

REQUEST FOR CONSULTATION

TO (Office/Division): OSE

FROM (Name, Office/Division, and Phone Number of Requestor):

Melinda Bauerlien, M.S.

Project Manager

Division of Dermatology and Dental Products

DATE
March 13, 2007

IND NO.

NDA NO.
21-738

TYPE OF DOCUMENT
NDA RS

DATE OF DOCUMENT
December 11, 2007

NAME OF DRUG
Extina (ketoconazole)
Foam, 2%

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
labeling scheduled for May
21, 2007

NAME OF FIRM: Connetics Corporation

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input checked="" type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input checked="" type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the Patient Package Insert for this product. Attached is the PI, PPI and carton/container labels.

Please let me know if you need anything further.

SIGNATURE OF REQUESTOR
Melinda Bauerlien, M.S.
Project Manager 9-0906

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

Melinda Bauerlien
3/13/2007 12:39:58 PM

Appears This Way
On Original

REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Medication Errors and Technical Support (DMETS)**

FROM (Name, Office/Division, and Phone Number of Requestor):
Melinda Bauerlien, M.S.
Project Manager
Division of Dermatology and Dental Products

DATE
March 13, 2007

IND NO.

NDA NO.
21-738

TYPE OF DOCUMENT
NDA RS

DATE OF DOCUMENT
December 11, 2007

NAME OF DRUG
**Extina (ketoconazole)
Foam, 2%**

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
**labeling scheduled for May
21, 2007**

NAME OF FIRM: **Connetics Corporation**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input checked="" type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input checked="" type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the tradename Extina. The Package Insert and carton and container labels are attached.

Please let me know if you need anything further.

SIGNATURE OF REQUESTOR
Melinda Bauerlien, M.S.
Project Manager 9-0906

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

Melinda Bauerlien
3/13/2007 12:17:37 PM

Appears This Way
On Original

REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Drug Marketing, Advertising, and Communications, HFD-42**
Andrew Haffer
WO22, Rm 1487

FROM (Name, Office/Division, and Phone Number of Requestor):
Melinda Bauerlien, M.S.
Project Manager
Division of Dermatology and Dental Products

DATE
March 13, 2007

IND NO.

NDA NO.
21-738

TYPE OF DOCUMENT
NDA RS

DATE OF DOCUMENT
December 11, 2007

NAME OF DRUG
Extina (ketoconazole)
Foam, 2%

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
labeling scheduled for May 21, 2007

NAME OF FIRM: **Connetics Corporation**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input checked="" type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input checked="" type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the Package Insert and carton and container labels that are attached.

Please let me know if you need anything further.

SIGNATURE OF REQUESTOR
Melinda Bauerlien, M.S.
Project Manager 9-0906

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

14 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Melinda Bauerlien
3/13/2007 11:49:22 AM

Appears This Way
On Original



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-738

Connetics Corporation
Attention: Edward Smith III, Ph.D., R.A.C., Senior Director, Regulatory Affairs
3160 Porter Drive
Palo Alto, CA 94304

Dear Dr. Smith:

We acknowledge receipt on December 12, 2006, of your December 11, 2006, resubmission to your supplemental new drug application for Extina (ketoconazole) Foam, 2% for the treatment of Seborrheic Dermatitis.

We consider this a complete, class 2 response to our November 23, 2004 action letter. Therefore, the user fee goal date June 12, 2007.

If you have any question, call Melinda Bauerlien, M.S., Regulatory Project Manager, at (301) 796-2110.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph, M.P.A
Acting Supervisory Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/

Margaret Kober
1/22/2007 01:02:53 PM

Appears This Way
On Original



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 16, 2007

To: Edward Smith	From: Melinda Bauerlien, M.S. Project Manager
Company: Connetics Corporation	Division of Dermatology & Dental Products
Fax number: (650) 843-2802	Fax number: (301) 796-9895
Phone number: (650) 739-2688	Phone number: (301) 796-2110
Subject: NDA 21-738	

Total no. of pages including cover: 2

Comments: Clinical request for information

While not the basis for the Not Approvable action, the resubmission was to present plans for a long-term, open-label safety study as per ICH E1A guidance (please see the action letter dated November 23, 2004). Please identify the location of the plans for the long-term safety study in the resubmission with correspondence date of December 11, 2006.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2110. Thank you.

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

/s/

Melinda Bauerlien
1/16/2007 01:31:23 PM
CSO

Appears This Way
On Original

PRESCRIPTION DRUG 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/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS
Connetics Corporation
3160 Porter Drive
Palo Alto, CA 94304

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
21-738

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
 YES 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:
 THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.
 THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA)

2. TELEPHONE NUMBER (Include Area Code)
(650) 739-2614

3. PRODUCT NAME
Extina (ketoconazole) Foam, 2%

6. USER FEE I.D. NUMBER
PD3006451

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 checked="" 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 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	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
Vice President, Regulatory Affairs

DATE
12/11/2006



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-738

INFORMATION REQUEST LETTER

Connetics Corporation
Attention: Katy Morton,
Senior Director, Regulatory Affairs
3160 Porter Drive
Palo Alto, CA 94304

Dear Ms. Morton:

Please refer to your January 23, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Extina (Ketoconazole Foam 2%). Further, please refer to your submission dated June 15, 2006.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and request for additional information. We request a prompt written response in order to continue our evaluation of your NDA.

1. T

2.

3.

4.

b(4)

5.

6.

7.

