


MEDICIS
PHARMACEUTICAL CORP.
The Dermatology Company*

September 20, 1999

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

~~NEW CORRESP~~
N2



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

Dear Ms. Lutwak,

Enclosed please find the final information requested in your telephone request last week, September 10, 1999.

There are two computer disks with the Proposed DRAFT Labeling as submitted in the NDA submission. Also, as written follow-up to your question regarding an additional "Patient Insert", there is no intention to provide one.

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

This should complete the requests of our telephone conversations last week.

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

Sincerely,



Lynn C. Hansen
Regulatory Affairs


MEDICIS
PHARMACEUTICAL CORP.
The Dermatology Company



September 15, 1999

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

ORIG NEW CORRES
NC

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

Ms. Lutwak:

In 1998 Medicis Pharmaceutical Corporation (Medicis) entered into a licensing agreement with Hoechst Marion Roussel (HMR) whereby Medicis would license rights to market the Ciclopirox line of products in the United States. Included in these rights was the impending Loprox Shampoo NDA. As part of these obligations, Medicis has been assigned as the Regulatory Agent for each of the ciclopirox NDAs.

Medicis will contact HMR about reassigning the Loprox Shampoo IND from Parexel to Medicis.

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

Sincerely,



Lynn C. Hansen
Regulatory Affairs



July 26, 2002

DUPLICATE

RECEIVED
JUL 29 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

Re: **NDA 21-159**
Loprox® (ciclopirox) Shampoo 1%
30-Day Notice of Submission of Amendment

NC
NEW COPY

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 March 11, 2002, fax from Victoria Lutwak, Project Manager, to Rosa Hernandez, former Regulatory Affairs Associate at Medicis Pharmaceutical Corp.

In accordance with the referenced fax, please accept this letter as formal 30-day notice of our intent to submit an Amendment to the referenced NDA that will include a response to the deficiencies outlined in the referenced Not Approvable letter. The target date for the resubmission is August 29, 2002.

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. Wortzmann, Ph.D.
Executive Vice President
Research and Development

MEMORANDUM OF MEETING MINUTES

Meeting Date: March 11, 2002 Time: 1:00 pm
Location: 9201 Corporate N225
Application: NDA 21-159 / _____
Telecon to discuss Clin/Stat response to NA
Meeting ID: 8287
Sponsor: Medicis Pharmaceutical Corporation
Meeting Chair: Jonathan Wilkin, M.D./Division Director
& Markham C. Luke, M.D., Ph.D.
Meeting Recorder: Victoria Lutwak/Project Manager



FDA Attendees, Titles, and Office/Division:

Jonathan Wilkin, M.D./Division Director DDDDP, HFD-540
Markham C. Luke, M.D., Ph.D./ Acting Clinical Team Leader, DDDDP, HFD-540
Phyllis Huene, M.D./Medical Officer, DDDDP, HFD-540
Mohamed Alesh, Ph.D./Team Leader, Biostatistics DBIII, HFD-725
James Minter, Ed.D./OIT, DTD, HFD-220
Victoria Lutwak/Regulatory Project Manager, DDDDP HFD-540

External Constituent Attendees and Titles:

Medicis:

Mitchell Wortzman, Ph.D./ Executive Vice President, R&D
Todd Plott, M.D./ Executive Director, clinical Research
Bhiku Patel, Ph.,/Director Development
Rosa Hernandez / Regulatory Affairs

PAREXEL International

Alberto Grignolo, Ph.D./Senior Vice President worldwide Regulatory Affairs
James Gourzis, M.D., Ph.D./Senior Medical director
Werner Wierich, Ph.D. /Senior Director, Biostatistics and Programming
Konrad Gaede, Ph.D./Senior Biostatistician
Emily Stube /Senior Medical Writer
Tracy Ross, M.S., RAC /Regulatory Affairs Associate II

Purpose:

To provide general guidance on the content and format of the response to the NA letter dated September 6, 2000. The agenda includes clinical and statistical issues for discussion.

Chemistry, Manufacturing and Controls

The NA issues are not addressed at this time, but will be the subject of another meeting prior to submitting a full response to the NA letter.

Clinical

The sponsor seeks the Division's concurrence with the following:

1. The proposed structure of the NDA Amendment, as detailed on page 7 of the Briefing Document.

Agency response: The proposed structure of the NDA amendment is satisfactory.

2. The proposed content of the NDA Amendment, as detailed on page 9 of the Briefing Document.

Agency response: This section of the briefing document addresses the clinical deficiencies noted in the non-approvable letter, namely, a) a rationale for the applicability of European data to the US population, b) subset analyses, and c) an explanation of the relapse rates in Study 3001. The sponsor has provided a discussion of each of these deficiencies and how they are to be addressed in the amendment. These are issues which will be evaluated by the Agency during the review of the amendment.

The sponsor has some question as to the method of analysis of the data on patients who also have involvement of non-scalp areas. In response, the Agency feels that an analysis of the response to treatment on the scalp in this group of patients would be satisfactory. Also, it is recommended that a detailed explanation of the relapse rates in Study 3001 be provided, as offered by the sponsor.

3. The proposed structure and content of the Integrated Summary of Efficacy and related Statistical Analysis Plan, as detailed on page 13 and Appendix B of the Briefing Document.

Agency response: The proposed structure and content of the Integrated Summary of Efficacy, as detailed on page 13, are satisfactory. The statistical analysis plan will be addressed by the biostatisticians.

4. The proposed structure and content of the Integrated Summary of Safety and related Statistical Analysis Plan, as detailed on page 14 and Appendix C of the Briefing Document.

Agency response: The proposed structure and content of the Integrated Summary of Safety, as detailed on page 14, are satisfactory. The statistical analysis plan will be addressed by the biostatisticians.

5. The proposed clinical data listings and retabulations, as detailed on page 16 of the Briefing Document.

Agency response: The proposed clinical data listings and retabulations, as detailed on page 16, regard the individual patient adverse event data to be provided in the Integrated Summary of Safety, and the pooling of safety data according to frequency of treatment. This is felt to be satisfactory.

6. The plan for the electronic filing of the NDA Amendment, as detailed on page 18 of the Briefing Document.

Agency response: As outlined, the plan for electronic filing appears to be satisfactory.

An additional clinical issue discussed involved the provision of updated clinical information. The sponsor will provide information on all studies and uses of the drug, but proposes to provide this only on the shampoo and not for other approved dosage forms. The Agency responded that this is not acceptable; such information as is available should be submitted on all dosage forms of ciclopirox.

Biostatistics

General Comments:

The sponsor is seeking the Division input about several points related to the structure and content of the NDA Amendment and that of the integrated summary of safety and efficacy. The following are general comments related to 'item 10: Statistical', as it would be difficult to provide specific comments without having the actual submission.

