CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-159

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-159

Medicis Pharmaceutical Corp
Attention: Carol Danielson
Director Regulatory Affairs
8125 North Hayden Road
Scottsdale, AZ 85258-2463

SEP - 6 2000

Dear Ms. Danielson:

Please refer to your new drug application (NDA) dated August 30, 1999, received September 8, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Loprox Shampoo (ciclopirox) Shampoo, 1%.

We acknowledge receipt of your submissions August 30, September 20, 28, October 20, 21, and December 9, 1999; January 10, 24, 31, February 3, March 22, 30, April 17, June 6, 9, July 13, 17, 20 (two), 25, and August 10, 2000.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

The sponsor needs to submit an adequate and well-controlled study to demonstrate the effectiveness of ciclopirox shampoo for the proposed labeling. Because there may be differences in populations, organisms, medical and/or hair care practices in Europe compared to the United States, it is recommended that this study either be performed in the United States or that the applicability of the study outcomes to the U.S. population, organisms, medical and/or hair care practices be documented.

Although not the basis for the Not Approvable action for this application, the following issues should be addressed in the resubmission:

Clinical

1. A rationale for the applicability of the clinical efficacy data collected in the European clinical studies and organisms studied to the US population and US medical practice.

2. Subset analyses of patients with dandruff, HIV infection, non-scalp seborrheic dermatitis, and different racial heritage.

3. An explanation of the the results of Study 3001, in which there was a higher disease relapse rate in the once per four day treatment arm than in the once per seven day treatment arm.

Chemistry

1. The drug product in US should have the same numeric microbial count specifications (i.e. , ≤ 100 CFU/g) as the EU specifications (see Vol. 1.3, page 6). This is also consistent with the acceptance limit of 100 aerobic microorganisms/g proposed elsewhere in the NDA. (Vol. 1.3, page 23). Revised regulatory specifications that include Total Aerobic Microorganism Counts of NMT 100 CFU/g should be provided.

2 Holding times and limits for the bulk drug product, both before and after ——— , are not stated in the manufacturing record. Please provide this information. If this information appears in a Standard Operating Procedure, please identify and provide a copy of it.

3. Release of the bulk drug product for filling is based solely on the appearance and viscosity testing. We recommend that an In-Process Control for Ciclopirox content be added at the point of release of bulk drug product for filling.

4. No specific reprocessing procedures are proposed. Please clarify that reprocessing operations will not be performed.

5. No description of the sampling procedure has been provided for the selection of stability samples to be taken during regular production runs. Please provide this information.

6. The applicant is advised to perform Microbial Contamination testing on each lot placed in the stability storage program; testing at expiry (at 36 months) would be adequate.

7. The statement "only one crystal form of ciclopirox is known" (Vol. 1.2, page 8) is not correct (See item #11 of the pre-NDA meeting minutes, Vol. 1.1, page 13). An amendment to the NDA with right of reference to approved NDAs for ciclopirox containing information on different crystal forms should be provided (see minutes from the telecon held on May 9, 2000).

Please be advised that at the time of approval you will be requested to conduct either a regular phase 4 carcinogenicity study, or a short-term study using the transgenic (TG.AC) mouse model.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop outs with new drop outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please call Victoria Lutwak, Project Management, at (301) 827-2020.

Sincerely,

/S/

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Office of Drug Safety

Memo

To: Jonathan Wilkin, M.D.
Director, Division of Dermatology and Dental Drug Products
HFD-540

From: Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator, Division of Medication Errors and Technical Support
HFD-420

Through: Alina R. Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

Jerry Phillips, R.Ph.
Associate Director, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

CC: Vickey Lutwak
Project Manger
HFD-540

Date: September 19, 2002

Re: ODS 00-0008-1; Loprox Shampoo 1% (Ciclopirox)
NDA 21-159

This memorandum is in response to a September 11, 2002, request from your Division for a re-review of the proprietary name, Loprox Shampoo 1%.

DMETS searched the *FDA Adverse Event Reporting System (AERS)* database for all postmarketing safety reports of medication errors associated with Loprox. The Meddra Preferred Term (PT), "Medication Error" and the drug names, Loprox% and Ciclopirox%, were used to perform the search.

A total of 1 report from the AERS search was retrieved and reviewed, however no report indicated name confusion with Loprox.

Additionally, DMETS held an Expert Panel discussion following the receipt of this consult and determined that the proposed name, Loprox Shampoo 1%, is a line extension of an already existing name. Therefore, DMETS has no objections to the use of this proprietary name.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-7847.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Tia Harper-Velazquez
9/23/02 10:45:11 AM
PHARMACIST

Alina Mahmud
9/23/02 11:32:32 AM
PHARMACIST

Carol Holquist
9/24/02 12:29:06 PM
PHARMACIST

Jerry Phillips
9/29/02 02:10:19 PM
DIRECTOR

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
DMETS	HFD-540 Vickey Lutwak

	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
-02		NDA 21-159	Resubmission to NA	August 29, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Loprox Shampoo 1%	6 mo review PDUFA date March 3, 2003		Jan 2003

NAME OF FIRM: Medicis Pharmaceutical Corp

REASON FOR REQUEST

I. GENERAL

Γ NEW PROTOCOL
Γ PROGRESS REPORT
Γ NEW CORRESPONDENCE
Γ DRUG ADVERTISING
Γ ADVERSE REACTION REPORT
Γ MANUFACTURING CHANGE/ADDITION
Γ MEETING PLANNED BY
Γ PRE-NDA MEETING
Γ END OF PHASE II MEETING
Γ RESUBMISSION
Γ SAFETY/EFFICACY
Γ PAPER NDA
Γ CONTROL SUPPLEMENT
Γ RESPONSE TO DEFICIENCY LETTER
Γ FINAL PRINTED LABELING
Γ LABELING REVISION
Γ ORIGINAL NEW CORRESPONDENCE
Γ FORMULATIVE REVIEW
xΓ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
Γ TYPE A OR B NDA REVIEW Γ END OF PHASE II MEETING Γ CONTROLLED STUDIES Γ PROTOCOL REVIEW Γ OTHER (SPECIFY BELOW):	Γ CHEMISTRY REVIEW Γ PHARMACOLOGY Γ BIOPHARMACEUTICS Γ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

Γ DISSOLUTION
Γ BIOAVAILABILTY STUDIES
Γ PHASE IV STUDIES
Γ DEFICIENCY LETTER RESPONSE
Γ PROTOCOL-BIOPHARMACEUTICS
Γ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

Γ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
Γ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
Γ CASE REPORTS OF SPECIFIC REACTIONS (List below)
Γ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
Γ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
Γ SUMMARY OF ADVERSE EXPERIENCE
Γ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

Γ CLINICAL
Γ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
Original consult sent 1-5-00

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

(Division/Office): DRA Peter Honig			FROM: HFD-540 Vickey Lutwak	
DATE 1-5-00	IND NO..	NDA NO. NDA 21-159	TYPE OF DOCUMENT	DATE OF DOCUMENT
NAME OF DRUG Loprox Shampoo 1%	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE April 2000	

NAME OF FIRM: Medicis Pharmaceutical Corp

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
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- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- x☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Evaluation of tradename: Loprox Shampoo 1%
Draft Bottle and Carton labels included for 30ml and ~~——~~ size.
Submitted 8-30-99
Goal Date July 8, 2000

URE OF REQUESTER Lutwak, PM, HFD-540 7-2073 V.L.	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

MEDICIS
PHARMACEUTICAL CORP.
The Dermatology Company•

RECEIVED
FEB 24 2003
MEGA/CDER

February 21, 2003

ORIGINAL

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Corporate 2, Room N214
Rockville, MD 20850

Minor Amendment

Re: NDA 21-159
Loprox® (ciclopirox) Shampoo 1%

BL

Dear Dr. Wilkin:

Reference is made to our NDA 21-159, dated August 30, 1999, submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Loprox (ciclopirox) Shampoo 1% and to the August 29, 2002, amendment to the referenced NDA.