8. U

If you have any questions, call Linda Mullins Athey, Regulatory Health Project Manager for Quality, at 301-796-2096.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/

Moo-Jhong Rhee
10/6/2006 03:42:36 PM
Chief, Branch III

Appears This Way
On Original

ACTION PACKAGE CHECKLIST

Application Information		
BLA # NDA # 21-738	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Extina Established Name: ketoconazole Dosage Form: Foam, 2%		Applicant: Stiefel Laboratories, Inc.
RPM: Melinda Bauerlien		Division: 540 Phone # 301-796-2110
<p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)</p> <p>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>Teva</p> <p>Provide a brief explanation of how this product is different from the listed drug. different dosage form</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</p> <p><input checked="" type="checkbox"/> Confirmed <input type="checkbox"/> Corrected</p> <p>Date: May 31, 2007</p>
❖ User Fee Goal Date		June 12, 2007
❖ Action Goal Date (if different)		
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input type="checkbox"/> None NA - November 23, 2004
❖ -Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

Appears This Way
On Original

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 3	
NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation	
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies
NDAs and NDA Supplements: <input type="checkbox"/> OTC drug	
Other: N/A	
Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

Appears This Way
On Original

❖ Exclusivity	
<ul style="list-style-type: none"> • NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity? • NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> • NDAs: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) • NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) • NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____ <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____ <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
❖ Patent Information (NDAs and NDA supplements only)	
<ul style="list-style-type: none"> • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> • Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. • [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii) <input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> • [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (<i>If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews).</i>) • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's</p>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified N/A <input type="checkbox"/> Yes <input type="checkbox"/> No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

N/A

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

N/A

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

N/A

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

N/A

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</p> <p>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</p>		
Summary Reviews		
❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)		June 12, 2007
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)		N/A
Labeling		
❖ Package Insert		
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)		N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)		June 12, 2007
• Original applicant-proposed labeling		December 11, 2006
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable		N/A
❖ Patient Package Insert		
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)		N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)		June 6, 2007
• Original applicant-proposed labeling		December 11, 2006
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable		N/A
❖ Medication Guide		
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)		N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)		N/A
• Original applicant-proposed labeling		N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling)		N/A
❖ Labels (full color carton and immediate-container labels)		
• Most-recent division-proposed labels (only if generated after latest applicant submission)		N/A
• Most recent applicant-proposed labeling		June 12, 2007
❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)		<input checked="" type="checkbox"/> DMETS June 1, 2007 <input checked="" type="checkbox"/> DSRCS May 21, 2007 <input checked="" type="checkbox"/> DDMAC May 8, 2007 <input checked="" type="checkbox"/> SEALD May 30, 2007 <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-738

Connetics Corporation
Attention: Katy Morton,
Senior Director, Regulatory Affairs
3160 Porter Drive
Palo Alto, CA 94304

Dear Ms. Morton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Extina (Ketoconazole Foam 2%). Further, please refer to the May 22, 2006, minutes for the Chemistry, Manufacturing and Controls meeting between the Office of New Drug Quality Assessment and Connetics Corporation held on April 25, 2006.

We also refer to your June 5, 2006, correspondence, received June 6, 2006, stating that there is a significant difference in your understanding of the outcomes of the meeting.

Specifically, you have requested that item 2 in the closing agreements and action items from the meeting minutes be revised. In your correspondence, you state that it may not be possible

Further, your correspondence indicates that at this time, _____ (previously submitted to the NDA).

b(4)

We have reviewed the referenced material and have considered the proposed revisions to the meeting minutes. We believe that the meeting minutes accurately reflect the conclusions and outcome of the meeting. We believe that the request _____ is reasonable, and that _____ . Therefore, the meeting minutes will not be revised.

b(4)

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Elaine Morefield, Ph.D.
Division Director
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

Elaine Morefield
7/7/2006 04:08:52 PM

Appears This Way
On Original



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-738

Connetics Corporation
Attention: Katy Morton, Senior Director, Regulatory Affairs
3160 Porter Drive
Palo Alto, CA 94304

Dear Ms. Morton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ketoconazole Foam, 2%. (Extina)

We also refer to the meeting between representatives of your firm and the FDA on April 25, 2006. The purpose of the meeting was to discuss outstanding CMC issues.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Regulatory Health Project Manager
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 25, 2006
TIME: 11:00 am -12:00 noon
LOCATION: Food and Drug Administration, White Oak Campus
APPLICATION: NDA 21-738
SPONSOR: Connetics
DRUG NAME: Ketoconazole Foam 2%
TYPE OF MEETING: CMC Type C
MEETING CHAIR: Moo-Jhong Rhee, PhD
MEETING RECORDER: Scott N. Goldie, PhD

FDA ATTENDEES:

CENTER OF DRUG EVALUATION AND RESEARCH

Office of New Drug Quality Assessment:

Elaine Morefield, PhD, Division Director, DPMA II
Moo Jhong Rhee, PhD, Branch Chief, DPMA II
Shulin Ding, PhD, Pharmaceutical Assessment Lead, DPMA II
Allan H Fenselau, PhD, Review Chemist, ONDQAIO
Scott N. Goldie, PhD, Regulatory Health Project Manager for Quality, DPMA I

Office of New Drugs, Office of Drug Evaluation II,

Brenda Carr, MD, Medical Officer, DDDP
Markham C Luke, MD, PhD, Clinical Team Leader, DDDP

Office of Regulatory Affairs:

Edwin Melendez, Consumer Safety Officer
Regina T. Brown, Consumer Safety Officer
Susan Laska, Investigator

CONNETICS ATTENDEES:

Matt Foehr, Senior Vice President, Technical Operations
John Statler, PhD, Senior Director, Analytical Technical Operations
Diana Chen, MD, VP Medical Affairs
Michael S. Eison, PhD, Vice President, Regulatory Affairs
Katy Morton, Senior Director, Regulatory Affairs
Dawne Horn, Associate, Regulatory Affairs

BACKGROUND:

Connetics Corporation, (Connetics) is developing a Ketoconazole 2% Foam, (Extina) proposed for the topical treatment of seborrheic dermatitis. Connetics requested a Chemistry, Manufacturing and Controls (CMC) type C meeting on February 21, 2005, to discuss the outstanding chemistry issues identified in the November 23, 2004, Regulatory Action Letter. Connetics submitted a pre-meeting CMC briefing document dated March 24, 2006, received March 27, 2006, providing additional information on discussion topics and questions. FDA provided written responses to all questions outlined in the briefing document in an email dated April 21, 2006. Connetics contacted FDA on April 21, 2006 and requested a response on the October 17, 2005 request for waiver of photosafety studies for Ketoconazole foam, and that the agenda for the face to face meeting be focused on clarifying FDA responses to Question 1 and the response to the photosafety study waiver. This exchange is recorded below, along with meeting discussion at the April 25, 2006 meeting.