1. Response to the sponsor's issues #1 and # 2 about the proposed structure and content of the NDA Amendment:
The overall structure seems acceptable; however, individual study reports are expected to contain the study protocol, results of statistical analyses, demographic/baseline data, efficacy data and the randomization list that show treatment allocation prior to enrollment. The NDA submission is expected to contain SAS data set for all baseline, efficacy and safety data.
2. Response to the sponsor's issues # 3, 4, and 5 about the proposed structure and content of the Integrated Summary of Efficacy and related statistical analysis plan, as detailed on pages 13 and 16 and Appendices B and C of the briefing document:
 - (a) Efficacy data derived from individual studies would be used independently to establish efficacy claim. Analysis based on pooling might be used as an overall summary for efficacy and for safety.
 - (b) Comment concerning the Sponsor's plan to combine the inflammation score from several studies with the erythema score (page 37): It should be noted that the primary efficacy analysis should be carried out for the primary endpoint based on the Investigator's Global Evaluation (Responders' Rate) in each study independently. The sponsor might add any additional analyses if they desire but such analyses cannot be used to establish the efficacy claim.
 - (c) Comments on the sponsor's 'Data Handling Rules (3.4.2 Missing Data, p.56)': Following the ICH guidance the primary efficacy analyses should be based on the ITT population. The ITT population include all patients randomized and dispensed drug medications, regardless of whether they had a rating of the primary efficacy variable. This is in contrast to the sponsor's definition requiring subsequent rating of the primary efficacy variable on page 35). For missing data usually the LOCF approach is used by the Division. Per protocol analysis (or analysis for study completers) should be viewed as supportive to that based on the ITT analysis.
 - (d) Subset analyses, which were requested by the Division, should be based on findings of the Phase 3 trials.
3. Response to the sponsor's issues # 6 about the Sponsor's plan for electronic filing:
The sponsor plans an electronic submission the NDA Amendment. This should be acceptable as long as the format and specification of the electronic submission follows those of the Agency guidance and the files are accessible. However, a hard copy for volume 1 which include overall

summary of the submission, integrated summary of safety and efficacy; as well as a hard copy of the study protocol and randomization list would be helpful to carry out the review.

The above comments are intended to be general based on the sponsor's briefing document; additional comments/requests might be made when the sponsor submits the NDA Amendment.

Project Management

1. We would like to know when you plan to make your resubmission in order to retrieve the archived NDA volumes for cross-referencing. We will need a 30 day notice to have these volumes brought to our building.
2. The pediatric waiver request in the original submission stands.

Regulatory

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.

Minutes Preparer: _____
Victoria Lutwak/Project Manager, DDDDP

Chair Concurrence: _____
Markham C. Luke M.D., Ph.D., for
Jonathan Wilkin, M.D./Division Director, DDDDP

FinalFile: Pre-NDA(-CMC) Meeting Minutes

MEETING MINUTES

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

/s/

Markham Luke
3/14/02 04:23:46 PM

**APPEARS THIS WAY
ON ORIGINAL**

10/18/99 4:13 PM

Fileability Meeting

Project Management

Everything that is required for the initial documentation for the action package has been submitted by the sponsor. This includes financial disclosure and pediatric exclusivity. OK from PM perspective.

Team Leaders and Reviewers

Agenda items: Went over the list with the reviewers and requested commitments for their drafts.
See attached.

Action Items:

1. Biopharm: Would like the assay method validation for the assay method which was provided
2. Biopharm: Want confirmation from the sponsor that the to-be-marketed- formulation was used for the pk studies.
3. CMC: Is there a separate microbiological section. And if so, where is it located in the NDA?
4. Clinical: Have the sponsor specify which dose-ranging study they intend to use as their second study.
5. Pharm/Tox: It was noted that the dermal carcinogenicity study is a Phase 4 commitment.

The above requests should to be conveyed to the sponsor with their response before the NDA is filed.

Addendum:

The above request for information was conveyed to sponsor 10-19-99. The sponsor will fax responses and send a hard copy the NDA. These are filing issues and not review issues. The sponsor was informed that if filed, we would be sending request for information at a latter date.

The response arrive via facsimile on 10-24099. The information for numbers. 1, 2, and3 was adequate for filling.

cc:

NDA 21-159

DivFile

HFD-540/Lutwak

V.L 10/29/99

**APPEARS THIS WAY
ON ORIGINAL**

NDA FILEABILITY CHECKLIST

NDA Number: 21-159

Applicant: Medicis Pharmaceutical Corporation

Stamp Date: 8/31/99

Drug Name: Loprox® (ciclopirox) Shampoo 1%

IS THE CMC SECTION OF THE APPLICATION FILABLE? (Yes or No) Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Has stability data and analysis been provided to support the requested expiration date?	X		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 (see item 17, page 14).
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?		X	Response to Item #11 and Item #16 ((the color pigment used in bottles?) of the pre-NDA meeting minutes could not be located. See comments to sponsor listed on page 2.
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?		X	Only clinical microbiology section included.

If the NDA is not fileable from a manufacturing and controls perspective state why it is not.

Reviewing Chemist: Mamta Gautam-Basak, Ph.D. *MB*

Date: *10/13/99*

Team Leader: Wilson H. DeCamp, Ph.D. *WHD*

Date: *10/18/99*

cc:
Original NDA 21,159
HFD-540/Division File
HFD-540/Gautambasak
HFD-540/Lutwak
HFD-830/Chen

NDA Number: 21-159 Applicant: Medicis Pharmaceutical Corporation
 Drug Name: Loprox® (ciclopirox) Shampoo 1%

Have all DMF References been Identified?

DMF Number	Holder	Description	LOA Included	Comment
134273	Patheon, Inc.	Type I	Yes (Vol.2, p. 232)	This DMF is actually #5252
		Type I	Yes (Vol.2, p. 312)	
		Type III DMF for _____	Yes (Vol.2, p. 309-310)	A copy of the letter from the holder to request a new DMF (with the authorization) is included

The following comments should be faxed to the sponsor:

1. 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.
2. Revised Letters of Authorizations for DMF 5252 and DMF _____ should be submitted.
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 (see item 17, page 14).
4. Response to Item #11 (page 13) of the pre-NDA meeting minutes was not located. Also, on p.8 of Vol. 2 you have indicated only one crystal form of ciclopirox is known which is incorrect.
5. The information regarding the color pigment used in the plastic bottle (see item #11, page 14) was not located.

MEMORANDUM OF TELEPHONE CONVERSATION

Meeting Minutes

Date: September 29, 1999

Type: T-con

NDA 21-159 Loprox Shampoo 1%

Sponsor: Medicis

Attendees:

FDA: Mamta Gautam-Basak, V Lutwak

Patheon: Stephanie Santarella

Request for information on referenced DMF 134,273:

Background: The FDA doesn't have on file a DMF with the above six-digit number. We are calling to confirm a possible mix-up with the numbers. Patheon does have a 5252 from on file. We believe this is the correct DMF file and are seeking clarification.