Further reference is made to our February 8, 2003, and February 14, 2003, Minor Amendments including mock final printed labeling

All of the labeling pieces have been further revised to correct the spelling of "ophthalmic" within the three lines recently added to each of the labeling pieces in accordance with the February 14, 2003, teleconference with FDA. :

No other changes were made at this time. Electronic copies of the revised labeling pieces were submitted to Jacquelyn Smith, Project Manager, this morning.

Medicis appreciates FDA's commitment and coordination efforts as we approach the PDUFA deadline for this application.

Should you have questions or need additional clarification, please do not hesitate to contact Michelle Wells, RAC, Regulatory Affairs Manager, at 602-808-8800 or direct at 602-808-3851.

Sincerely,

Mitchell S. Wortzman, Ph.D.
Executive Vice President
Research and Development

8125 North Hayden Road, Scottsdale, AZ 85258
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: http://www.medicis.com
NYSE Symbol: MRX

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PHARMACEUTICAL CORP.
The Dermatology Company®

ORIGINAL

RECEIVED
FEB 19 2003
MEGA/CDER

February 14, 2003

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Corporate 2, Room N214
Rockville, MD 20850

Minor Amendment

Re: NDA 21-159
Loprox® (ciclopirox) Shampoo 1%

BL
ORIG AMENDMENT

Dear Dr. Wilkin:

Reference is made to our NDA 21-159, dated August 30, 1999, submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Loprox (ciclopirox) Shampoo 1% and to the August 29, 2002. amendment to the referenced NDA.

Further reference is made to our February 8, 2003, Minor Amendment including mock final printed labeling and to both the February 14, 2003, teleconference between Medicis representatives and FDA, and the subsequent fax from Jacquelyn Smith.

This amendment is being submitted in response to FDA's comments presented in the referenced teleconference. Complete responses to all of FDA's recommendations are included and summarized in Section II of the amendment.

Medicis appreciates FDA's commitment and coordination efforts as we approach the PDUFA deadline for this application.

Should you have questions or need additional clarification, please do not hesitate to contact Michelle Wells, RAC, Regulatory Affairs Manager, at 602-808-8800 or direct at 602-808-3851.

Sincerely,

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Executive Vice President
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N-000/41T

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PHARMACEUTICAL CORP.
The Dermatology Company®

RECEIVED
FEB 12 2003
MEGA/CDER

February 10, 2003

ORIG AMENDMENT

Jonathan K. Wilkin, M.D.
Director,
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Corporate 2, Room N214
Rockville, MD 20850

Re: NDA 21-159
Loprox® (ciclopirox) Shampoo 1%

Dear Dr. Wilkin:

Reference is made to our NDA 21-159, dated August 30, 1999, submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Loprox (ciclopirox) Shampoo 1% and to the August 29, 2002, amendment to the referenced NDA.

Further reference is made to the February 10, 2003, FDA fax requesting a commitment to a pharmacology/toxicology Phase 4 study.

Medicis commits to conducting an alternative, dermal carcinogenicity in transgenic mice — assay) with the ciclopirox shampoo in accordance with the time requirements specified in FDA's fax dated February 10, 2003.

Should you have questions or need additional clarification, please do not hesitate to contact Michelle Wells, RAC, Regulatory Affairs Manager, at 602-808-8800 or direct at 602-808-3851.

Sincerely,

for MW

Mitchell S. Wortzman, Ph.D.
Executive Vice President
Research and Development

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NYSE Symbol: MRX

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PHARMACEUTICAL CORP.
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RECEIVED
FEB 10 2003
MEGA/CDER

February 8, 2003

Jonathan K. Wilkin. M.D.
Director,
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Corporate 2, Room N214
Rockville, MD 20850

B2
ORIG AMENDMENT

Minor Amendment

Re: NDA 21-159
Loprox® (ciclopirox) Shampoo 1%

Dear Dr. Wilkin:

Reference is made to our NDA 21-159, dated August 30, 1999, submitted under section 505(b) of the Federal Food. Drug and Cosmetic Act for Loprox (ciclopirox) Shampoo 1% and to the August 29, 2002, amendment to the referenced NDA.

Further reference is made to the February 7, 2003, teleconference between Medicis representatives and Jacquelyn Smith, Regulatory Health Project Manager; Wilson DeCamp, Chemistry Team Leader; and Mamta Gautam-Basak, Chemistry reviewer.

Finally, reference is also made to the February 7, 2003, draft package insert labeling received from Ms. Smith.

This amendment is being submitted in response to FDA's comments presented in the referenced teleconference. Complete responses to all of FDA's recommendations are included and are summarized in Section II of the amendment.

Medicis appreciates FDA's commitment and coordination efforts as we approach the PDUFA deadline for this application.

Should you have questions or need additional clarification, please do not hesitate to contact Michelle Wells, RAC, Regulatory Affairs Manager, at 602-808-8800 or direct at 602-808-3851.

Sincerely,

for MW

Mitchell S. Wortzman, Ph.D.
Executive Vice President
Research and Development

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NYSE Symbol: MRX

14-000/C

MEDICIS
PHARMACEUTICAL CORP.
The Dermatology Company®

NEW CORRESP

RECEIVED
FEB 0 7 2003
MEGA/CDER

February 6, 2003

Jonathan K. Wilkin, M.D.
Director,
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Corporate 2, Room N214
Rockville, MD 20850

Re: **NDA 21-159**
Loprox® (ciclopirox) Shampoo 1%

Dear Dr. Wilkin:

Reference is made to our NDA 21-159, dated August 30, 1999, submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Loprox (ciclopirox) Shampoo 1%. Further reference is made to August 29, 2002, amendment to the referenced NDA and to the February 6, 2003 telephone request for safety update information.

Specifically this information is in response to the teleconference this morning with Jacquelyn Smith, Dr. Markham Luke, and Dr. Phyllis Huene regarding the safety update report reference in the Table of Contents of Volume 1, page 01-009 of the August 29. 2002. amendment to NDA 21-159 that incorrectly states that the update is "not applicable".

The Table of Contents should have referenced the Integrated Summary of Safety in Volume 14 of the referenced amendment. Specifically, page 14-063 begins the Summary of Periodic Safety Update Reports (PSURs) through July 31, 2002 (attached).

No additional clinical studies have been conducted in support of this application.

Should you have questions or need additional clarification, please do not hesitate to contact Michelle Wells, RAC, Regulatory Affairs Manager, at 602-808-8800 or direct at 602-808-3851.

Sincerely,

Mitchell S. Wortzman, Ph.D.
Executive Vice President
Research and Development

ORIGINAL

5125 North Hayden Road, Scottsdale, AZ 85258
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ORIGINAL

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RECEIVED
NOV 2 2 2002
MEGA/CDER

November 21, 2002

Jonathan K. Wilkin, M.D.
Director,
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Corporate 2, Room N214
Rockville, MD 20850

Bm
ORIG AMENDMENT

Re: **NDA 21-159**
Loprox® (ciclopirox) Shampoo 1%

Dear Dr. Wilkin:

Reference is made to our NDA 21-159, dated August 30, 1999, submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Loprox (ciclopirox) Shampoo 1%. Further reference is made to August 29, 2002, amendment to the referenced NDA and to the October 28, 2002, fax request from FDA for additional adverse event information.

Attachment 1 is a copy of the patient data listings of adverse reactions, as described in the original terms on the case report forms, together with the preferred terms. The table was previously submitted by fax to Victoria Lutwak on October 29, 2002.

Attachment 2 is a complete table with listing of adverse events for these individual categories:

- Subjects who received placebo
- Subjects who received treatment once per week
- Subjects who received treatment twice per week

Further reference is made to the voicemail left by Victoria Lutwak and Dr. Huene in which they indicated that the patient data listings were required only for skin and appendages, not all systemic reactions.