FDA PRELIMINARY PRE-MEETING RESPONSES:

The following are the firm's questions, FDA pre-meeting responses, related verbatim. Where further discussion during the teleconference occurred, a summary is included in the Related Meeting Discussion section.

1. *With regard to the chemistry issues raised in the 23 November 2004 Not Approvable letter, does the Division agree that Connetics has satisfied the Agency's request to attempt ~~_____~~ (Reference: issues 1 through 5 and issue 10 in Not Approval letter in Appendix I)*

b(4)

FDA Pre Meeting Response: It is difficult for us to determine if the ketoconazole assay is stability indicating primarily because the meeting package dated March 24, 2006 did not unambiguously demonstrate that the ~~_____~~

b(4)

~~_____~~ We also request a comprehensive technical report to provide experimental details for those studies described in the meeting package.

Once you provide a satisfactory spectrum for the ~~_____~~ and a comprehensive technical report, CMC deficiencies 1-5, and 10 listed in Not Approval letter dated November 23, 2004 will be resolved.

b(4)

2. *Does the Division agree that the response to the chemistry issues in the 23 November 2004 Not Approvable letter can be submitted in an NDA Amendment?*

FDA Pre Meeting Response: You may submit an amendment to the NDA responding to the Not Approvable letter at anytime. However, the PDUFA User Fee clock will not be restarted until we receive a complete response to our November 23, 2004, Not Approvable letter; i.e., a response to all of the items listed in the November 23, 2004, Not Approvable letter. Any partial responses received prior to a complete response may or may not be reviewed prior the receipt of the complete response depending upon the timing of the amendment and our resources.

3. *Only the 50 g product size was submitted in the original NDA. Rather than proceeding with the Comparability Protocol included in the original NDA that provides for the addition of a 10 g and 100 g product size, will the Division accept real-time, _____ stability data for these sizes in the proposed NDA Amendment?*

FDA Pre Meeting Response: Submission of _____ stability data for the 10g and 100g product sizes in the resubmission is acceptable. However, the adequacy of the submitted information to support approval of these new sizes will not be made until we have reviewed your resubmission. We are expecting submission of all the relevant information for these new fill sizes as was provided for the 50g fill size.

4. *Does the Division agree that photosafety studies for Ketoconazole Foam can be waived based on the negligible absorption in the UVB, UVA and visible regions?*

FDA Pre Meeting Response: In reference to the March 24th 2006 amendment to IND 63,153/S054 in which you (Connetics) provided absorption spectra for undiluted Ketoconazole Foam samples. The agency response to this question is: If any component of the sponsor's product shows absorption in the UVB, UVA or visible light spectra, photoallergenicity (at least 50 evaluable subjects) and phototoxicity (at least 30 evaluable subjects) will be required.

MEETING DISCUSSION:

In an email from Katy Morton (Connetics) to Scott N. Goldie, Ph.D. (FDA) dated April 21, 2006, Connetics agreed with the responses to questions 2 and 3 and removed them from the discussion agenda. The following are the firm's clarifying questions submitted to focus the agenda on original questions 1 and 4, related verbatim. Where further discussion during the meeting occurred, a summary is included.

b(4)

1 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Photosafety Waiver:

Connetics Question: Based on the information provided in the October 17, 2005, Table 1 and in the March 24, 2006 IND submissions, do the chemistry and clinical reviewers agree that there is no meaningful absorption in the UVB, UVA or visible light regions and therefore no photoallergenicity and phototoxicity studies are required?

FDA Meeting Response:

Photosafety studies, including phototoxicity and photoallergenicity are required of all products that have measurable absorbances between _____ . This includes colorations visible to the naked eye or detectable with appropriate optical instrumentation. _____

_____ The determination if the level under or over ICH guidelines is unknown at this time, and the _____ will help to address these issues. It is recommended that at least 50 evaluable subjects be used for the photoallergenicity studies, and at least 30 evaluable subjects be used for the phototoxicity studies. It is recommended that a batch of final to-be-marketed formulation of product stored under normal conditions near the end of but still within the expiry period be used.

b(4)

CLOSING AGREEMENTS AND ACTION ITEMS:

1. Connetics agreed _____
_____ Connetics proposes to submit in the NDA 1) _____ along with 2) a comprehensive technical report that will provide experimental details of all studies relied upon to resolve these issues.

b(4)

2. Connetics committed to submit a protocol and experimental design as general correspondence to the NDA _____
_____ Connetics also committed _____
_____ These data resulting from the proposed protocol were to be submitted no more than six months post approval.

b(4)

3. Connetics committed to submit dermatology battery studies of photoallergenicity with at least 50 evaluable subjects, and phototoxicity studies with at least 30 evaluable subjects using product stored under normal conditions near the end of but still within the expiry period.

{See appended electronic signature page}
Minutes Preparer: _____
Scott N. Goldie, Ph.D.
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

{See appended electronic signature page}
Chair Concurrence: _____
Moo-Jhong Rhee, PhD
Branch Chief
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

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/

Scott Goldie
5/22/2006 04:26:38 PM

Moo-Jhong Rhee
5/22/2006 04:50:06 PM
Chief, Branch III

Appears This Way
On Original

11 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III**

FACSIMILE TRANSMITTAL SHEET

Date: February 7, 2006

To: Michael S. Eison, Ph.D.
Connetics Corporation
Phone: (650) 739-2614
Fax: (650) 843-2802

From: Margo Owens, Project Manager
Phone: (301) 796-0966
Fax: (301) 796-9894

This transmission includes 3 pages (including this page)

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED BY APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is *unauthorized and strictly prohibited*. If you have received this facsimile in error, **please notify Margo Owens by telephone at 301-796-0966 immediately**, return it to HFD-540, 10903 New Hampshire Ave., Room 5165, Silver Spring, MD 20903 by US Mail.

FDA Facsimile Memorandum

Date: February 7, 2006
To: Michael S. Eison, Ph.D.
Connetics Corporation
From: Margo Owens, Project Manager
Subject: NDA 21-738 Extina (ketoconazole) Foam, 2%

Dr. Eison,

The clinical and statistical reviewers' have reviewed the information submitted in your meeting request dated January 16, 2006 for your NDA 21-738 Extina (ketoconazole) Foam, 2% and have asked that the following comments be conveyed to you.

