | | | | |

cc:

Orig IND 50,726
HFD-540
HFD-540/DIV DIR/Wilkin
HFD-830/DIV DIR/Chen
HFD-830/DEP DIV DIR/Dunn/10.25.00
HFD-540/CHEM TL/DeCamp/10.25.00
HFD-540/CHEM/Hathaway/10.25.00
HFD-540/PHARM TOX TL/Jacobs/10.25.00
HFD-540/PHARM TOX/Mainigi/10.25.00
HFD-880/BIOPHARM TL/Bashaw
HFD-880/BIOPHARM/Lee/10.25.00
HFD-540/DERM TL/Walker/10.25.00
HBFD-725/BIOSTAT TL/Alosh
HFD-725/BIOSTAT/Freidlin/10.25.00
HFD-540/PROJ MGR/Cross
Drafted by: fhc/October 25, 2000
d:\word\sertaconazole\ind50726\prendamina.doc

**MEMORANDUM OF MEETING**

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 6, 1998 Number of Pages (including cover sheet) - 9

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

MESSAGE: Please find enclosed our minutes of the End of Phase 2 meeting for IND 50,726, Sertaconazole Nitrate Cream, 2%.

Thank you.

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

Meeting Date: June 23, 1997 Time: 1000 Location: N225
Meeting ID# 1073

IND 50,726, Sertaconazole Nitrate Cream, 2%

Sponsor: Mylan Pharmaceuticals, Inc.

End of Phase 2 Meeting for IND 50,726

Meeting Chair: Jonathan K. Wilkin, M.D.

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., LCDR

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Susan Walker, M.D., Acting Dermatology Team Leader, DDDDP, HFD-540
R. Srinivasan, Ph.D., Biostatistics Team Leader, DOBIV, HFD-725
Cheryl Dixon, Ph.D., Biostatistician, DOBIV, HFD-725
Kumar Mainigi, Ph.D., M.P.H., D.A.B.T., Toxicologist, DDDDP, HFD-540
Norman See, Ph.D., Toxicologist, DDDDP, HFD-540
Steve Hathaway, Ph.D., Chemist, DNDCIII, HFD-540
Sue-Chih Lee, Ph.D., Biopharmaceuticist, DPEIII, HFD-880
Frank H. Cross, Jr., M.A., LCDR, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

Mylan Pharmaceuticals, Inc.:

Thomas S. Clark, M.D., Medical Director
John P O'Donnell, Ph.D., Executive Vice President, Research and Quality Control
Peter B. Bottini, PharmD., Director, Clinical Research
Patrick McGrath, Ph.D., Assistant Director, Clinical Research
Mei-Ying Huang, Director, Pharmacokinetics
Andrea B. Miller, R.Ph., Manager, Regulatory Affairs
Greg Ford, Project Manager

Mylan Pharmaceuticals' Consultants:

[redacted]

Meeting Objectives:

1. To obtain concurrence from the Agency that, based on the existing body of data on Sertaconazole, Mylan can proceed to initiate the proposed Phase 3 Clinical Development Program.

2. To determine the acceptability of the revised Phase 3 Clinical Development Plan to provide the efficacy and safety data considered appropriate to support the approval of Sertaconazole 2% Cream (STZ) for the treatment of tinea pedis.

3. [redacted]

4. To confirm the acceptability of the Toxicological Development Program to provide the data considered appropriate the support the clinical safety of STZ for the treatment of [redacted]

Agenda:

1. Introduction: Peter B. Bottini, PharmD, Director, Clinical Research, Mylan.

2. Presentation of Previous Human Experience: Peter B. Bottini, PharmD, Director, Clinical Research, Mylan.

3. Presentation of Proposed Clinical Development plan to support the efficacy and safety of STZ in the treatment of tinea pedis [redacted] . Peter B. Bottini, Mylan.

4. Discussion of the Proposed Clinical Development Plan and the Division's May 5, 1997, Clinical/Statistical Comments: FDA/Mylan.

5. Presentation of the existing preclinical toxicology data for Sertaconazole and plans for additional studies: [redacted] h.D., Consultant Toxicologist, Mylan.

6. Brief discussion of the acceptability of the current and proposed preclinical toxicology studies to support the approval of Sertaconazole 2% Cream for its intended use: FDA/Mylan.

With regard to general guidance:

Chemistry:

Agency: The Agency recommended that the Sponsor submit the following:

1. Revised specifications for the drug substance and the drug product.

2. Verification of the manufacturing scale especially as pertains to SUPAC changes which may be made in the future.

3. Other CMC changes that may have occurred with this drug since the filing of the IND.

4. Clarification of the actual formulation being brought to market.

5. Impurity profile: specifications for impurities in drug substance and drug product need to be tightened.

6. Will an Annual report for this IND be submitted in the near future?

7. Previous marketing information needs to be sent.

8. [redacted]

9. Spectra (and not just peaks) for UV and visible light absorption from [redacted]

The Agency also encouraged a separate CMC meeting/teleconference.