After talking with Jeff Derraugh's assistant Stephanie Santarella, she stated that from the information she has their DMF appeared to be for facilities. We asked her 1) send us a fax copy of the FDA acknowledgement letter, and 2) if their number is not correct, provide the correct number.

cc:

NDA 21-159

Div File

HFD-540/ Gautam-Basak/ Lutwak *mlb*

After reviewing DMF 5252 it was confirmed that 5252 is the Master File for Patheon facility and we also found that # 134273 is the Drug Establishment Registration number for this facility.

*JSI
10/1/99.*



Minutes of Meeting

Date: May 9, 2000
Sponsor: Medicis and Aventis
NDA: 21-159
Type: t-con
Purpose: The purpose of the meeting was to review the reasons and necessity to rename/re-title the USP/USAN monograph for ciclopirox olamine to ciclopirox. This applies to only NDAs 18-748 and 19-824. And to amend NDA 21-159 to include information for the existence of known polymorphs for ciclopirox. Right of reference to previous approved NDA submissions for ciclopirox can do this.

FDA Attendees: Wilson DeCamp, Mamta Gautam-Basak, Saleh Turujman, and Vickey Lutwak

Sponsor Attendees: Lynn Hansen, Medicis, Mitchell Wortzman, Dhiren Shah, Aventis

Action Items:

Lynn Hansen will supply a copy of Vol. 2 p 61-66, NDA 21-159 to Dhiren Shah
 Dhiren Shah will determine the status of the Hoechst-Roussell (now Aventis) supplement dated December 14, 1994 submitted to USP.
 Dhiren Shah will send the drug substance information from NDAs 18-748 and 19-824 to USP and a desk copy to the Agency.

Meeting:

The first part of the meeting concerned a brief history and discussion regarding the fact that ciclopirox is not a salt but a solvate. Presently, the labeling for the gel, shampoo, and nail lacquer are correctly labeled, but the cream and lotion are not. The problem resided in the monograph that has the wrong name—ciclopirox-olamine. The name change has to happen in the monograph first before the others can occur. To accomplish the renaming USP will need the information in Wilson DeCamp's memo dated July 24, 1997, discussing the proof of structure. See Attached. But before that can be submitted, the drug substance information, ciclopirox, from NDAs 18-748 and 19-824 should be submitted to USP by Aventis and clarification for NDA 21-159 (currently under review) the status of the October 1996 stability supplement to USP for the drug substance. When this is completed, the Agency will formally submit the July 24, 1997, memo to USP/USAN to initiate the name change.

The second part of the meeting concerned the issue that know information about the existence of polymorphs of ciclopirox was absent from the NDA 21-159, Loprox Shampoo 1%, currently under review in this division. It was agreed by the parties present that this would be corrected with an amendment to the NDA with right of reference to approved NDAs for ciclopirox containing information on these polymorph forms.

Attachment:

Draft supplement request letter dated July 24, 1997
 USP XXII monograph
 USP XXII, supplement 8
 USP 23 monographs

cc:

NDA 18-748

NDA 19-824

NDA 21-159

Div Files

HFD-540/ DeCamp/ Gautam-Basak/ Turujman

HFD-540/ Lutwak

HDF-354/ Mille

reljs 6/20/00

APPEARS THIS WAY
ON ORIGINAL

**MEMORANDUM OF TELECONFERENCE
MEETING MINUTES**



Meeting Date: August 2, 2000 **Time:** 10:00 am EST (7am PST)

Application: NDA 21-159

Sponsor: Medicis Pharmaceutical Corp

Meeting Chair: Jonathan Wilkin, M.D./Division Director

Meeting Recorder: Victoria Lutwak/Project Manager

FDA Attendees, titles, and Office/Division:

Jonathan Wilkin, M.D./Division Director DDDDP, HFD-540
Victoria Lutwak/ Regulatory Project Manager, DDDDP HFD-540

External Constituent Attendees and titles:

Medicis Pharmaceutical Corp.:

Mr. Joseph Cooper, Sr. VP M&D

Ms. Carol Danielson, Director Regulatory Affairs

Ms. Lynn C. Hansen, Regulatory Affairs Manager

Dr. Mitchell Wortzman, Sr. VP Research & Development

Parexel:

Dr. Alberto Grignolo – SR VP & GM Worldwide Regulatory Affairs

Dr. Werner Wierich – Head of Biostatistics & Data Management

Mr. Konrad Galde, Project Statistician.

Purpose:

At the request of Johnathan Wilkin, M.D., we scheduled a teleconference with the sponsor to discuss the conclusion(s) of the clinical review for NDA 21-159 before taking an action.

Teleconference:

The sponsor was informed by Jonathan Wilkin, M.D., that the NDA will be a NA. They will at least need to do an additional clinical trial. At this time, all the reviews are not in; there may be other deficiencies/issues.

The action letter will address all the deficiencies in the NDA.

The sponsor was encouraged to schedule a meeting after receiving the action letter.

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-159	Efficacy Supplement Type SE- N/A	Supplement Number : N/A
Drug: Loprox Shampoo 1% (ciclopirox)		Applicant: Medicis Pharmaceutical Corporation
RPM: Jacquelyn Smith		HFD-540 Phone # 301-827-2020
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): N/A
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		3S
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		March 3, 2003
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified
❖ Exclusivity Summary (approvals only)		x
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		N/A

General Information	
❖ Actions	
• Proposed action	(x) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	NA letter, September 6, 2000
• Status of advertising (approvals only)	(x) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (x) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	() None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	February 14, 2003
• Original applicant-proposed labeling	August 29, 2002
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)	9-29-02 (ODS trade name review)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	August 29, 2002
• Reviews	February 25, 2003
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	February 10, 2003
• Documentation of discussions and/or agreements relating to post-marketing commitments	February 10, 2003; October 23, 30, 2002
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	x
❖ Memoranda and Telecons	x
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	No EOP2 meeting
• Pre-NDA meeting (indicate date)	April 29, 1999; March 11, 2002
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	2-7-03, 2-14-03
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Summary Information

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	
❖ Clinical review(s) (indicate date for each review)	January 22, 2002, February 4, 2003, February 25, 2003
❖ Microbiology (efficacy) review(s) (indicate date for each review)	January 17, 2003
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	MCL/PH review goes here
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	x
❖ Statistical review(s) (indicate date for each review)	January 8, 2003
❖ Biopharmaceutical review(s) (indicate date for each review)	January 28, 2003
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	February 19, 2003
• Bioequivalence studies	N/A

CMC Information

❖ CMC review(s) (indicate date for each review)	February 26, 2003
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	February 26, 2003
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: February 12, 2003 (x) Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested () Not yet requested (X) Pending

Nonclinical Pharm/Tox Information

❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	January 7, 2003
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA <u>21-159</u> Drug <u>Loprex Shampoo 1%</u> Applicant <u>Medicis Pharmaceuticals</u>	
RPM <u>/S/</u>	Phone <u>301.827.2023</u>
<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Reference listed drug _____	
<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rolling Review
Review priority: <input checked="" type="checkbox"/> S <input type="checkbox"/> P	
Pivotal IND(s) _____	
Application classifications: Chem Class <u>Antifungal</u> Other (e.g., orphan, OTC) <u>NA</u>	PDUFA Goal Dates: Primary <u>July 8, 2000</u> Secondary <u>Sept 8, 2000</u>

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- ◆ User Fee Information: User Fee Paid
 User Fee Waiver (attach waiver notification letter)
 User Fee Exemption

- ◆ Action Letter..... AP AE NA

- ◆ Labeling & Labels
 - FDA revised labeling and reviews..... _____
 - Original proposed labeling (package insert, patient package insert) _____
 - Other labeling in class (most recent 3) or class labeling..... _____
 - Has DDMAC reviewed the labeling? Yes (include review) No
 - Immediate container and carton labels _____
 - Nomenclature review DPOEA.....