Clinical and Biostatistics Reviewers' Comments:

Reference is made to your communication of January 16, 2006, in which you request a teleconference to discuss the comments in the Agency communication of December 28, 2005.

The clinical comments which were conveyed to you were made in the belief that the study had not already been initiated. While our comments reflect the Division's preferred study design for seborrheic dermatitis, we acknowledge that there is more than one acceptable definition of the primary endpoint. We therefore agree with the fourth proposal in your communication dated January 16, 2006, namely, that the present study be completed as per protocol.

4. *Should the Division not agree that the analysis in the original NDA provides a sufficient basis for approval, we propose that given the advanced stage of conduct of study KFD.C.005, it be completed as per current protocol; the Statistical Analysis Plan could be amended to reflect prospectively that exploration of the outcome measure as now defined by the Division in item #1 would be provided as a principal secondary endpoint. However, induration would not be removed as an Inclusion Criteria or as a component of the disease assessment.*

We will be happy to hold the scheduled teleconference if the above response requires further discussion.

Respectfully,

Margo Owens
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/

Margo Owens
2/7/2006 03:09:31 PM
CSO

Appears This Way
On Original



NDA 21-738

Connetics Corporation
Attention: Michael Eison, PhD
Vice President, Regulatory Affairs
3160 Porter Drive
Palo Alto, CA 94304

Dear Dr. Eison:

We received your January 16, 2006 correspondence on January 17, 2006, requesting a clinical/statistical telephone conference to discuss the requested protocol changes to study protocol KFD.C.005, for **Ketoconazole Foam, 2%**.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February, 2000). Your teleconference is scheduled for:

Date: Monday, February 13, 2006
Time: 3:00-4:00 PM, Eastern

We note that the background material has been submitted and will be reproduced for FDA meeting attendees.

Please provide a telephone or conference dial-in number at least 2 working days prior to the scheduled date.

If you have any questions, call Sandy Childs, Consumer Safety Technician, at 301-796-0867.

Sincerely,

{See appended electronic signature page}

Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatology & Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Suzanne Childs
1/25/2006 10:34:25 AM
Signed for Mary Jean Kozma-Fornaro

Appears This Way
On Original



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-738

Connectics
ATTN: Zane Rogers
Regulatory Affairs
3290 West Bayshore Road
Palo Alto, CA 94303-4230

Dear Mr. Rogers,

Please refer to your New Drug Application (NDA) file for Extina (ketoconazole) Foam, 2%, topical for the treatment of seborrheic dermatitis.

We also refer to the meeting between representatives of your firm and the FDA on May 23, 2005. The purpose of the meeting was to discuss development program Extina (ketoconazole) Foam, 2%, topical for the treatment of seborrheic dermatitis.

The official minutes of that meeting are enclosed. If you have any questions, call Felecia Curtis, Regulatory Project Manager, at (301)827-2020.

Sincerely,

{See appended electronic signature page}

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

Enclosure

Appears This Way
On Original

MEMORANDUM OF MEETING MINUTES



Meeting Date: May 23, 2005 **Time:** 1:00 P.M.
Location: N225 **Meeting ID:** 15268
Topic: NDA 21-738
Subject: Pre-Meeting briefing document submitted April 22, 2005.
Sponsor: Connetics
Meeting Chair: Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540
Meeting Recorder: Felecia Curtis/Regulatory Management Officer, DDDDP, HFD-540

FDA Attendees:

Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540
Stanka Kukich, M.D./Deputy Director, DDDDP, HFD-540
Markham Luke, M.D., Ph.D./Clinical Team Leader, Dermatology, DDDDP, HFD-540
Phyllis Huene, M.D./Clinical, Dermatology, DDDDP, HFD-540
Mohamed Al-Osh, Ph.D./Team Leader, Biostatistics, DBIII, HFD-725
Kathleen Fritsch, Ph.D./Biostatistics Reviewer, DBIII, HFD-725
Felecia Curtis/Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees:

Connectics Corporation

Alex Yaroshinsky, PhD. /VP of Clinical Operations and Biostatics
Lincoln Krochmal, M.D. /EVP, Research & Product Development
Greg Vontz, Chief Operating Officer, Connetics

Michael Eison, PhD/VP, Regulatory Affairs
Zane Rogers, Regulatory Affairs, Connetics

b(4)

Purpose: To provide general guidance on the content and format of the New Drug Application under 21CFR 314. The pre-meeting briefing document (submitted April 22, 2005) provides background and questions (pages 3-4) for discussion.

Clinical/Statistical

Sponsor's Questions:

- 1) Does the Agency agree with the proposed Phase 3 study design? (Protocol KFD.C.005 is provided in the briefing package.)

Agency's Response:

The Agency does not agree with the proposed Phase 3 study design. This should be a three-arm study, which compares Ketoconazole Foam, 2%, to Nizoral Cream and to the foam vehicle in the treatment of seborrheic dermatitis. The results of the study should show that Ketoconazole Foam is non-inferior to Nizoral Cream and is superior to the foam vehicle.

The non-approvable letter states that "results from one additional adequate and well-controlled study will need to be submitted demonstrating superiority of ketoconazole foam, 2%, over its vehicle and non-inferiority to the active comparator." Although the comparison between ketoconazole foam and Nizoral cream met the criteria for the non-inferiority component of the analysis in Study KFD.C.002, from a statistical perspective it is not possible to assert that ketoconazole foam has been shown to be non-inferior to Nizoral cream. Efficacy results are expected to vary from trial to trial due to various factors, and it is difficult to establish efficacy by piecing together components from different trials. Study KFD.C.002 had two hypotheses that needed to be rejected to establish efficacy. In order to control multiplicity under such a paradigm, if one component fails to achieve its objective, then no conclusions can be drawn about the efficacy of the remaining objective. In addition, it is difficult to interpret a non-inferiority result when a product has not been shown to be superior to its vehicle.