Should you have questions or need additional clarification, please do not hesitate to contact Michelle Ignace, Regulatory Affairs Manager, at 602-808-8800.

Sincerely,

for MW

Mitchell S. Wortzman, Ph.D.
Executive Vice President
Research and Development

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NYSE Symbol: MRX

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The Dermatology Company•

Barbara —
FYI —
The jacket is on its way from the doc. room —
We need to talk. —
/S/

RECEIVED
OCT 24 2002
MEGA/CDER

NEW CORRESP
nc

October 23, 2002

Jonathan K. Wilkin, M.D.
Director,
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Corporate 2, Room N214
Rockville, MD 20850

Re: NDA 21-159
Loprox® (ciclopirox) Shampoo 1%

Dear Dr. Wilkin:

In the not-approvable letter dated September 6, 2000, Medicis was advised that at the time of approval we would be requested to accept a Phase 4 commitment to conduct either a regular 2-year carcinogenicity study, or a 6-month study using the transgenic (TG.AC) mouse model.

After review of the two test methodologies, we propose meeting the commitment by conducting the 6-month study using the transgenic mouse model. We are seeking additional clarification on the potential ramifications of this decision. We would like the FDA to confirm that if the transgenic mouse test is positive, that we may repeat the test using the 2-year study as the definitive assay prior to affecting a labeling change. If the transgenic mouse study is negative, the FDA will consider the product negative.

Should you have questions or need additional clarification, please do not hesitate to contact Michelle Ignace, Regulatory Affairs Manager, at 602-808-8800.

Sincerely,

MIgnace/for

Mitchell S. Wortzman, Ph.D.
Executive Vice President
Research and Development

DUPLICATE

8125 North Hayden Road, Scottsdale, AZ 85258
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: http://www.medicis.com
NYSE Symbol: MRX

Message to be conveyed to the sponsor

The sponsor should be encouraged to conduct either a regular phase IV dermal carcinogenicity study, or a short-term study using the transgenic (TG.AC) mouse model.

APPEARS THIS WAY
ON ORIGINAL

MEDICIS
PHARMACEUTICAL CORP.
The Dermatology Company®

RECEIVED
SEP 2 0 2002
MEGA/CDER

September 19, 2002

NEW CORRESPONDENCE
BC

Jonathan K. Wilkin, M.D.
Director,
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Corporate 2, Room N214
Rockville, MD 20850

Re: NDA 21-159
Loprox® (ciclopirox) Shampoo 1% **Methods Validation Package**

Dear Dr. Wilkin:

Reference is made to our NDA 21-159, dated August 30, 1999, submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Loprox (ciclopirox) Shampoo 1%.

Further reference is made to the August 29, 2002, Major Amendment, and the subsequent fax from Victoria Lutwak dated September 18, 2002.

As requested in the referenced fax, enclosed please find three identical copies of the Methods Validation Package as submitted in Volume 1.3, paged 235-328, of the original NDA submission dated August 30, 1999. The methods remain unchanged.

Should you have questions or need additional information, please do not hesitate to contact Michelle Ignace, Regulatory Affairs Manager, at 602-808-8800.

Sincerely,

Mitchell S. Wortzman, Ph.D.
Executive Vice President
Research and Development

ORIGINAL

8125 North Hayden Road, Scottsdale, AZ 85258
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: http://www.medicis.com
NYSE Symbol: MRX

MEDICIS
PHARMACEUTICAL CORP.
The Dermatology Company®

August 29, 2002

RECEIVED
SEP 03 2002
MEGA/CDER

Jonathan K. Wilkin, M.D.
Director,
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Corporate 2, Room N214
Rockville, MD 20850

NDA ORIG AMENDMENT
BZ changed in doc. from to
A2

Re: NDA 21-159
Loprox® (ciclopirox) Shampoo 1%

Major Amendment

Dear Dr. Wilkin:

Reference is made to our NDA 21-159, dated August 30, 1999, submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Loprox (ciclopirox) Shampoo 1%.

Further reference is made to the September 6, 2000, Not Approvable letter from FDA to Carol Danielson, former Director of Regulatory Affairs at Medicis Pharmaceutical Corp. and to the July 26, 2002, letter from Dr. Mitchell Wortzman, providing formal 30-day notice of our intent to submit an Amendment to the referenced NDA.

Electronic and paper copies of this amendment are enclosed . This amendment is a complete response to the deficiencies outlined in the September 6, 2000, Not Approvable letter.

Should you have questions or need additional information, please do not hesitate to contact Michelle Ignace, Regulatory Affairs Manager, at 602-808-8800.

Sincerely,

Mitchell S. Wortzman, Ph.D.
Executive Vice President
Research and Development

ORIGINAL

8125 North Hayden Road, Scottsdale, AZ 85258
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: http://www.medicis.com
NYSE Symbol: MRX

MEDICIS
PHARMACEUTICAL CORP.
The Dermatology Company®

March 12, 2001

Jonathan K. Wilkin, M.D. Director
Food and Drug Administration
Division of Dermatologic and Dental Drug Products (HFD 540)
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Corporate 2, Room N214
Rockville, MD 20850

RE: ———
Loprox® (ciclopirox) Shampoo, 1%
Request for Type A (critical path) Meeting
Serial No. 23

Dear Dr. Wilkin:

This correspondence is a formal request for a type A (critical path) meeting (teleconference) with the Division of Dermatological and Dental Drug Products as defined under your draft "Guideline for Industry; Formal Meetings for Sponsors and Applicants for PDUFA Products". The purpose of this meeting is to discuss your correspondence with Medicis Pharmaceutical Corporation dated February 16, 2001 in which you provided us with detailed comments on protocol 00-017 (Parexel study number 14262) entitled:

> A Vehicle-controlled, Randomized, Double-blind, Multicenter Study of the efficacy and safety of 1%Ciclopirox Shampoo in the Treatment of Seborrheic Dermatitis of the Scalp.

We received a telephone call from Ms. Victoria Lutwak, project manager, following your February 16, 2001 letter informing us that Medicis would be required to address FDA comments Nos. 5 and 7 prior to requesting a meeting with the Division. In addition, we are including our response to comment No. 9, because we believe that resolution of the twice — a week dosing is critical to our protocol design.

In addition to the three comments and responses noted above, Medicis would like to reach agreement with FDA on the remaining issues raised in the 45-day protocol review. Medicis will submit responses to all the agency comments prior to our scheduled meeting date and

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in the timeframe outlined in the guidance. Because the design of this protocol is critical to the approval of Loprox Shampoo 1%, it is Medicis' intention to reach agreement with FDA on all the issues raised by the agency.

Medicis would like to thank the Division of Dermatological and Dental Drug for responding to our request for 45-day protocol review. We understand from your February 16, 2001 correspondence that if statistical significance is reached for primary efficacy analysis in the Intent-to-Treat population, as defined by FDA, and if there is adequate representation of U.S. ethnic groups, Loprox Shampoo 1% will have met FDA requirements for both demonstration of efficacy and applicability to the US population. We also understand that agreement must be reached with FDA on all the protocol-related issues raised in your correspondence.

Medicis representatives will be available for a teleconference with the Division of Dermatological and Dental Drugs at any time convenient to the agency with the exception of March 19, March 23 through March 28 and April 6 and 9. Medicis' responses to FDA comments No's. 5, 7, and 9 are included as an attachment along with a list of Medicis representatives who will participate in the teleconference. Medicis' responses to the remaining comments will be forwarded to FDA prior to our teleconference.

If there are any questions regarding this request please contact me at (602) 667-3965.

Sincerely,

Carol H. Danielson
Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Responses to FDA 45 day Protocol Review

The following are responses to FDA comments No's. 5, 7, and 9 on Study Protocol 00-017. The bolded information reflects comment from FDA followed by the response from Medicis Pharmaceutical Corp.

Clinical

Comment No. 5.