- ◆ Application Integrity Policy (AIP) Applicant is on the AIP. This application is is not on the AIP.
 - Exception for review (Center Director's memo)..... _____
 - OC Clearance for approval..... _____

- ◆ Safety Update review(s) NA - Studies Completed
- ◆ Pediatric Information
 - Waiver/partial waiver (Indicate location of rationale for waiver) Deferred Pediatric Page..... ✓
 - Pediatric Exclusivity requested? Denied Granted Not Applicable
- ◆ Statistical review(s) and memoranda ✓
- ◆ Biopharmaceutical review(s) and memoranda..... ✓
- ◆ Abuse Liability review(s) NA
 Recommendation for scheduling
- ◆ Microbiology (efficacy) review(s) and memoranda ✓
- ◆ DSI Audits ✓
 - Clinical studies bioequivalence studies

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ CMC review(s) and memoranda ✓
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability ✓
- ◆ DMF review(s) NA
- ◆ Environmental Assessment review/FONSI/Categorical exemption.....
- ◆ Micro (validation of sterilization) review(s) and memoranda ✓
- ◆ Facilities Inspection (include EES report)
 - Date completed 6-Oct-99 Acceptable Not Acceptable
 - 30-sept-99
- ◆ Methods Validation Completed Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ Pharm/Tox review(s) and memoranda ✓
- ◆ Memo from DSI regarding GLP inspection (if any) NA

◆ Status of advertising (if AP action) <input type="checkbox"/> Reviewed (for Subpart H – attach review)	<input type="checkbox"/> Materials requested in AP letter
◆ Post-marketing Commitments	NA
Agency request for Phase 4 Commitments.....	NA
Copy of Applicant's commitments	NA
◆ Was Press Office notified of action (for approval action only)?.....	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Copy of Press Release or Talk Paper.....	
◆ Patent	
Information [505(b)(1)]	✓
Patent Certification [505(b)(2)].....	NA
Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....	NA
◆ Exclusivity Summary	✓
◆ Debarment Statement	✓
◆ Financial Disclosure	
No disclosable information	✓
Disclosable information – indicate where review is located	NA
◆ Correspondence/Memoranda/Faxes	✓
◆ Minutes of Meetings	
Date of EOP2 Meeting <u>no EOP2 of phase 2</u>	
Date of pre NDA Meeting <u>April 29, 1999</u>	
Date of pre-AP Safety Conference _____	
◆ Advisory Committee Meeting	NA
Date of Meeting	~
Questions considered by the committee	~
Minutes or 48-hour alert or pertinent section of transcript	~
◆ Federal Register Notices, DESI documents	NA

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo)	Team leader's memo in action PUG
◆ Clinical review(s) and memoranda	✓

- ◆ Statistical review(s) of carcinogenicity studies NA
 will request CAP @ S Phase 4
- ◆ CAC/ECAC report NA

APPEARS THIS WAY
ON ORIGINAL

NDA 21-159

Memo to File

Date: March 3, 2003

Subject: NDA 21-159/Loprox Shampoo 1%

In the HOW SUPPLIED section, "LOPROX® (ciclopirox) Shampoo, 1%, is supplied in 120 mL plastic bottles. _____ Store between 15°C and 30°C (59°F and 86°F) is the correct wording to be incorporated when the Sponsor submits the Final Printed Labeling.

Sincerely,

Jacquelyn Smith
Project Manager

**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/

Jacquelyn Smith

3/3/03 11:07:33 AM

CSO

Sponsor has been notified and will receive a fax
of the memo.

**APPEARS THIS WAY
ON ORIGINAL**

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdofa/default.htm>

1. APPLICANT'S NAME AND ADDRESS Mitchell S. Wortzman, Ph.D. Executive Vice President, Research and Development Medicis Pharmaceutical Corp. 8125 N. Hayden Road Scottsdale, AZ 85258	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
2. TELEPHONE NUMBER (Include Area Code) (602) 808 8800	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA).
3. PRODUCT NAME Loprox® (Ciclopirox) Shampoo 1%	6. USER FEE I.D. NUMBER 37751

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

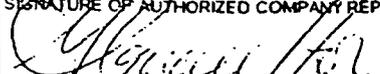
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and 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:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Mitchell S. Wortzman, Ph.D. Executive VP, R&D	DATE 08/29/02
---	---	------------------

INSTRUCTIONS FOR COMPLETING USER FEE COVER SHEET FORM FDA 3397

Form FDA 3397 is to be completed for and submitted with each new drug or biologic product original application or supplemental application submitted to the Agency on or after April 30, 2001, unless specifically exempted below. Form 3397 should be placed in the first volume of the application with the application form.

NOTE: Form FDA 3397 need not be submitted for:

CDER

- 505(j) applications
- Supplements to 505(j) applications

CBER

Any supplement that does not require clinical data for approval
Applications (including supplements) for:

- Products for further manufacturing only
- Whole Blood or Blood Component for Transfusion
- Bovine Blood Product for Topical Application Licensed before September 1, 1992
- A crude Allergenic Extract Product
- An *In-Vitro* diagnostic biological product licensed under section 351 of the PHS Act

ITEM NO.:

INSTRUCTIONS

1-2. Self-explanatory

3. **PRODUCT NAME** - Include generic name and trade name, as applicable.

4. **BLA STN / NDA NUMBER**

FOR BIOLOGIC PRODUCTS - Indicate the 6-digit Biologics License Application STN if known.

FOR DRUG PRODUCTS - Indicate the NDA number, including a leading zero. NDA numbers can be obtained by calling the Center for Drug Evaluation and Research, Central Document Room, at (301) 827-4210.

EXAMPLE: For NDA 99999, the number would be: N099999.