A three-arm study designed to demonstrate the superiority of ketoconazole foam to its vehicle and non-inferiority of ketoconazole foam to ketoconazole cream might be possible without a substantial increase in total sample size compared to the proposed sample size for Protocol KFD.C.005. Based on the information from the previous study, the non-inferiority component of the study may require fewer subjects than the superiority component. The total sample size could be reduced by enrolling ketoconazole foam and vehicle foam subjects in a 1:1 ratio rather than in a 2:1 ratio. A small cream vehicle arm to promote blinding is recommended, but this need not be very large.

The sponsor stated that in their view, a 505(b)2 non-inferiority study needs to answer three questions: (1) assay sensitivity, (2) demonstrating a non-inferior benefit of the new product to the existing product, and (3) demonstrating the contribution of the active component over the vehicle. The sponsor stated that demonstrating assay sensitivity and the interpretation of the non-inferiority finding were linked, but that the contribution of the active component could be assessed in a separate study. The sponsor stated that their demonstration that Nizoral cream was superior to vehicle cream was adequate to demonstrate the assay sensitivity, so that the non-inferiority of ketoconazole foam to Nizoral cream could also be concluded from the previous study.

The Agency responded that the utility of the vehicle cream arm from a regulatory point of view is to promote blinding. Assay sensitivity needs to be established by demonstrating that the new product is superior to its own vehicle. The Agency does not find it possible to interpret the non-inferiority comparison when a product has not demonstrated superiority to its own vehicle. In future trials, the Agency recommends explicitly stating that the hypotheses will be tested sequentially as (1) superiority of test product over vehicle, and (2) non-inferiority of test product to reference listed drug.

In addition, the Agency and sponsor discussed that the vehicle cream may have been manufactured somewhat differently and was not a true vehicle for the reference listed product. No superiority comparison of the 505(b)2 reference product vs. this ersatz vehicle is needed for such a study. The regulatory utility of such a comparison is limited.

The sponsor inquired as to whether it was possible to go the 505(b)2 route relying only on the Agency's findings of safety for the reference listed drug and not on their findings of efficacy. The Agency responded that in cases where a test product could not be shown to be non-inferior to a reference listed drug, but had a better safety profile that it is possible to establish efficacy through two adequate and well-controlled, vehicle-controlled trials.

The Agency also has the following comments on Protocol KFD.C.005:

- a. The primary efficacy hypotheses should be tested in a sequential fashion: first, demonstrate that ketoconazole foam is superior to its vehicle, and second, demonstrate that ketoconazole foam is non-inferior to ketoconazole cream.
- b. Although the previous study used the percent change in the sum of individual sign scores as the secondary endpoint, an endpoint that sums the scores of individual signs may not be clinically meaningful and difficult to interpret. In the secondary analyses, it is preferable to evaluate the changes in the individual scores for the clinical signs rather than in the sum of these scores. This provides a more clinically meaningful assessment.
- c. The protocol should include a sensitivity analysis with an alternate method of imputation for missing data to ensure that the conclusions are not driven by the method of handling missing data.

Sponsor's Questions:

- 2) Does the Agency agree that a successful outcome of the proposed Phase 3 study will support the conclusion that Ketoconazole Foam, 2%, is safe and effective for the treatment of seborrheic dermatitis, and will resolve the deficiency identified as the basis of non-approvability in the Agency's Regulatory Action Letter dated 23 November 2004?

Agency's Response:

The Agency does not agree. The study design is not adequate to support such a conclusion, as noted in the response to Question #1.

Sponsor's Questions:

- 3) Does the Agency agree that a long term open label safety study as per ICH E1A guidance is not required as the marketing application for Ketoconazole Foam, 2%, is a 505(b)(2) application which relies on the Agency's previous finding of safety for the listed drug, Nizoral (ketoconazole) Cream, 2%, including the safety of long term treatment?

Agency's Response:

The Agency does not agree. A long term open label safety study as per ICH E1A guidance is required. Since the results of Study KFD.C.003 (the comparative bioavailability study) show that, the absorption of ketoconazole was higher with Ketoconazole Foam than with Nizoral Cream. _____, a study is needed to ascertain the long term safety. This may not be needed prior to approval, but could be submitted as a post-marketing commitment.

b(4)

Regulatory

Sponsor's Questions:

- 4) Does the Agency agree that Connectics' response to all issues identified in the Regulatory Action Letter will be considered a Class 1 resubmission to NDA 21-738?

Agency's Response:

No. The Sponsor's complete response will contain information that will require the resubmission to be classified as Class 2. Class 2 resubmissions have a 6-month review clock. The sponsor may reference the "Guidance for Industry: Classifying Resubmission in Response to Action Letters".

Administrative Comments

1. Comments shared today with the Sponsor are based upon the contents of the briefing document, which is considered an informational aid to facilitate today's discussion. As today's meeting, is a Pre-IND meeting, the comments from the Agency serves as guidance to the Sponsor at this preliminary stage. The comments are not meant to be viewed as commitments from the Agency. Review of the information submitted to the IND might identify additional comments or informational requests.
2. For applications submitted after February 2, 1999, the applicant is required to either certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
3. The Sponsor is reminded to please submit appropriate patent certification at the time of NDA resubmission.
4. The applicant notes in the cover letter of the briefing document that, "Connectics will contact the Agency to obtain closure on the CMC issues identified in the 23 November 2004 Regulatory Action Letter".

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

/s/

Jonathan Wilkin
6/7/05 09:55:04 AM

Appears This Way
On Original



NDA 21-738

Connetics Corporation
Attention: Darlene O'Banion
Senior Manager, Regulatory Affairs
3160 Porter Drive
Palo Alto, CA 94304

Dear Ms. O'Banion:

We received your March 18, 2005 correspondence on March 21, 2005, requesting a meeting to discuss the study design for an additional pivotal study for **Ketoconazole Foam, 2%**.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February, 2000). The meeting is scheduled for:

Date: Monday, May 23, 2005
Time: 1:00-2:00 PM
Location: 9201 Corporate Blvd., Rockville, MD 20850

Provide the background information for this meeting at least 1 month prior to the meeting. Submit the original copy to your NDA, and **10 bound copies**, each marked "DESK COPY", directly to Sandy Childs at the above address. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by April 23, 2005, we may have to cancel the meeting.