Before we can commit to a possible two-week washout period proceeding the treatment period, please provide a discussion of how this would simulate marketed conditions of use for your product.

Response

Medicis will delete the two week wash out period included in the current protocol. However, an exclusion criterion will be added for patient recruitment. Patients will be excluded from enrollment if a prescription or over-the-counter medicated shampoo is used within the 2 weeks period prior to study enrollment. Excluded medicated shampoos include anti-fungals, tar, selenium sulfide, zinc pyrithione, salicylic acid, sulfur, or any combination of these agents. In addition, Medicis may, after consultation with our statisticians, choose to increase the study population to take into account any unforeseen impact that may result from deletion of the wash out period.

Comment No. 7

Before we can commit to a possible change in enrollment criteria during the study, please provide a discussion of how this will affect the statistical analysis of the data.

Response

FDA requested for study 3001 that at least 70% of the patients should have scores of 3 (moderate) or worse at inclusion. The procedure outlined in section 5.1 of the study protocol has been adopted from study 3001 to meet this request. No change of the enrollment criteria for study 3001 due to this was required because the percentage of mild cases was very low. Should a change be needed in the current study, it would affect both treatment groups in the same way and thus not bias the treatment comparison; nevertheless in this case the sponsor suggests that an exploratory subgroup analysis be provided for the primary efficacy criterion (stratification: enrolled before/after this change of the enrollment criteria).

Comment No. 9

Please provide adequate justification for the proposed use of the drug product twice weekly in Study 00-017. Results of Study 3001 (Segment A) indicate that both [redacted] and twice weekly were equally efficacious. Use of the product twice weekly appears to provide additional drug exposure without apparent clinical benefit. A rational for using the product twice weekly instead of [redacted] weekly should be provided.

Response

Although both the [redacted] and twice per week treatment arms were significantly more efficacious than vehicle alone (P=0.0015 and P=0.0001) the response rate in the twice per week group was superior. Patients treated [redacted] per week has a response rate of 45.5% compared to 31.6% for vehicle and patients in the twice per week group had a response rate of 58.5% compared to 31.6% for vehicle.

Ciclopirox has a long history of topical use in the form of creams, lotion and gels with an excellent safety profile. Therefore, given the greater clinical response in the twice a week treated group and the low level of adverse events associated with ciclopirox use generally, the sponsor believes that twice a week treatment is the preferred regimen for Loprox Shampoo 1%.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DURG ADMINISTRATION

Form Approved: OMB NO. 0910-0014.
Expiration Date: September 30, 2002
See OMB Statement on Reverse.

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

/S/ OFFICIAL COPIES HAVE BEEN SUBMITTED TO APPROPRIATE IND OR NDA

1. NAME OF SPONSOR
Medicis Pharmaceutical Corp.

2. DATE OF SUBMISSION
4/12/2001

3. ADDRESS (*Number, Street, City, State and Zip Code*)
8125 N. Hayden Road, Scottsdale, AZ 85258

4. TELEPHONE NUMBER (*Include Area Code*)
602.808.8800

5. NAME(S) OF DRUG (*Include all available names: Trade, Generic, Chemical, Code*)
Loprox (ciclopirox) Shampoo 1%

6. IND NUMBER (*If previously assigned*)

7. INDICATION(S) (*Covered by this submission*)
Treatment of seborrheic dermititis of the scalp

8. PHASE(S) OF CLINICAL INVISTIGATION TO BE CONDUCTED:
☐ PHASE 1 ☐ PHASE 2 ☒ PHASE 3 ☐ OTHER _____ (Specify)

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC *APPLICATIONS (21 CFR Part 314)*, DRUG MASTER FILES (*21 CFR Part 314.420*), AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.
NDA 21-159

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
023

11. THIS SUBMISSION CONTAINS THE FOLLOWING: (*Check all that apply*)

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☐ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☐ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO WRITTEN REPORT
☐ NEW INVESTIGATOR	☐ CLINICAL	

☒ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☒ OTHER **Formal request for a type A meeting** (*Specify*)

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUMBITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7 (d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- ☑ 1. Form FDA 1571 *[21 CFR 312.23 (a)(1)]*
- ☐ 2. Table of Contents *[21 CFR 312.23 (a)(2)]*
- ☐ 3. Introductory statement *[21 CR 312.23 (a)(3)]*
- ☐ 4. General Investigational plan *[21 CR.312.23 (a)(3)]*
- ☐ 5. Investigator's brochure *[21 CR 312.23 (a)(5)]*
- ☐ 6. Protocol(s) *[21 CR 312.23 (a)(6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23 (a)(6)]*
  - ☐ b. Investigator data *[21 CFR 312.23 (a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23 (a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23 (a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23 (a)(7)(iv)(e)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23 (a)(7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23 (a)(9)]*
- ☐ 10. Additional information *[21 CFR 312.23 (a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, WIL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE COTRACT RESEARCH ORGANIZATION? ☐ YES ☒ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICAITON OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

NAME AND TITLE OF THE PERSON REPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINCAL INVESTINGATIONS

Mitchell Wortzman Ph.D., Executive Vice President Research & Development, Medicis Pharmaceutical Corp.

15. NAME(S) AND TITLE(S) OF THER PERSON(S) REPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

John Strauss M.D., University of Iowa Hospitals and Clinics

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Carol Danielson, Director Regulatory Affairs	Carol Danielson	
17. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
8125 N. Hayden Road, Scottsdale, AZ 85258	**602.808.8800**	3-12-01

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
5516 Nicholson Lane
Kensington, MD 20835

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please **DO NOT RETURN** this application to this address.

MEDICIS
PHARMACEUTICAL CORP.
The Dermatology Company

August 10, 2000

AMENDMENT

Vickey Lutwak
Food and Drug Administration
Division of Dermatologic and Dental Products
CDER-HFD-540, Room 242
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 21-159 Loprox (ciclopirox) Shampoo 1% - Information request dated August 8, 2000, M&C Chemist Specification and Stability Protocol update

Ms. Lutwak:

Attached please find the updated information stated above. The Product Regulatory Specifications dated August 10, 2000 are the specifications that represent the regulatory specifications for the drug product. These specifications are adequate to insure the identity, strength, quality and purity of LOPROX Shampoo manufactured at Patheon Inc.

The post-approval commitments are included for the Stability Protocol they are located on the preceding page, Vol. 1.3, page 220.

If there is further information regarding this agreement please feel free to call me at (602) 808-3813.

Sincerely,

Lynn C. Hansen

Lynn C. Hansen
Regulatory Affairs

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MEDICIS
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July 25, 2000

AMENDMENT
BC

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MEGA
EVALUATION AND RESEARCH

Vickey Lutwak
Food and Drug Administration
Division of Dermatologic and Dental Products
CDER-HFD-540, Room 242
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 21-159 Loprox (ciclopirox) Shampoo 1%
Information per request of May 25, 2000

Ms. Lutwak:

Enclosed please find the information requested on May 25, 2000 for the above stated subject.

1. *The container-closure system, as described in Vol. 1.2, page 277, does not include a — From the draft labeling, it is clear that a ——— . Please clarify your intended marketing configuration. If ar —— is used, please describe how the ——— . (as needed for use). Furthermore, for comparison, please submit a design drawing for the container-closure system used in the clinical trials, if different from that to be marketed, or a description of how this volume was measured in the clinical trials.*

Response:
The container-closure system described on page 277 of Vol. 1.2 does provide a — it is referenced as the ——— The reference to the possible use of the ——— for the shampoo in package insert was to provide the customer with an easy reference to the amount of shampoo needed for coverage of the effected area. The ——— I dose but should only be considered as a reference. The capacity of the ——— is determined by the manufacturing dimensions of the — Medicis would like to propose similar wording to other medicated shampoos for the insert that would ——— for measurement purposes. Medicis would like to propose the following under the Dosage and Administration Section:

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Bottles used in the clinic were the same as the bottles on stability and intended for commercialization but were taller in height. The — were adjusted to accommodate the length of the bottleneck.