Sponsor: The Sponsor said that an Annual report for this IND will be submitted in the near future. In addition, the Sponsor will be requesting a teleconference to discuss CMC issues in the near future. The Sponsor also agreed to submit all of the other CMC requested data.

Pharmacology/Toxicology:

Agency: The Agency recommended that the Sponsor submit the following::

1. Final study reports.

2. Depending on the UV and visible light absorption spectra, the Agency may request that the Sponsor conduct a phototoxicity study in animals.

Sponsor: The Sponsor said that it may submit these spectra with the Annual Report but will double check this and so inform the Agency. If the Sponsor does not submit the requested data with the Annual Report, it will be submitted in the near future.

Biopharmaceutics:

Agency: The Agency recommended the following:

1. [redacted] For example, 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.

2. In general, PK studies are to be conducted in patients with severe disease conditions in large surface area of the skin consistent with labeling. If the drug product can be used with occlusion, the study should take this into consideration. The purpose is to examine the possible maximum systemic exposure. We would like to see results from a single topical application as well as from multiple applications.

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

Sponsor: The Sponsor said that [redacted] only tinea pedis will be studied. The Agency advised conducting one large surface area study. The Sponsor will submit a draft protocol for our review prior to conducting such a study. The Sponsor will conduct the multiple dose study during the Phase 3 clinical trials. The Sponsor will submit all of the data requested above in the near future.

The Agency and the Sponsor also discussed the following additional topics:

- Dose Ranging:

Agency: The Sponsor's Studies CL-3/CL-1 demonstrate 100% cure with [redacted] 2% sertaconazole. Will the Sponsor be providing information which informs all three elements of dose ranging - concentration, duration, and frequency? Could the Sponsor speak to the reasons for pursuing the 2% formulation?

Sponsor: The Sponsor presented graphs demonstrating time to clinical cure. Discussion of these graphs ensued, with comments from the Agency concerning the apparent end of treatment results at which time the 1% cream appeared to have increased efficacy over the 2% cream. The Sponsor will present additional dose ranging information to the Agency which addresses concentration, duration and frequency.

- Sample size calculations:

Agency: The Agency expressed concern that the sample size may be overpowered, and questioned the Sponsor's 40% lack of KOH/culture positivity.

Sponsor: The Sponsor discussed their basis for this percentage. The Sponsor and Agency will continue to look at this issue.

Biostatistics:

Agency: The Agency recommended that the Sponsor submit the following:

1. References to a [redacted] need to be removed from the protocol. Specific sections which include these references are sections which discuss total sample size, the randomization, and the design summary.

2. For the sample size calculation, the Sponsor should provide an explanation for the chosen estimates of the placebo and treatment responses. Also, the rationale for the chosen percentages of patient attrition and lack of confirmatory microscopy and cultures should be provided. Given the percentages chosen, the sample size calculation provided should be corrected to reflect 109 patients per treatment arm rather than [redacted] stated in the briefing package dated June 9, 1997.

3. A Modified Intent-to-Treat analysis, where only those patients with a positive baseline culture are included in the MITT population, should be performed on the data. The MITT includes <u>all</u> such patients dispensed study treatment.

Sponsor: The Sponsor will examine issue #2 in more detail and then submit the revised calculations to the Agency for its review.

Discussion Questions

1. Adapting the Global Assessment Scale to the recommendations of the Division, may MYLAN use 90-100% improvement as the index for "Clinical Cure"?

Agency: The Agency said that the clinical trial outcomes of interest should fall into 3 groups: completely cured, effectively treated, and mycological cure. Patients judged completely cured will be called **treatment successes** for statistical purposes. The Agency then discussed the TIME POINTS for assessment and the TRIAL OUTCOME CATEGORIES.

- Patient assessment time points:

  At a minimum, patient assessment should be documented at these clinical endpoints:

  1 ) Treatment Initiation (day 0).
  2) Final Treatment Visit (FTV), also known as End of Therapy (EOT).
  3) Final treatment visit plus two weeks (FTV + 2wks), also known as **Proof of Cure (POC) time point.** This visit should be considered the primary efficacy endpoint for proof of treatment success.

- Clinical trial outcomes - Patients should be classified for analysis into three groups: completely cured, effectively treated, and mycological cures:

  Completely Cured ($1^0$ efficacy endpoint): These are patients in whom all signs and symptoms have completely resolved. The KOH and culture should be negative, and physician's global assessment should be "cleared" - i.e., skin normal, not evidence of dermatophyte infection. Clinical signs and symptoms should be absent (i.e., 0 in scale, erythema, and pruritus) The Sponsor's four level ordinal scale (0-3) with O=None, 1=Mild, 2=Moderate and 3=Severe is appropriate for scoring. The Sponsor should DEFINE these levels to ensure similar coding among sites.

  Effectively Treated ($2^0$ efficacy endpoint): These are patients in whom the drug is determined to be therapeutically effective, although all clinical signs and symptoms have not completely resolved. This category is intended to include patients who have minimal residual clinical signs, but are essentially normal. The KOH and culture should be negative; global assessment should indicate at least 90% of interdigital area is clear; there should be no greater than minimal erythema, minimal scale; there should be no vesicles, papules, or pruritus.