5. **CLINICAL DATA** - The definition of 'clinical data' for the assessment of user fees is found in FDA's Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees. FDA's guidance on the definition of clinical data can be found on CDER's web site: <http://www.fda.gov/cder/pdufa/default.htm>

6. **USER FEE I.D. NUMBER - PLEASE INCLUDE THIS NUMBER ON THE APPLICATION PAYMENT CHECK.** If the application is exempted from a fee, a User Fee I.D. Number is not required. To obtain the appropriate User Fee I.D. Number, read and complete the following:

FOR DRUG PRODUCTS - A unique identification number will be assigned to each submission. This individual identification number may be obtained by calling the Center for Drug Evaluation and Research, Central Document Room, at (301) 827-4210. Questions regarding the CDER User Fee I.D. Number should be directed to CDER's User Fee Staff at (301) 594-2041.

FOR BIOLOGIC PRODUCTS - The User Fee I.D. Number is the applicant's four digit U.S. License Number, followed by a sequential number for each fee paying submission from the applicant, starting with number 1. If the firm is unlicensed, a number may be obtained by calling CBER's Regulatory Information Management Staff (RIMS) at (301) 827-3503. Questions regarding the CBER User Fee I.D. number should also be directed to RIMS.

EXAMPLE: For U.S. License Number 0222, the fifth submission would be given the User Fee I.D. Number: 0222-5.

7. **EXCLUSIONS:**

Section 505(b)(2) applications, as defined by the Federal Food, Drug, and Cosmetic (FD&C) Act, are excluded from application fees if: they are NOT for a new molecular entity which is an active ingredient (including any salt or ester of an active ingredient); and NOT a new indication for a use.

The application is for an orphan product. Under section 736(a)(1)(E) of the FD&C Act, a human drug application is not subject to an application fee if the proposed product is for a rare disease or condition designated under section 526 of the FD&C Act (orphan drug designation) AND the application does not include an indication that is not so designated. A supplement is not subject to an application fee if it proposes to include a new indication for a rare disease or condition, and the drug has been designated pursuant to section 526 for a rare disease or condition with regard to the indication proposed in the supplement.

The submission is a supplement for a new pediatric indication. Under section 736(a)(1)(F) of the FD&C Act, a supplement to a "human drug application" proposing to include a new indication for use in pediatric populations is not subject to a fee.

8. **WAIVER** - Complete this section only if a waiver of user fees, including the small business waiver, has been granted for this application. A copy of the official FDA notification that the waiver has been granted must be provided with the submission.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS Medicis Pharmaceutical Corporation 4343 East Camelback Road Phoenix, AZ 85018	3. PRODUCT NAME Loprox [®] (ciclopirox) Shampoo 1%
2. TELEPHONE NUMBER (Include Area Code) 602-808-8800	4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).
5. USER FEE I.D. NUMBER 3753	6. LICENSE NUMBER / NOA NUMBER N021159

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

FOR BIOLOGICAL PRODUCTS ONLY

<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION	<input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT
<input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY	<input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
<input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and 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:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
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 form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Corporate Controller	DATE August 27, 1999
---	-------------------------------	-------------------------

APP # 21-159

DOCUMENT ID/LETTER DATE

August 30, 1999

APPLICANT NAME

MEDICIS (PHARMACEUTICAL CORP.)

PRODUCT NAME

LOPROX (CICLOPIROX) SHAMPOO

FORM MUST BE COMPLETED ASAP

YES

User Fee Cover Sheet Validated?

NOTE TO DOCUMENT ROOM

PLEASE MAKE THE FOLLOWING CHANGES TO THE COMES DATA ELEMENTS

Blank lines for notes to document room.

YES NO

CLINICAL DATA?

[Check YES if contains study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials. Clinical data do not include data used to modify the labelling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labelling).]

REF

IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION?

YES NO

NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (OTHER THAN BUNDLING)? IF YES, list ALL NDA numbers, review divisions & indicate those for which application fees apply.

NDA # DIVISION FEE NO FEE
N _____ FEE NO FEE

YES NO

BUNDLING POLICY APPLIED CORRECTLY? NO DATA ENTRY REQUIRED FOR ELEMENT

[Check YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Check NO if application should be split into more than one application or submitted as an original instead of a supplement. IF NO, list resulting NDA numbers, and review divisions.]

NDA # DIVISION NDA # DIVISION
N _____ N _____

P S

PRIORITY OR STANDARD?

Handwritten initials 'IS/' and date '7/2/99'

CSO SIGNATURE/DATE

SCSO CONCURRENCE SIGNATURE/DATE

DISTRIBUTION: ORIGINAL TO ARCHIVAL AFTER DATA ENTRY, ONE COPY EACH TO DIVISION FILE AND CDER, ASSOCIATE DIRECTOR FOR POLICY HPD-5



Debarment Certification

Medicis Pharmaceutical Corporation hereby certifies that we did not and will not use in any capacity the services of any person debarred under Section 306(a) or (b) in connection with this application.



Joseph Cooper
Sr. Vice President
Manufacturing and Distribution

8/5/99
Date

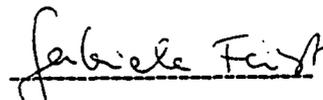
PAREXEL
GmbH

Independent Pharmaceutical Research Organization

Debarment Certificate for the NDA HOE296b

PAREXEL GmbH hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic act in connection with the conduct of Ciclopirox Shampoo HOE296b-203, -204, -3001, -3003 performed under contract with Hoechst AG.

Berlin, 27th April, 1999



Gabriele Faist
Director
Project Management

Loprox® (ciclopirox) Shampoo 1%
New Drug Application
Item 13. Patent Information

ITEM 13. PATENT INFORMATION

The patent for the subject of this NDA, ciclopirox shampoo 1% formulation, is pending. The U.S. serial number is 09/77,194. This pending patent application claims a method of using ciclopirox shampoo for the treatment of seborrheic dermatitis.

**APPEARS THIS WAY
ON ORIGINAL**

ITEM 14. PATENT CERTIFICATION

Certification under 21 CFR 314.50(i)(B)(ii)

In the opinion and to the best knowledge of Hoechst Marion Roussel, Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

Certification under 21 CFR 314.53(c)(3)

The applicant certifies that there are no patents, currently, which claim the drug or the drug product.

Declaration under 21 CFR 314.53(d)

The applicant declares that if a patent is issued after the application is filed with FDA but before the application is approved, the applicant shall, within 30 days of the issuance of the patent, submit the required patent information in an amendment to the application under 21 CFR 314.60.

MEMORANDUM OF TELECON

DATE: 2-14-03; 1:00 PM

APPLICATION NUMBER: NDA 21-159

DRUG PRODUCT: Loprox® (ciclopirox) Shampoo 1%

BETWEEN:

Name: Mitchell Wortzman, Ph.D., Executive Vice President, R&D
Bhiku Patel, Ph.D., Director, R&D
Todd Plott, M.D., Vice President, Clinical Affairs
Michelle Wells, RAC, RA Manager

Phone: (602) 808-8800

Representing: Medicis Pharmaceutical Corporation

AND

Name: Markham C. Luke, M.D., Ph.D., Clinical Team Leader
Phyllis Huene, M.D., Clinical Reviewer
Kathleen Fritsch, Ph.D., Biostatistics Reviewer
Jacquelyn Smith, Regulatory Health Project Manager

SUBJECT: NDA 21-159

The teleconference was requested by the Division to discuss the following labeling insert issues.