If you have any questions, call Sandy Childs, Consumer Safety Technician, at 301-827-2061.

Sincerely,

{See appended electronic signature page}

Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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

/s/

Suzanne Childs
3/29/05 07:30:05 AM
Signed for Mary Jean Kozma-Fornaro

Appears This Way
On Original



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-738

Connectics
ATTN: Zane Rogers
Regulatory Affairs
3290 West Bayshore Road
Palo Alto, CA 94303-4230

Dear Mr. Rogers,

Please refer to your New Drug Application (NDA) file for Extina (ketoconazole) Foam, 2%, topical for the treatment of Seborrheic Dermatitis.

We also refer to the meeting between representatives of your firm and the FDA on February 7, 2005. The purpose of the meeting was to discuss development program Extina (ketoconazole) Foam, 2%, topical for the treatment of Seborrheic Dermatitis.

The official minutes of that meeting are enclosed. If you have any questions, call Felecia Curtis, Regulatory Project Manager, at (301)827-2020.

Sincerely,

{See appended electronic signature page}

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

Enclosure

Appears This Way
On Original

MEMORANDUM OF MEETING MINUTES



Meeting Date: February 7, 2005 **Time:** 1:00 P.M.
Location: N225 **Meeting ID:** 14632
Topic: NDA 21-738
Subject: Post NA Meeting 21-738, Sponsor's briefing document submitted January 7, 2004.
Sponsor: Connetics
Meeting Chair: Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540
Meeting Recorder: Felecia Curtis/Regulatory Management Officer, DDDDP, HFD-540

FDA Attendees:

Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540
Stanka Kukich, M.D./Deputy Director, DDDDP, HFD-540
Markham Luke, M.D., Ph.D./Clinical Team Leader, Dermatology, DDDDP, HFD-540
Jill Lindstrom, M.D./Clinical Team Leader, Dermatology, DDDDP, HFD-540
Phyllis Huene, M.D./Clinical, Dermatology, DDDDP, HFD-540
Mohamed Al-Osh, Ph.D./Team Leader, Biostatistics, DBIII, HFD-725
Kathleen Fritsch, Ph.D./Biostatistics Reviewer, DBIII, HFD-725
Felecia Curtis/Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees:

Connectics Corporation

Sharon Hall/Sr. Regulatory Affairs
Alex Yaroshinsky, PhD./VP of Clinical Operations and Biostatics
Terri Koller/ Sr. Director/ Project Management
Zane Rogers, Regulatory Affairs, Connetics

Lincoln Krochmal, M.D./EVP, Research & Product Development
Greg Vontz, Chief Operating Officer, Connetics

b(4)

Purpose: To provide general guidance on the content and format of the proposed new Investigational New Drug Application under 21CFR 312. The pre-meeting briefing document (submitted November 18, 2004) provides background and questions (page 7) for discussion.

Clinical & Biostatistics Comments:

Sponsor's Discussion:

Much of material in the sponsor's briefing document focused on the argument that demonstrating the superiority of Extina to its vehicle foam was not a primary objective in Study KFD.C.002. However, during the meeting the sponsor acknowledged that superiority was included as a primary objective in the protocol, even though portions of the protocol indicated that superiority was included as a way to validate the non-inferiority comparison rather than as an efficacy criterion in and of itself.

The sponsor spent most of the meeting making the argument that the totality of the data from Study KFD.C.002 does support that Extina is superior to its vehicle. The sponsor noted the following points.

- Ketoconazole is a well-known active for the treatment of seborrheic dermatitis. The foam is a novel vehicle for this active ingredient.
- If the two active arms and two vehicle arms are pooled together then the superiority comparison is statistically significant.
- The single pre-specified secondary endpoint was statistically significant.
- The two post-hoc endpoint presented by the sponsor (complete clearance: global=0, and effective treatment: global, erythema, and scaling all equal to 0 or 1 with at least 2 grades reduction from baseline) are more stringent than the protocol-specified endpoint, are clinically relevant, are similar to endpoints used in other NDAs, and were the only post-hoc endpoints considered by the sponsor.
- Treatments were only allocated in a 3:1 ratio for Extina and its vehicle limiting the power for this comparison.
- _____ noted that the combination of a novel dosage form and a subjective primary endpoint may have led to some unblinding of the investigators which may have led to efficacy not being observed.

b(4)

In addition, the sponsor identified three products, Differin gel, Penlac nail lacquer, and Clindagel which were previously approved by the Division even though not all superiority objectives appeared to have been met in all studies. The Agency requested that the sponsor provide a written response regarding the three product approvals within a week of the meeting.

Sponsor's Post-Meeting Written Response (Amendment 027 dated 2/15/05)

The sponsor's written response focused on the Clindagel application as the Clindagel application was most analogous to the Extina situation and the response did not further discuss the Differin and Penlac cases. The sponsor noted that Clindagel and ketoconazole foam share the following characteristics (page 6 of Amendment 027)

- Single Phase 3 study conducted to provide evidence of safety and effectiveness of the drug product;
- Demonstration of superiority of the drug product compared to vehicle for the endpoint of symptomatic improvement (lesion counts and seborrheic dermatitis, respectively);
- Additional post-hoc analyses of the Investigator's Global Assessment to support effectiveness of the drug product for its intended indication; and
- Use of the 505(b)(2) application to obtain approval.

Agency's Response:

The Agency noted that demonstrating superiority to vehicle is a key objective for establishing efficacy in a 505(b)2 submission. The two efficacy comparisons, test product versus vehicle and test product versus reference listed drug, provide separate pieces of efficacy evidence for a single-trial 505(b)2 submission. The Agency noted that the sponsor elected not to conduct a Phase 2 trial to estimate treatment and vehicle effects before proceeding to the Phase 3 trial, instead relying on historical data for ketoconazole cream to power the study. Since Study KFD.C.002 was the only study conducted comparing Extina to its vehicle, the sponsor has no additional data on the relative effects of Extina and the foam vehicle. Although the sponsor did allocate the treatments in a 3:1 ratio for Extina and vehicle, the protocol indicates that the sponsor considered this sample size allocation to have adequate power.