  Mycological Cure ($2^0$ efficacy endpoint): The KOH and culture should be negative.

  Treatment Success: This includes patients who are completely cured at **point of cure.**

2. Can mycologic evidence of fungal infection be redefined to only a positive KOH preparation for all entrance and analysis criteria?

   Agency: Mycologic evidence of fungal infection at entry requires both a KOH and positive culture. Mycologic evidence at POC (FTV + 2 wks.) requires a negative KOH and negative culture. The Agency prefers that the KOH be read by a qualified individual who is not the principal investigator.

   Sponsor: The Sponsor will drop patients at two weeks if the fungal culture is negative.

3. Using the Division's recommendations for Treatment Success and Failure, recorded at the end of treatment and at two weeks following treatment, is there any regulatory requirement for a four week post treatment visit?

   Agency: The Agency stated that there is no such requirement.

Sponsor: The Sponsor acknowledged this advice.

4. [redacted]

Sponsor: The Sponsor indicated that they will consider this advice in their clinical development plan. At this time, they are [redacted] considering the indication interdigital tinea pedis.

The Agency and the Sponsor also discussed the following additional topics:

- Is the placebo the vehicle in these proposed trials?

Agency: The Agency inquired as to whether the "placebo" in the past and proposed trials was the vehicle?

Sponsor: The Sponsor confirms that the "placebo" was/will be the vehicle.

- [redacted]

Agency: The division asked the Sponsor how they intended to utilize this information, as this does not inform labeling or efficacy.

Sponsor: The Sponsor said that they will take this portion out of the protocol and use it for internal use only.

- [redacted]

Sponsor: The Sponsor asked if there was any Problem [redacted] . inclusion age [redacted] to 12 years.

Agency: The Agency agreed, provided that there are no preclinical concerns.

- The Agency and Sponsor agreed that the cut off date for removal of subjects due to negative culture results would be visit 3 (day 14).

The Agency advised the Sponsor of the following recommendations, which the Sponsor acknowledged. The Sponsor is actively reviewing and editing the protocol and will communicate with the Agency in the near future concerning these items:

- Inclusion criteria:

  The Agency advised the Sponsor that labeling may be based upon -information obtained in the pivotal trials, and items in the inclusion/exclusion criteria could impact the label. The Sponsor's protocol excludes women of child bearing potential. If all the pharmacology/toxicology data has been collected, the rationale for this exclusion should be presented to the Agency. Additionally, the protocol excludes persons with various concurrent diseases/conditions. Rationales for these exclusions should be presented.

  Inclusion criteria should include moderate involvement in each of the indicants (erythema, scale, and pruritus) in addition to a positive KOH and Culture.

- Concurrent medications:

  Attention should be given to the assessment of medications allowed during the trial. Topical antifungal lotions, powders, foot care products should be specifically excluded.

- Patient instructions:

  The Sponsor should understand that any instructions to the patient may be reflected in labeling, for example,

- Assessment questions:

  The responses on page 76 of the briefing packet are devoid of regulatory value, therefore we do not need this information included in the submission.

- Measurement of target lesion:

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

- Protocol correct population:

  The Agency considers it appropriate that dropouts be carried forward as **failures**. (The Sponsor's Per Protocol population excludes patients with a major protocol violation, which could exclude patients who dropped out (i.e., not compliant) due to therapy failure). The MITT is the efficacy population.

Decisions (agreements) reached:

The Sponsor agreed with all of the above-mentioned points and will submit all of requested data in the near future. In addition, the Sponsor said it would formally request a meeting to discuss CMC issues.

Unresolved issues or issues requiring further discussion:

None.

Signature, minutes preparer: LS
Concurrence Chair (or designated signatory): LS
Attachment/Handouts:

Briefing Package, dated June 9, 1997, submitted to FND 50,726, S/N 004
Copies of Overhead slides, dated June 23, 1997

cc:

Orig IND 50,726
HFD-540
HFD-540/DIV DIR/Wilkin
HFD-540/ACTING DERM TL/Walker/6.27.97
HFD-540/PHARM TOX TL/Jacobs
HFD-540/PHARM TOX/Mainigi/6.24.97
HFD-540/PHARM TOX/See/6.30.97
HFD-830/DIV DIR/Chen
HFD-540/CHEM TL/DeCamp
HFD-540/CHEM/Hathaway/6.30.97
HBFD-725/BIOSTAT TL/Srinivasan/7.1.97
HFD-725/BIOSTAT/Dixon/6.24.97
HFD-880/BIOPHARM TL/Bashaw
HFD-880/BIOPHARM/Lee/6.24.97
HFD-540/PROJ MGR/Cross
Drafted by: fhc/June 23, 1997 c:\wpfiles\ind\i50726a.mod
Initialed by:
final:

**MEMORANDUM OF MEETING**