1. Clinical Studies section, 1st paragraph, 2nd to last line, replace _____ with "vehicle."

Sponsor agreed to this revision.

2. Clinical Studies section, delete the last paragraph _____

Sponsor wanted to consider possible revision to this statement, but not deletion. Agency agreed to look at any revisions.

3. Information for Patients section, item 3, replace _____ with "allergic Reaction."

The Sponsor stated that this was an oversight. Was to be changed with Agency previous request.

Carton/Container issue:

4. Replace the existing “

With “FOR TOPICAL USE ONLY. NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE. KEEP OUT OF REACH OF CHILDREN.” on the bottles and cartons.

The Sponsor agreed to this change.

Addendum: In a faxed memo, the Sponsor removed for consideration the issue raised in #2.

**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/

Jacquelyn Smith
2/24/03 04:13:17 PM
CSO

Markham Luke
2/24/03 05:01:47 PM
MEDICAL OFFICER
Labeling discussion with Sponsor

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELECON

DATE: 2-7-03, 2:30 PM

APPLICATION NUMBER: NDA 21-159

DRUG PRODUCT: Loprox® (ciclopirox) Shampoo 1%

BETWEEN:

Name: Mitchell Wortzman, Ph.D., Executive Vice President, R&D
Bhiku Patel, Ph.D., Director, R&D
Todd Plott, M.D., Vice President, Clinical Affairs
Willy Brondum, RAC, RA Associate
Michelle Wells, RAC, RA Manager

Phone: (602) 808-8800

Representing: Medicis Pharmaceutical Corporation
AND

Name: Wilson DeCamp, Ph.D., Chemistry Team Leader
Mamta Gautam-Basak, Ph.D., Chemistry Reviewer
Jacquelyn Smith, Regulatory Health Project Manager

SUBJECT: NDA 21-159

The teleconference was requested by the Division to discuss the following issues.

Labeling:

- container label should include dosage and administration info

The Sponsor agreed to incorporate this change into the container label.

- the recommended usage (5-10 mL per application, 2x weekly for 4 weeks) is more consistent with _____ sizes than 30 and 120 mL

The Sponsor selected an alternate to the originally proposed _____ bottles and intends to use the 30 mL and 120 mL white bottles as submitted in the August 29, 2002 Amendment.

CMC:

There can only be one specification; we can't have different acceptance criteria for release and stability (see vol. 2, page 6). The acceptance criteria for the specification should apply throughout the shelf-life of the product.

The Sponsor agreed to revise the specification.

NDA 21-159

Loprox® (ciclopirox) Shampoo 1%
teleconference, 2/7/03
page 2 of 2

Additional general comment on container sizes:

If the application is amended to revise the sizes within the bracketed range we would not anticipate any delay in our action. This assumes that there would be no change in the container material or the DMF reference.

Addendum: The Sponsor responded to the chemistry comments by facsimile on February 8, 2003 and by official submission on February 10, 2003.

**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/

Jacquelyn Smith
2/11/03 12:44:20 PM
CSC

Tony send the previous DFS back to me. This
one supercedes because I left the header with
the track changes(shows Red)

Wilson H. DeCamp
2/11/03 12:56:11 PM
CHEMIST
concur; minutes are accurate

APPEARS THIS WAY
ON ORIGINAL

Number of Pages
Redacted 46



Draft Labeling
(not releasable)

February 26, 2003

The MO's Executive Summary does not reflect the MO's conclusions with specific regard to the following analysis of Study 3001:

"The results of Study 3001 have demonstrated the safety and effectiveness of Loprox shampoo for the prevention of recurrence of seborrheic dermatitis of the scalp, when administered once weekly or once every other week for 12 weeks. These results, however, have not been duplicated in a second study."

It is both the MO's and TL's conclusion that two studies are needed to demonstrate the safety and efficacy of the use of Loprox shampoo for any claim of prevention. This is reiterated in the MO's conclusion statement:

"It is felt that the safety and effectiveness of Loprox shampoo has been adequately demonstrated for the treatment of seborrheic dermatitis of the scalp, but not for prophylactic use in the prevention of recurrence of seborrheic dermatitis of the scalp. An additional study on preventive use is needed to demonstrate the effectiveness for this indication."

It is noted that the Executive Summary does not reflect this conclusion. Thus, it is recommended that the Executive Summary be replaced as follows:

Executive summary

- 1) Recommendations: It is recommended that the application be approved for the proposed labeling indication, namely, for the topical treatment of seborrheic dermatitis of the scalp in adults.
- 2) Summary of clinical findings: In support of the indication, the sponsor has provided three Phase 3 studies; these are Studies 204, 3001, and 017.
 - A. Study 204: This was a double blind, multicenter, randomized comparison of Loprox shampoo at different frequencies of application with the vehicle in 177 patients with mild to pronounced seborrheic dermatitis of the scalp. The study was performed in Europe. Applications of Loprox shampoo were made once weekly, twice weekly, and three times weekly, and the vehicle was applied three times weekly, for four weeks.

The efficacy variables were scores for itching, scaling, and inflammation, based on scales of from 0 to 5. The protocol was amended after the study had been initiated to include a global evaluation of the status of the disease, but this was applied retroactively after some patients completed the study and so was not considered to be valid. The primary efficacy variable was determined to be the proportion of patients who were 'Effectively Treated', which consisted of those patients who were 'Cleared' or 'Almost Cleared' at the end of treatment. Cleared was defined as a score of 0 for inflammation, scaling, and itching. Almost Cleared was defined as a score of 0 for inflammation, and scores of 0 for itching and scaling, or scores of 1 if the baseline score were 3 or greater.

Statistical analyses of the results of Study 204 showed no significant differences between Loprox shampoo once weekly, twice weekly, or three times weekly and the vehicle in the proportion of patients that were Effectively Treated. It was therefore concluded that this study had not demonstrated the effectiveness of Loprox shampoo for the labeling indication. Adverse events which were considered to be possibly treatment related were pruritus in one patient treated once weekly and hair loss in one patient treated twice weekly with Loprox shampoo. No treatment related events occurred in the three times weekly Loprox patients.

B. Study 3001: The initial treatment phase (Segment A) was a double blind, multicenter, randomized comparison of Loprox shampoo with the vehicle in 942 patients with moderate to severe seborrheic dermatitis of the scalp. The study was performed in Europe. Applications of Loprox shampoo were made once weekly and twice weekly, and the vehicle was applied twice weekly, for four weeks. In the prophylaxis phase (Segment B), those patients that were considered to have responded during the treatment phase were treated in a double blind manner with Loprox shampoo once weekly or once every other week, or with the vehicle once weekly, for an additional twelve weeks.