2. *Many times in the submission there is reference to the —. size along with the 30 and —. sizes, would you clarify for the Agency which size(s) you plan to market in the US.*

Response:
Currently Medicis has chosen not to launch LOPROX Shampoo in a — presentation. We acknowledge that data has been presented on the — presentation by Aventis, Germany and will determine the time frame for inclusion at a later date. FDA permitted bracketing of the — bottle on the stability program at Patheon, Inc. (see page 13 of submission, item 8, of the pre-NDA meeting minutes). Medicis commits to place the first batch of the — presentation on stability and report the initiation of the presentation to market in an Annual Report.

3. *The absorption spectrum form —— for the drug product and drug substance was not found in the NDA. If this information was provided, provide us the volume and page number(s), or, if not in the NDA, send us this information.*

Response:
Attached are the absorption spectra for the drug substance and the drug product. The Drug Substance lot measured was A046.01 and the Drug Product lot number was FD347B003. Please see Attachment 2 for the spectra.

4. *To date the Agency has 1 month of stability data for the batch manufactured at the commercial site (Patheon, Inc.) in the NDA submission. (See your amendment dated April 17, 2000.) What are the intentions as to supplying more stability data before the 10 month PUDFA goal date?*

Response:
The nine (9) month stability study for LOPROX Shampoo product manufactured at the commercial site, Patheon, Inc., has been submitted to the agency. The stability report was submitted on June 06, 2000.

If there is further information regarding this agreement please feel free to call me at (602) 808-3813.

Sincerely,

Lynn C. Hansen RA

Lynn C. Hansen
Regulatory Affairs

Attachments:
1) FDA Request for Information – May 25, 2000
2) Absorption spectrum
3) Page 13 of Submission, Item 8 of the pre-NDA meeting minutes
4) Cover Letter – June 06, 2000 Submission to NDA

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ON ORIGINAL

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Vickey Lutwak
Food and Drug Administration
Division of Dermatologic and Dental Products
CDER-HFD-540, Room 242
9201 Corporate Blvd.
Rockville, MD 20850

July 20, 2000

AMENDMENT

BB

Re: NDA 21-159 Loprox (ciclopirox) Shampoo 1% - Information requested on May 25, 2000 regarding Pharmacokinetics and Pharmacodynamics sections of package insert and Study 202.

Ms. Lutwak:

Enclosed please find the information requested on May 25, 2000 for the above stated subject.

- *Request*
  "At what level was the trial reported as study #202 originally powered and, what was the eventual power of the study (i.e. post-hoc power)?"

- Response

  For study HOE296B/2/D/202/SE —— , titled: 'Study on the serum and urine pharmacokinetics, safety and efficacy of ciclopirox 1% shampoo after exaggerated use with increasing contact time in patients suffering from seborrhoeic dermatitis', no confirmatory statistical test was scheduled and so no formal power consideration was carried out.

  Regarding the sample size it is stated in the protocol under '3.3.1 Statistical basis for sample size': Due to the explorative character of this study, 12 patients were regarded as sufficient for obtaining data about the pharmacokinetic profile of ciclopirox after exaggerated use.

  The primary objectives of this study were:

  (1) To determine the serum concentrations and the pharmacokinetic characteristics of total (free and conjugated) and free ciclopirox in patients with seborrhoeic dermatitis after single dosing of 1% shampoo with 3 minutes contact time as well as after multiple dosing of 1% shampoo with 3 and 6 minutes contact time.

  (2) To measure the urinary excretion of total (free and conjugated) ciclopirox during 24 hours after single dosing with 3 minutes contact time and after multiple dosing with 3 and 6 minutes contact time.

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The first aim couldn't be accomplished with this study. Due to the large number of serum concentration samples of ciclopirox below LOQ the evaluation of pharmacokinetic characteristics from serum concentrations of ciclopirox was not reasonable.

Concerning the second point, the amount of excreted ciclopirox after the first administration with 3 minutes contact time, after two weeks of daily administration with 3 minutes contact time, and after two weeks of daily administration with 6 minutes contact time were determined.

For this multiple comparison test, power calculations are normally not done because even the definition of "power" is unclear. However, a post hoc analysis by means of the Dunnett test was performed.

Regardless of the variable and time points for comparison specified a paired t-test with a sample size of 12 (0.050 one-sided significance level) would have 80% power to detect a difference in means between two measurement points of 0.77 of true effect size (i.e. mean difference / standard deviation).

The additional request to update the package insert under Pharmacokinetics and Pharmacodynamics Sections remains in process. This will be included in the updates with the various other changes to the package insert, product name change request (dated July 13 and 17, 2000) and the amendment to package insert dated July 20, 2000.

If there is further information regarding this response please feel free to call me at (602) 808-3813.

Sincerely,

Lynn C. Hansen

Lynn C. Hansen
Regulatory Affairs

Attachments: 1) FDA Request for Information – May 25, 2000
2) Response to FDA Request – July 13 and 17, 2000
3) Amendment to Package Labeling – July 20, 2000

MEDICIS
MANUFACTURING CORP.
The Dermatology Company

Vickey Lutwak
Food and Drug Administration
Division of Dermatologic and Dental Products
CDER-HFD-540, Room 242
9201 Corporate Blvd.
Rockville, MD 20850

July 17, 2000

NDA DRUG AMENDMENT

Re: NDA 21-159 Loprox (ciclopirox) Shampoo 1% - Response to remaining issue presented in June 26, 2000 FDA request.

BC

Ms. Lutwak:

Enclosed please find the information requested on June 26, 2000 for the above stated subject.

- Request:
  On page 100 (Tab Annotated Package Insert) under How Supplied it is indicated that "once opened, the shampoo may be used for up to 8 weeks." This should also be indicated on the primary container labeling under the same section.

- Response:
  Medicis would like to have this statement removed from the original referenced section and would not like to have this on any labeling. Aventis, Germany performed an in-use stability evaluation on one lot packaged in the 100 ml presentation. There was no significant change to the samples when stored at room temperature at the 8 week end point of this single test (see Vol. 1.3, page 153, Stability Report, section 11.6). Therefore, we do not feel that a statement limiting the usage of an opened container to eight (8) weeks on the primary container label or the package insert is appropriate or needed.

If there is further information regarding this agreement please feel free to call me at (602) 808-3813.

Sincerely,

Lynn C. Hansen
Regulatory Affairs

ORIGINAL

Attachments: FDA Request for Information – June 26, 2000
Vol. 1.3, page 153, Stability Report, section 11.6

8125 North Hayden Road, Scottsdale, AZ 85258-2463
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Web Site: http://www.medicis.com

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Vickey Lutwak
Food and Drug Administration
Division of Dermatologic and Dental Products
CDER-HFD-540, Room 242
9201 Corporate Blvd.
Rockville, MD 20850

July 20, 2000

AMENDMENT
BL

Re: NDA 21-159 Loprox (ciclopirox) Shampoo 1% - Amendment to Draft Labeling

Dear Ms. Lutwak:

There are some additional changes to the package insert that we would like to modify. The changes are not administrative in content and do not effect the clinical aspects of the document. Comments from FDA would be appreciated so the DRAFT labeling can be completed.

1. Storage statement:
   Current wording submitted: "Store between 15° and 30°C (59° and 86°F)"

   Proposed wording: —

2. Remove – —

   Proposed wording and addition to section:
   Information for Patients:
   5. —

I hope to send in the updated package insert with all the updates that have been requested by FDA including these modifications by early next week so the NDA submission review can proceed. Please forward your comments on these proposed changes.

If there is further information regarding this agreement please feel free to call me at (602) 808-3813.