The Agency does not consider the analysis which pools the active arms together and the vehicle arms together valid for establishing the efficacy of ketoconazole foam, as this analysis averages effects across different vehicles and is difficult to interpret. In addition, because the vehicle effects are very different, the pooling of the poorly performing cream vehicle and better performing foam vehicle artificially inflates the treatment effect. A test product must be superior to its own vehicle to demonstrate the contribution of the active ingredient to the complete drug product.

Although the two post-hoc endpoints presented by the sponsor have stricter definitions for a success than the primary endpoint, they were nonetheless selected after viewing the data results and were not specified in the protocol. Although the sponsor claims that the two post-hoc endpoints presented were the only two post-hoc endpoints considered, this does not negate the fact that many post-hoc endpoints or other approaches to modifying the primary endpoint to achieve significance could have been proposed instead. To ensure that the type I error is controlled, the Agency puts primary weight on establishing efficacy for the primary endpoint, which was pre-specified in the protocol and agreed upon with the Division. The Agency does not consider the statistical significance of a secondary endpoint and two post-hoc endpoints to outweigh the lack of significance on the primary endpoint.

Agency's Response to the 2/15/05 Submission

In response to the Clindagel case study, the protocol specified four primary endpoints: percent reduction in inflammatory, non-inflammatory, and total lesions, and at least a two grade reduction in the physician's global assessment (see the statistical review for NDA 50-782, pg. 4). Once daily Clindagel was superior to its vehicle for all three lesion count endpoints ($p \leq 0.043$) and the reduction in the physician's global assessment ($p=0.033$). Although Clindagel was superior to its vehicle in the protocol-specified endpoint of at least two grades reduction in the physician's global assessment, it did not achieve statistical significance in the analysis considered more clinically relevant by the Division (0 or 1 on the global assessment, $p=0.076$). In the case of Extina, Study KFD.C.002 had a single non-significant primary endpoint for the ketoconazole foam versus vehicle foam comparison ($p=0.132$).

The meeting ended amicably.

NDA 21-738
2/07/05
Pre Meeting

Addendum:

As noted in the November 23, 2004 Not Approvable letter, results from one additional adequate and well-controlled study will need to be submitted demonstrating superiority of ketoconazole foam, 2%, over its vehicle and non-inferiority to the active comparator.

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/

Jonathan Wilkin
3/9/05 03:06:19 PM

Appears This way,
On Original



NDA 21-738

Connetics Corporation
Attention: Sharon Hall
Senior Director, Regulatory Affairs
3290 West Bayshore Road
Palo Alto, CA 94303

Dear Ms. Hall:

We received your December 3, 2004 correspondence requesting a meeting to discuss the basis for non-approvability of your NDA for **Ketoconazole Foam, 2%**.

You have requested a Type C meeting. Your meeting is scheduled for:

Date: Monday, February 7, 2005
Time: 1:00-2:00 PM, EST
Location: 9201 Corporate Blvd., Rockville, MD 20850

Please provide a list of your specific questions and concerns, at least a month prior to the meeting. Submit the original copy to your NDA, and 12 bound copies, each marked "DESK COPY", directly to Sandy Childs at the above address. If we do not receive it by January 7, 2005, we may need to reschedule the meeting.

If you have any questions, call Sandy Childs, Consumer Safety Technician, at 301-827-2061.

Sincerely,

{See appended electronic signature page}

Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/

Suzanne Childs
12/15/04 10:26:57 AM
Signed for Mary Jean Kozma-Fornaro

Appears This Way
On Original

MODE = MEMORY TRANSMISSION

START=NOV-23 11:32

END=NOV-23 11:33

FILE NO.=199

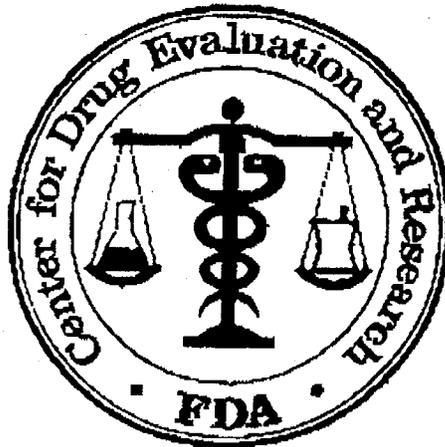
STN NO.	COMM.	ONE-TOUCH/ ABBR NO.	STATION NAME/EMAIL ADDRESS/TELEPHONE NO.	PAGES	DURATION
001	OK	*	916508432802	006/006	00:00:50

-FDA/CDER/DDDDP/HFD540 -

***** -301 827 2091 - ***** 301 827 2091- *****

FOOD AND DRUG ADMINISTRATION
 DIVISION OF DERMATOLOGIC AND
 DENTAL DRUG PRODUCTS
 HFD-540
 9201 CORPORATE BLVD.
 ROCKVILLE, MARYLAND 20850

DATE: 11/23/04



TO:

Name Sharon Hall
 Fax No. 650 843 2802
 Phone No. _____
 Location Amnition Corp

FROM:

Name MARY JEAN KOZMA-FORNARO
 Fax No. 301 827-2075/2091
 Phone No. 301 827-2020

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

Comments:

Sharon
The action letter for NDA 21735.
Mary Jean

Office of Drug Safety

MEMO

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

From: Linda Y. Kim-Jung, Pharm.D.
Safety Evaluator, Division of Medication Errors and Technical Support, HFD-420

Through: Denise P. Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, HFD-420

CC: Mary Jean Kozma-Fornaro
Project Management Supervisor, Division of Dermatologic and Dental Drug Products, HFD-540

Date: September 13, 2004

Re: ODS Consult 03-0177-2; Extina (Ketoconazole Foam) 2%; NDA 21-738

*****Note: This review contains proprietary and confidential information that should not be released to the public.*****

This memorandum is in response to an August 11, 2004 request from your Division for a final review of the proprietary name, Extina. The proposed proprietary name was found acceptable by DMETS in the first review dated October 23, 2003 (ODS Consult 03-0177). The revised container label, carton and insert labeling were provided for review and comment.