In Segment A the efficacy variables were scores for itching, scaling, and inflammation, based on scales of from 0 to 5, and an investigator's global evaluation of the status of the disease as none to severe, on a scale of from 0 to 5. The primary efficacy variable was a 'Primary Response', defined as a score of 0, or a score of 1 if the baseline score was 3 or greater, to be met simultaneously by the global status, inflammation and scaling at endpoint.

The results in Segment A showed that Loprox shampoo administered once weekly or twice weekly for four weeks was significantly superior to the vehicle in the rate of Primary Response. The proportion of patients with a Primary Response was 46% in the Loprox once weekly group, 59% in the Loprox twice weekly group, and 32% in the vehicle group. It was concluded that Segment A of the study adequately demonstrated the effectiveness of Loprox shampoo once weekly or twice weekly in the treatment of seborrheic dermatitis of the scalp.

In Segment B the primary efficacy variable was the relapse rate, defined as the worsening of the condition by 2 or more points on the global evaluation scale of from 0 to 5. The results in Segment B showed that Loprox shampoo administered once weekly or once every other week for 12 weeks was significantly superior to the vehicle in the rate of relapse. The proportion of patients that had a relapse was 15% in the once weekly Loprox group, 22% in the once every other week Loprox group, and 35% in the vehicle group. It was concluded that Segment B of the study demonstrated the possible effectiveness of Loprox shampoo once weekly and once every other week in the prevention of relapse in those patients that had responded to four weeks of active treatment. An adequate and well-controlled second study designed to look at "prevention" is needed in order to make a sufficient determination as to efficacy and safety of a longer-term regimen.

Adverse events in Segment A were minor dermatological events of the scalp, such as pruritus, rash, dry skin, and

alopecia, in 1% or less in all treatment groups. Adverse events were similar in Segment B.

C. Study 00-017: This study has been provided in this amendment to the NDA, and is a double blind, multicenter, randomized comparison of Loprox shampoo with its vehicle in 499 patients with mild or more severe seborrheic dermatitis of the scalp. Treatment was administered twice weekly for four weeks. The efficacy parameters were scores for erythema, scaling, and the global status of the seborrheic dermatitis, which were graded at biweekly intervals on scales of from 0 to 5. The primary efficacy variable was the proportion of patients that were 'Effectively Treated', defined as having a score of 0 (none), or a score of 1 (slight) if the baseline score were 3 or greater, for scaling, erythema, and global status.

Results of the statistical analysis showed that Loprox shampoo was significantly superior to the vehicle in the proportion of patients that were Effectively Treated. It is concluded that Study 017 has adequately demonstrated the effectiveness of Loprox shampoo in the treatment of seborrheic dermatitis of the scalp, when administered twice weekly for four weeks.

Adverse events were similar to those in the other studies consisting of minor local dermatological effects in a few patients.

Markham C. Luke, M.D., Ph.D.
Lead Medical Officer, Dermatology

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this page is the manifestation of the electronic signature.

/s/

Markham Luke
2/26/03 10:04:06 AM
MEDICAL OFFICER
Revised Executive Summary for Loprox Shampoo

Jonathan Wilkin
2/26/03 01:05:52 PM
MEDICAL OFFICER

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ON ORIGINAL**



N-000/UT

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FEB 12 2003
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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 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,

A handwritten signature in black ink, appearing to read "M. S. Wertzman for MW".

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Part 314 & 601)

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT Medicis Pharmaceutical Corp.	DATE OF SUBMISSION February 10, 2003
TELEPHONE NO. (Include Area Code) 602.808.8800	FACSIMILE (FAX) NO. (Include Area Code) 602.808.3895
APPLICANT ADDRESS (Number, Street, City, State, County, ZIP Code or Mail Code and U.S. License number if previously issued): 8125 N. Hayden Road, Scottsdale, AZ 85258	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, County, ZIP Code, Telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-159	
ESTABLISHED NAME (e.g., Proper Name, USP/USAN name) Ciclopirox	PROPRIETARY NAME (trade name) IF ANY Loprox[®] Shampoo
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) 6-Cyclohexyl-1-hydroxy-4-methyl-2-(1H)pyridone	CODE NAME (if any)
DOSAGE FORM: Shampoo	STRENGTHS: 1%
ROUTE OF ADMINISTRATION: Topical	
(PROPOSED) INDICATION(S) FOR USE: Topical treatment and prevention of recurrence of seborrheic dermatitis of the scalp.	

APPLICATION INFORMATION

APPLICATION TYPE (check one)	
<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)	
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)	
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug: _____ Holder of Approved Application: _____	
TYPE OF SUBMISSION (check one)	
<input type="checkbox"/> ORIGINAL APPLICATION	<input checked="" type="checkbox"/> AMENDMENT TO PENDING APPLICATION
<input type="checkbox"/> RESUBMISSION	<input type="checkbox"/> PRESUBMISSION
<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT
<input type="checkbox"/> EFFICACY SUPPLEMENT	<input type="checkbox"/> LABELING SUPPLEMENT
<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT	<input type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____	
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)	
REASON FOR SUBMISSION Phase IV study commitment as requested by FDA on 2/10/03.	

PROPOSED MARKETING STATUS (check one)	
<input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx)	<input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.	
Drug Substance: Aventis (formerly HMR), Brueningstrasse 50, D-65926 Frankfurt am Main, Germany, Reg # (CFN) 96 10 129, Contact: Dr. Gerd Fischer, Tel: +49 69 305 17932, Fax +49 69 305 5343	
Drug Product: Patheon Inc, 2100 Syntex Court, Mississauga Ontario, L5N 7K9, Canada, Reg # (CFN) 96 90 045, DMF #134273; Contact: Peter Lucyshyn, Tem: 905 812 6818, Fax 905 812 6708.	

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

RECEIVED
FEB 12 2003
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This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one) Draft Labeling Final Printed Labeling
- 3. Summary (21CFR 314.50 (c)) (as an INTRODUCTION)
- 4. Chemistry section
 - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50) (d)(1); 21 CFR 601.2)
 - B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
 - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355(b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 301(k)(1))
- 17. Field copy certification (21 CFR 314.50(i)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify) Phase IV study commitment as requested by FDA on 2/10/03.