Sincerely,

Lynn C. Hansen

Lynn C. Hansen
Regulatory Affairs

8125 North Hayden Road, Scottsdale, AZ 85258-2463
Telephone: 602 808-8800 Facsimile: 602 808-0822
Web Site: http://www.medicis.com

This application contains the following items: *(Check all that apply)*

- [x] 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- [ ] 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- [ ] 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- [ ] 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- [ ] 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- [x] 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - [x] a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - [ ] b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - [ ] c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - [ ] d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- [ ] 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - [ ] Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- [ ] 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- [ ] 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- [ ] 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? [x] YES [ ] NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? [x] YES [ ] NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Rosario G. Ramirez
Medical / Regulatory Affairs

Jerry S. Roth
President

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notific by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the I those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each o studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applic regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Rosario G. Ramirez	Rosario G. Ramirez	
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
2650 So. Mellonville Ave. Sanford, Florida 32773	(407) 323-1887	21 JULY 2000

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instruc searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send com regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Office:
Paperwork Reduction Project 0910-0014
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please **DO NOT RETURN** this application to this address.

MEDICIS
MANUFACTURING CORP.
The Dermatology Company

July 13, 1999

Vickey Lutwak
Food and Drug Administration
Division of Dermatologic and Dental Products
CDER-HFD-540, Room 242
9201 Corporate Blvd.
Rockville, MD 20850

AMENDMENT
BC

Re: NDA 21-159 Loprox (ciclopirox) Shampoo 1% - Information per request of June 26, 2000

Ms. Lutwak:

Enclosed please find the information requested on June 26, 2000 for the above stated subject.

- *Request*
  All Labeling (carton, bottle and package insert) must be modified to reflect the proprietary name and to show the dosage form in the following format:

  LOPROX® (ciclopirox) Shampoo, 1%

- Response
  Final "DRAFT" labeling for Loprox Shampoo carton, bottle labeling and package insert are in the process of being created and finalized. Medicis would like to request an amendment to the modification of the proprietary name format provide in the June 26 communication. The following change is requested:

  FDA:
  LORPOX® (ciclopriox) Shampoo, 1%

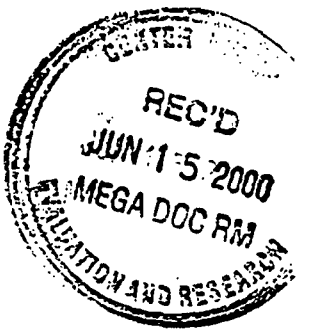
  Medicis Proposal:
  Loprox® (ciclopriox) Shampoo 1%.

Currently Medicis maintains the proprietary name of products as stated in the proposal above for the first time the name appears in a document (Description section of the insert), column or page followed by LOPROX Shampoo after the first appearance. Medicis would appreciate following this format for the shampoo product.

8125 North Hayden Road, Scottsdale, AZ 85258-2463
Telephone: 602 808-8800 Facsimile: 602 808-0822
Web Site: http://www.medicis.com

PHARMACEUTICAL CORP.
The Dermatology Company®

June 6, 2000



Vickey Lutwak
Food and Drug Administration
Division of Dermatologic and Dental Products
CDER-HFD-540, Room 242
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 21-159 Loprox (ciclopirox) Shampoo 1% - Stability Report for Patheon Manufacturing Facility.

Ms. Lutwak:

Enclosed please find the requested Stability Report from Patheon Inc., the alternate manufacturing facility filed in the above stated NDA. The stability report contains nine (9) month controlled room temperature and intermediate temperature, and six month (6) accelerated data on the three (3) lots manufactured by Patheon. This now finalizes the request from FDA dated November 17, 1999.

If there is further information regarding this agreement please feel free to call me at (602) 808-3813.

Sincerely,

Lynn C. Hansen

Lynn C. Hansen
Regulatory Affairs

8125 North Hayden Road Scottsdale, AZ 85258-2463
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: http: www.medicis.com
NYSE Symbol: MRX

MEDICIS
PHARMACEUTICAL CORP.
The Dermatology Company

AMENDMENT
BC

VIA PRIVATE COURIER

June 9, 2000

Vickey Lutwak
Food and Drug Administration
Division of Dermatologic and Dental Drug Products
CDER/HFD-540 Room 242
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 21-159
Loprox (ciclopirox) Shampoo 1% - Methods Validation Package
UPDATE: FDA Request of February 25, 2000

Dear Ms. Lutwak:

Enclosed please find the information requested on February 25, 2000 regarding the update of the Samples and Analytical Data Validation Package. The information request is included for your reference as Attachment A. The Validation Section, Attachment B, has been updated to include the following information.

Attachment C: Certificates of Analysis for Drug Product manufactured at Patheon Inc.

Attachment D: Certificates of Analysis for the Reference Standard 6-cyclohexyl-4-methyl-2-pyrone. Updated analysis originally submitted in the submission, page 263.

Attachment E: Labeling of Ciclopirox Shampoo FDA Samples Manufactured by Patheon Inc.

Attachment F: Labeling of Ciclopirox Drug Substance and Reference Standards FDA Samples

Attachment G: Regulatory Specification of Ciclopirox Substance.

Attachment H: Material Safety Data Sheets for Reference Standards and LOPROX Shampoo

If there is further information regarding this agreement please feel free to call me at (602) 808-3813.

Sincerely,

Lynn C Hansen

Lynn C. Hansen
Regulatory Affairs Manager

8125 North Hayden Road, Scottsdale, AZ 85258-2463
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: http://www.medicis.com
NYSE Symbol: MRX

MEDICIS
PHARMACEUTICAL CORP.
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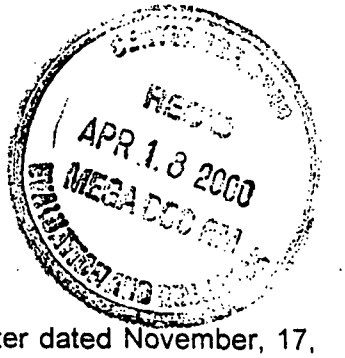
Ms. Vickey Lutwak
Food and Drug Administration
Division of Dermatologic and Dental
Drug Products, (HFD-540)
DNDC III, Office of New Drug Chemistry
Center for Drug Evaluation and Research
Rockville, MD 20857

April 17, 2000



RE: NDA 21-159: Information Request

Dear Ms. Lutwak:

The following are responses to your request for information letter dated November, 17, 1999 regarding our NDA submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Loprox® (ciclopirox) Shampoo 1%. I have included a copy of the letter for ease of review as Attachment A. The bolded information reflects the comment from FDA followed by the response from Medicis Pharmaceutical Corporation.

1. **For your information the DMF Number for Patheon's manufacturing facilities is 5252 (not 134273 as stated in the Letter of Authorization on Volume 2, p.232). The Establishment Registration Number for the manufacturing site is 134273.**

The correction of Patheon's manufacturing facility DMF number to 5252 has been noted.

2. **Revised Letters of Authorizations for DMF 5252 ( ) should be submitted.**

Please see the attached Letter of Authorization from Patheon regarding DMF 5252. Additionally, please find the updated information from on the DMF an authorization letter allowing Medicis Pharmaceutical Corporation to reference the DMF and correspondence from FDA, acknowledgment of DMF submission, to Dated June 17, 1999. These documents are provided in Attachment B.

3. **On p. 121 (Vol. 1) it is indicated that stability results for batches produced at the commercial site will be submitted in the annual reports. This is not consistent with the commitment made at the pre-NDA meeting on April 29, 1999, concerning (see item 17, page 14).**

Nine (9) month stability data at 25°C/60%RH has just completed testing in the laboratory. An interim stability report is being generated and will be submitted to this submission as soon as it is finalized.

ORIGINAL

8125 North Hayden Road, Scottsdale, AZ 85258-2463
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: http://www.medicis.com
NYSE Symbol: MRX

Aventis Pharmaceuticals

Aventis

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
APR 0 6 2000
MEGA

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Document Control Room 17B-45
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-159
Loprox 1% Shampoo
(ciclopirox)

General Correspondence:
Confirm Dating of Documents of Study #201, 202 and 3001 Assay Methods

Dear Sir/Madam:

Please refer to the telefax dated March 27, 2000 requesting confirmation that the documents referred to in the study reports (#201, 202, and 3001 Assay methods) and the report sent in the NDA amendment are the same.

Aventis Pharmaceuticals Inc. confirms that these documents are the same. The difference is in the European dating (day/month/year) vs. US dating (month/day/year).

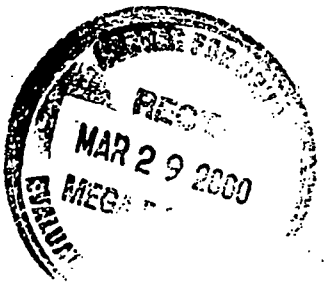
Sincerely,
Aventis Pharmaceuticals Inc.
Mail Station H4-M2316

J. Michael Nicholas, Ph.D.
Vice President, US Drug Regulatory Affairs

ORIGINAL

Aventis Pharmaceuticals · 10236 Marion Park Drive · P.O. Box 9627 · Kansas City, MO 64134-0627
Telephone (816) 966-5000 · www.aventispharma-us.com

MEDICIS
PHARMACEUTICAL CORP.
The Dermatology Company



NDA DRUG AMENDMENT

March 22, 2000

Food and Drug Administration
Document Control
Division of Dermatologic and Dental Products
5600 Fishers Lane
Rockville, MD 20857

BM

Re: Amendment to NDA 21-159 Loprox (ciclopirox) Shampoo 1%

Dear Madam/Sir:

Enclosed please find the updated table as requested by the clinical reviewer. Please amend the NDA with this page, Volume 1.37 page 78.

If there are any further questions please feel free to call me at (602) 808-3813.

Sincerely,

Lynn C. Hansen

Lynn C. Hansen
Regulatory Affairs

cc: Desk Copy – Ms. Vickey Lutwak – Program Manager FDA

ORIGINAL

8125 North Hayden Road, Scottsdale, AZ 85258-2463
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: http://www.medicis.com
NYSE Symbol: MRX

MEDICIS
PHARMACEUTICAL CORP.
The Dermatology Company®

February 3, 2000

NC

FEB 0 4 2000

Food and Drug Administration
Document Control Room 17B-45/PKLN
CDER/ODEV/DDDDP HFD-540
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-159 LOPROX Shampoo 1%
GENERAL CORRESPONDENCE; REPORT CHANGE OF ADDRESS

Dear Madam/Sir:

This letter is to inform you that the address of the corporation sponsoring the above-mentioned application has been changed. Enclosed please find an updated FDA Form 356h reflecting the change of address.

Thank you in advance for reflecting our new address in your records. The new mailing address is:

8125 North Hayden Road
Scottsdale, AZ 85258

602.808.8800 - Telephone
602.808.3894 - Facsimile

This address change will be effective on **February 7, 2000**. Please note that MEDICIS' telephone numbers and direct facsimile numbers will remain unchanged.

Please be advised that there have been no other changes in relation to the studies ongoing or the responsible individuals. You will be advised if any changes occur as appropriate.

Sincerely,

Lynn C. Hansen

Lynn C. Hansen
Regulatory Affairs Manager

ORIGINAL

4343 East Camelback Road, Phoenix, AZ 85018-2700
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: http://www.medicis.com
NYSE Symbol: MRX

MEDICIS
MANUFACTURING CORP.
The Dermatology Company

NDA
SU

January 31, 2000

Vickey Lutwak
Food and Drug Administration
Division of Dermatologic and Dental Products
CDER-HFD-540, Room 242
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 21-159 Loprox (ciclopirox) Shampoo 1% - Periodic Safety Update Report

Ms. Lutwak:

Enclosed please find the information stated above. The date range ends October 1999, do you require a different date range? If the range needs to be modified please forward that request on to me.

If there is further information regarding this agreement please feel free to call me at (602) 808-3813.

Sincerely,

Lynn C Hansen

Lynn C. Hansen
Regulatory Affairs

4343 East Camelback Road Phoenix, AZ 85018-2700
Telephone: 602 808-8800 Facsimile: 602 808-0822
Web Site: http://www.medicis.com

ORIGINAL

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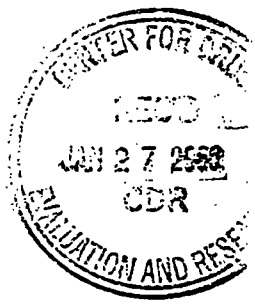
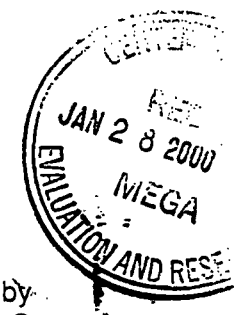
PHARMACEUTICAL CORP.
The Dermatology Company®





January 24, 2000

Vickey Lutwak
Food and Drug Administration
Division of Dermatologic and Dental Products
CDER-HFD-540, Room 242
9201 Corporate Blvd.
Rockville, MD 20850

B 1

Re: NDA 21-159 Loprox (ciclopirox) Shampoo 1%

Ms. Lutwak:

Enclosed please find an additional copy of the information sent to FDA on October 24, 1999. The documents are listed below for easy reference;

Determination of HOE 296b (Ciclopirox; Batrafen®, Loprox®) in urine by — , 26 pages and Determination of HOE 296b (Ciclopirox; Batrafen®, Loprox®) in serum by — 23 pages.

Page 153 from the submission, discussing the microbial purity and preservative efficacy of the Drug Product.

The index, page 65 of the submission, for a special Microbiology Section.

If there is further questions regarding this information please feel free to call me at (602) 808-3813.

Sincerely,

Lynn C Hansen

Lynn C. Hansen
Regulatory Affairs

ORIGINAL

4343 East Camelback Road, Phoenix, AZ 85018-2700
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: http://www.medicis.com
NYSE Symbol: MRX

Aventis Pharmaceuticals

Aventis

NEW CORRESP

January 10, 2000

Food and Drug Administration
Division of Dermatologic and Dental Drug Products (HFD-540)
Central Document Room 17B-45
9201 Corporate Blvd
Rockville, MD 20850

Subject: NDA 21-159
LOPROX® Shampoo
(ciclopirox)

GENERAL CORRESPONDENCE
Company Name Change

Dear Sir/Madam:

This letter is to inform you that the name of the corporation sponsoring the above-captioned application has been changed recently from Hoechst Marion Roussel to Aventis Pharmaceuticals. There has been no transfer of ownership of this application. Enclosed is an updated FDA Form 356h reflecting the name change.

Please be advised that there have been no other changes in relation to the studies ongoing or the responsible individuals. You will be advised if any changes occur as appropriate.

If you should have any questions or comments concerning this submission, please contact the undersigned at:

AVENTIS PHARMACEUTICALS
P.O. Box 9627
Kansas City, Missouri 64134-0627

Sincerely,

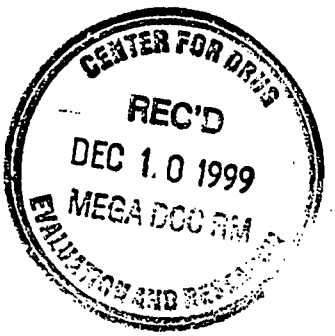
J. Michael Nicholas, PhD
Director, US Regulatory Affairs
Marketed Products
816-966-5720

ORIGINAL

CC:
Medicis
Lynn Hansen, Regualtory Affairs Manager
4343 East Camelback Road, Suite #250
Phoenix, AZ 85018

MEDICIS
PHARMACEUTICAL CORP.
The Dermatology Company®

NC



December 9, 1999

Dr. Jose Carreras
Food and Drug Administration
Division of Scientific Investigations
CDER-HFD-344, MPN1/125
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 21-159 Loprox (ciclopirox) Shampoo 1% - Clinical Investigators

Dear Dr. Carreras:

Enclosed please find an exact duplicate copy of the investigators listing that was sent to you on October 21, 1999.