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

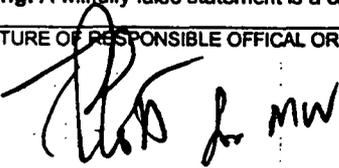
1. Good manufacturing practice regulations in 21 CFR Part 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81
7. Local, state, and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in the submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT



TYPED NAME AND TITLE

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

DATE

02/10/03

ADDRESS (Street, City, State, and ZIP Code)

8125 N. Hayden Road, Scottsdale, AZ 85258

TELEPHONE NUMBER (Including Area Code)

(602) 808.8800

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimated or any other aspect of this collection of information, including suggestions for reducing this burden to:

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

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

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USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdofa/default.htm>

1. APPLICANT'S NAME AND ADDRESS Mitchell S. Wortzman, Ph.D. Executive Vice President, Research and Development Medicis Pharmaceutical Corp. 8125 N. Hayden Road Scottsdale AZ 85258	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER NDA 21-159
2. TELEPHONE NUMBER (Include Area Code) (602) 808 8800	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA).
3. PRODUCT NAME Loprox® (Ciclopirox) Shampoo 1%	6. USER FEE I.D. NUMBER 37751

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and 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:

Department of Health and Human Services
Food and Drug Administration
CDER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Mitchell S. Wortzman, Ph.D. Executive VP, R&D	DATE 02/10/03
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MODE = MEMORY TRANSMISSION

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END=FEB-10 11:18

FILE NO.=115

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: February 10, 2003

To: Michelle Wells, RAC Manager, Regulatory Affairs	From: Jacquelyn Smith, Project Manager
Company: Medicis	Division of Dermatologic and Dental Drug Products
Fax number: 602-778-6051	Fax number: 301-827-2075
Phone number: 602-308-3851	Phone number: 301-827-2027
Subject: NDA 21-159/Phase 4 Commitment	

Total no. of pages including cover: 3

Document to be mailed: YES NO

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: February 10, 2003

To: Michelle Wells, RAC Manager, Regulatory Affairs	From: Jacquelyn Smith, Project Manager
Company: Medicis	Division of Dermatologic and Dental Drug Products
Fax number: 602-778-6051	Fax number: 301-827-2075
Phone number: 602-808-3851	Phone number: 301-827-2027
Subject: NDA 21-159/Phase 4 Commitment	

Total no. of pages including cover : 3

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NDA 21-159

Pharmacology/Toxicology Phase 4 Study Request for Commitment

1. To commit to conduct an alternative, dermal carcinogenicity study in transgenic mice with the ciclopirox shampoo, 1%.

Protocol Submission: Within 4 months of approval of the product
Study Start: Within 6 months of the date of the approval of the protocol
Final Report Submission: Within 12 months after the study completion

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/s/

Jacquelyn Smith
2/10/03 10:38:38 AM
CSO

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MEMORANDUM

Date: 10/30/02
To: NDA 21-159 (NC; CDER receipt date – 10/24/02); Loprox (ciclopirox) shampoo, 1%
From: Barbara Hill, Ph.D., Reviewing Pharmacologist, DDDDP, CDER
Through: Abigail Jacobs, Ph.D., Pharmacology Supervisor, DDDDP, CDER
Topic: Request for clarification for dermal carcinogenicity study as a Phase 4 commitment

Background:

The sponsor (Medicis Pharmaceutical Corporation) re-submitted an NDA application for Loprox shampoo, 1% on September 3, 2002. The re-submitted NDA application addresses clinical and chemistry deficiencies that were relayed to the sponsor in a non-approval letter dated September 6, 2000 for the original Loprox shampoo NDA submission. The non-approval letter included a recommendation for a phase 4 commitment to conduct either a traditional 2 year dermal carcinogenicity study or a 6 month Tg.AC mouse dermal carcinogenicity study. The current submission contains a proposal by the sponsor to fulfill the recommended phase 4 commitment.

The sponsor proposed to conduct a 6 month Tg.AC mouse dermal carcinogenicity study. The sponsor is seeking additional clarification on the potential ramifications of this decision. The sponsor would like the division to confirm that if the transgenic mouse test is positive, that they may repeat the test using the traditional 2 year study as the definitive assay prior to affecting a labeling change. If the transgenic mouse study were negative, the sponsor would like the division to consider the product negative. It would appear the sponsor's proposal is attempting to figure out a way to only place potential negative dermal carcinogenicity results in a potential label for Loprox shampoo. This is not an acceptable proposal. The division's response is provided in the next section.

Division's Recommendation for the Sponsor:

It is recommended that the following information be relayed to the sponsor concerning the 10/24/02 submission to NDA 21-159 for Loprox Shampoo:

- 1) It is acceptable to conduct a 6 month Tg.AC dermal mouse carcinogenicity study with the Loprox shampoo formulation. If the results of the Tg.AC dermal mouse carcinogenicity study are positive, then these positive results would be incorporated into the Loprox Shampoo label without waiting for the results of any other studies. It would be acceptable for the sponsor to conduct a second traditional 2 year dermal mouse carcinogenicity study if the results of the 6 month Tg.AC dermal mouse carcinogenicity study were positive. It would not be necessary for the sponsor to conduct another dermal carcinogenicity if the results of the 6 month Tg.AC dermal mouse carcinogenicity study were positive. Incorporation of the positive results of the 6 month Tg.AC dermal mouse carcinogenicity study into the Loprox shampoo label will fulfill the recommended Phase 4 commitment. If the sponsor should decide to conduct a traditional 2 year dermal mouse carcinogenicity study after conduct of a 6 month Tg.AC dermal mouse carcinogenicity study, then the traditional 2 year mouse dermal carcinogenicity study would not be viewed as the definitive dermal carcinogenicity study. If the results of the traditional 2

year mouse dermal carcinogenicity study were negative, this would not replace the potential positive results obtained in the 6 month Tg.AC mouse dermal carcinogenicity study. The results from both dermal carcinogenicity studies would be incorporated (potential positive results in 6 month Tg.AC mouse dermal carcinogenicity study and potential negative results in traditional 2 year mouse dermal carcinogenicity study) into the Loprox shampoo label.

- 2) If the results of the 6 month Tg.AC mouse dermal carcinogenicity study with the Loprox shampoo formulation were negative, then the label would incorporate the potential negative results of this study into the label. However, the label would not state that the carcinogenic potential of the Loprox shampoo formulation is negative. It would be more appropriate to incorporate the negative results of the 6 month Tg.AC dermal mouse carcinogenicity study into the Loprox shampoo label. This would fulfill the recommended Phase 4 commitment.
- 3) It is recommended that the protocol for the dermal carcinogenicity study (6 month Tg.AC mouse dermal carcinogenicity study or traditional 2 year mouse dermal carcinogenicity study) be submitted to the division, with appropriate results from a dose range finding study, prior to initiation of the study. The protocol for the study, along with the supporting dose range finding study, will be presented to the Exec CAC for concurrence. The results from the Exec CAC meeting will be shared with the sponsor within a 45 day period if the dermal carcinogenicity study is submitted as a special protocol. Refer to the following guidances for additional information.
 - a) Guidance for Industry – Carcinogenicity Study Protocol Submissions (May 2002)
 - b) Guidance for Industry – Special Protocol Assessment (May 2002)

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/s/

Barbara Hill
10/30/02 11:16:31 AM
PHARMACOLOGIST

Abby Jacobs
10/30/02 11:53:14 AM
PHARMACOLOGIST

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