If you should need anything further please call me at 602-808-3851.

Sincerely,

Rosa Hernandez

Rosa Hernandez
Regulatory Affairs Associate

ORIGINAL

4343 East Camelback Road, Phoenix, AZ 85018-2700
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: http://www.medicis.com
NYSE Symbol: MRX

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PHARMACEUTICAL CORP.
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October 21, 1999

Dr. Jose A. Carreras
Food and Drug Administration
Division of Scientific Investigations
CDER-HFD-344, MPN1/125
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 21-159 Loprox (ciclopirox) Shampoo 1% - Clinical Investigators

Dr. Carreras:

Enclosed please find the requested information regarding the above stated subject.

The listing of the investigators and the number of patients enrolled is located in can be found in Item 8, pages 08-52, Volume 1.30, Book 30 of 85. The studies you were requesting are 204, 3001 and 3003.

Please feel free to call me at (602) 808-3813 if there are any further requests.

Sincerely,

Lynn C. Hansen

Lynn C. Hansen
Regulatory Affairs

cc: Vickey Lutwak

4343 East Camelback Road, Phoenix, AZ 85018-2700
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: http://www.medicis.com
NYSE Symbol: MRX

ORIGINAL

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NEW CORRESP
NC

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT 26 1999
MEGA DOC RM

October 20, 1999

Vickey Lutwak
Food and Drug Administration
Division of Dermatologic and Dental Products
CDER-HFD-540, Room 242
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 21-159 Loprox (ciclopirox) Shampoo 1% - Information per request of October 13, 1999

Ms. Lutwak:

Enclosed please find the information requested on October 13, 1999 for the above stated subject.

- *Question*
- *Has the applicant stated that the integrated summary of safety includes all safety data for this product of which they were aware from all sources, domestic and foreign? What is the cut off date for the preparation of the ISS?*

Response
As stated in the Final Integrated Summary of Safety, page 14, Volume 1.1, ending paragraph. "HMR certifies that this ISS reflects All safety data from all known foreign and domestic sources. The cut off date for the information presented in this ISS is October 1998."

If there is further information regarding this agreement please feel free to call me at (602) 808-3813.

Sincerely,

Lynn C. Hansen

Lynn C. Hansen
Regulatory Affairs

Attachments: Page 14, Volume 1.1 NDA 21-159 original submission.
Facsimile Transmission Record dated October 13, 1999 from FDA to Medicis Pharmaceutical Corp.

4343 East Camelback Road Phoenix, AZ 85018-2700
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: http://www.medicis.com
NYSE Symbol: MRX

MEDICIS
PHARMACEUTICAL CORP.
The Dermatology Company®

ORIG NEW CORRES
NC

September 28, 1999

Food and Drug Administration
Attn.: Ms. Vickey Lutwak
CDER-HFD-540, Room 242
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 21-159 Loprox (ciclopirox) Shampoo 1%

Dear Ms. Lutwak,

Enclosed please find part of the information requested in your fax of September 26, 1999.

A copy of the Financial Disclosure is enclosed. The information is located in Volume 80 of 85, pages 500-523.

If there are any questions please feel free to call me at (602) 808-3813.

Sincerely,

Lynn Hansen

Lynn Hansen
Regulatory Affairs

LH:tl
Enc. (1)

4343 East Camelback Road, Phoenix, AZ 85018-2700
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: http://www.medicis.com
NYSE Symbol: MRX

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CENTER FOR DRUG
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AUG 31 1999
CDR
EVALUATION AND RESEARCH

Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Central Document Room
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG
REC'D
SEP 0 1 1999
MEGA DOC RM
EVALUATION AND RESEARCH

RE: NDA 21-159
Loprox® (ciclopirox) Shampoo 1%
NEW DRUG APPLICATION

Dear Dr. Wilkin:

In accordance with the regulations set forth in 21 CFR 314.50, Medicis Pharmaceutical Corporation is submitting a New Drug Application (NDA) for LOPROX (ciclopirox) Shampoo 1% for the treatment, — twice per week; of seborrheic dermatitis of the scalp — .. It is also indicated for —

The NDA includes data from one Phase III, randomized, double blind, controlled study (study 3001) conducted under — involving over 900 patients. Supportive safety and effectiveness data from two Phase II randomized, double blind, studies (studies 203 and 204) involving over 350 patients are also included. Safety information from an additional Phase III randomized, double blind, comparison study (study 3003) involving over 700 patients are included as well.

Item 19 contains a copy of FDA's meeting minutes from our pre-NDA Meeting held at the Division on April 29, 1999 (Meeting ID# 3905).

The manufacturing facility for the Drug Product is:

Patheon Inc.
Syntex Court Operations
2100 Syntex Court, Mississauga, Ontario L5N 7K9.

Patheon Inc. will be the manufacturing, packaging and testing facility for LOPROX Shampoo 1%. The formulation and method of manufacturing will be the same as those utilized by HMR, Frankfurt.

4343 East Camelback Road, Phoenix, AZ 85018-2700
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: http://www.medicis.com
NYSE Symbol: MRX

[redacted] batches have been manufactured packaged and set up on stability to support this submission. The stability studies have been performed per FDA and ICH guidance.

We commit to continue to monitor the primary stability batches, manufactured by HMR, and the [redacted] batches for the length of the expiration dating period and report results in annual progress reports. We commit to monitor the stability of the [redacted] production batches from Patheon Inc. for the length of the expiration dating period and report the results according to 21 CFR 314.81(b)(2).

An identical field copy of this submission has been provided for simultaneous submission to the Los Angeles District Office. I hereby certify that the copy submitted to the District Office is identical to that submitted to the Division of Dermatologic and Dental Drug Products.

The user fee in the amount of $272,282.00 (User Fee ID #3753) was sent to Mellon Bank, Pittsburgh, PA on August 27, 1999.

We look forward to working with you during the review of this NDA. Please be advised the information submitted is considered confidential under 21 CFR 314.430.

Please contact Ms. Lynn Hansen or myself at (602) 808-8800 if you have any questions concerning this submission.

Sincerely,

Joseph Cooper
Senior Vice President
Medicis Pharmaceutical Corporation

Desk Copy: Ms. Mary Jean Kozma-Fornaro

Field Copy: District Director, Los Angeles
Food and Drug Administration
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

Hoechst Marion Roussel

August 5, 1999

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-0627
Telephone (816) 966-5000

Jonathan Wilkin, MD
Director
Center for Drug Evaluation and Research
Division of Dermatologic Drug Products
(HFD-540)
Food and Drug Administration
9201 Corporate Blvd, Bldg. 2, 2nd floor
Room N229
Rockville, MD 20850

Re: LOPROX® Shampoo 1%
(ciclopirox)

Dr. Wilkin:

Hoechst Marion Roussel, Inc., hereby authorizes the Food & Drug Administration to cross-reference the following applications during the review of this NDA.

Approved NDAs:

LOPROX® (ciclopirox) Cream 0.77% (Formerly LOPROX® (ciclopirox) Cream 1%)	NDA 18-748
LOPROX® (ciclopirox) Lotion 0.77% (Formerly LOPROX® (ciclopirox) Lotion 1%)	NDA 19-824
LOPROX® (ciclopirox) Gel 0.77%	NDA 20-519

Pending NDA:

LOPROX® (ciclopirox) Nail Lacquer 8%	NDA 21-022

Open IND:

[redacted]

If you have any questions, please contact me at:

Hoechst Marion Roussel, Inc.
Mail Drop: H3-M2112
P.O. Box 9627
Kansas City, MO 64134-0627
(816) 966-5720

Sincerely,

FOR JMN

J. Michael Nicholas, PhD
Director, US Drug Regulatory Affairs

js

cc: Medicis Pharmaceutical Corporation

Parexel International

APPEARS THIS WAY
ON ORIGINAL