Since the initial review on October 23, 2003, DMETS has identified four additional proprietary names as having potential sound-alike confusion with Extina (Exna, Lessina, Levitra, and Lexiva). Additionally, two proprietary names were identified as having potential look-alike confusion with Extina (Exidine and Evista). Upon further review, DMETS notes that Exna and Exidine have been discontinued per the electronic Orange Book. Despite the discontinued status of Exna and Exidine, both drug names still appear in the Internet and some drug product reference materials. However, due to distinct drug product characteristics and lack of convincing look and or sound-alike similarities with Extina, Exna and Exidine will not be discussed in this review. Additionally, Lessina, Levitra, and Lexiva were not reviewed further due to lack of convincing sound-alike similarities with Extina in addition to numerous differentiating product characteristics such as the product strength, indication for use, frequency of administration, route of administration and dosage formulation.

Evista could potentially look similar to Extina when scripted. Evista (Raloxifene) is indicated for the prevention and treatment of osteoporosis. Evista is available as 60 mg tablets and the usual recommended dose is one tablet daily. Both drug names start with the letter 'E', share the letter 'T' and ends with the letter 'A' which may contribute to the look-alike similarities between the two names. Additionally, depending on how the letters are scripted, the letter 'v' and 'x' could potentially look-alike as well. However, the ending of the names (-ista vs. -tina) look different and the position of the letter 'T' (upstroke of the letter 't' in Evista) in the latter portion of the name vs. upstroke of the letter 'T' in Extina in the beginning of the name) helps to differentiate between the two names. Moreover, the two products have differentiating product characteristics such as the product strength (60 mg vs. 2%), frequency of administration (once daily vs. twice daily), route of administration (oral vs. topical), and dosage formulation (tablets vs. foam) which minimizes the potential for confusion between Evista and Extina. Thus, the potential for confusion between the two names is minimal.

Extina
Evista

Upon review of the labels and labeling submitted for this review, we note that the sponsor addressed most of DMETS' label and labeling comments included in the second review dated June 1, 2004 (ODS Consult 03-0177-1). DMETS has identified the following additional areas of possible improvement which might minimize potential user error.

A. GENERAL COMMENTS

1. We note the sponsor has revised the trade dress. The revised trade dress still does not address DMETS' recommendation against the use of same layout for the sponsor product line of topical foams (please refer to ODS Consult #03-0177-1). Upon further review, we note the sponsor is proposing the same product layout for another pending ~~_____~~. Thus, it appears that the sponsor is potentially planning to use the same product layout for other current and or future products as well. Postmarketing surveillance has shown that similar labeling across manufacturers' product lines may result in medication errors due to similarity in appearance. DMETS recommends that the sponsor differentiate each product label and labeling so that it is readily distinguishable from other topical foam products. b(4)

2. The sponsor has used the phrase '~~_____~~' on the labels and labeling for this product to indicate the route of administration. However, the term '~~_____~~' does not appear in the CDER Data Standards Manual under the listing for Data Element Name: Route of Administration. Other terminology listed in the CDER Data Standards Manual for the Route of Administration that may be appropriate include "Topical" and "Cutaneous". We recommend revising the route of administration to read "For Topical Use Only". b(4)
3. Please disclose where the expiration date is noted. Currently, the expiration date is not indicated on the label and labeling of the product.

B. PACKAGE INSERT LABELING (Instruction for applying Extina)

1. Please clarify the statement. ~~_____~~ to include the amount of time necessary or some guidance to enable the patient to know when the product is ready. b(4)
2. Please address if shaking the can is permitted or not advised.
3. Please address what effect refrigeration will have on the product. Due to the need for the can to feel cool, patients may refrigerate the product which prompts the necessary knowledge of how this will affect the chemical efficacy and/or delivery mechanism.
4. Revise "~~_____~~" to read "~~_____~~". b(4)

In summary, DMETS has no objection to the use of the proprietary name, Extina, from a safety perspective. Additionally, DDMAC finds the proprietary name, Extina, acceptable from a promotional perspective. We consider this a final review. If the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from this date forward. We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

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

/s/

Linda Kim-Jung
9/28/04 10:43:08 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
9/28/04 12:25:58 PM
DRUG SAFETY OFFICE REVIEWER
Signing for Carol Holquist, Director Division of Medication Errors
and Technical Support

Appears This Way
On Original



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

FACSIMILE TRANSMITTAL SHEET

DATE: September 22, 2004

For Ginny Giroux, RPM

**To: Sharon Hall
Katy Morton**

**From: Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff**

Company: Connetics

**Division of Dermatologic & Dental Drug
Products**

Fax number: 650 843-2802

Fax number: (301) 827-2091/2075

Phone number: 650 843-2860

Phone number: (301) 827-2020

Subject: NDA 21-738 ketoconazole foam

Total no. of pages including cover: 2

Comments: Minutes of telephone conference call Sept. 13, 2004

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS
ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL,
AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

**If you are not the addressee, or a person authorized to deliver this document to the
addressee, you are hereby notified that any review, disclosure, dissemination, copying, or
other action based on the content of this communication is not authorized. If you have
received this document in error, please notify us immediately by telephone at (301) 827-
2020. Thank you.**

**Appears This Way
On Original**

MEMORANDUM OF TELEPHONE CONVERSATION

DATE: September 13, 2004
DRUG: Ketoconazole Foam, 2%
NDA: 21-738
SPONSOR: Connetics Corporation:
Sharon Hall, Senior Director, Regulatory Affairs
Katy Morton, Director, Regulatory Affairs
FDA: Division of Dermatologic and Dental Drug Products:
Jonathan Wilkin, M.D., Director
Stanka Kukich, M.D., Deputy Director
Mary Jean Kozma-Fornaro, Supervisor, Project Management Staff
Subject: Review Status Update for NDA 21-738

Sponsor was contacted to inform and comment that:

- Reviewers are in final stages of closing reviews as of September 13, 2004
- We are waiting for Chemistry information request response
- It is noted that there was no Phase 2 study conducted to demonstrate how well the vehicle works
- It is noted that the response rate for the product compared to the vehicle was marginal, and there was a substantial improvement in the vehicle group.

Sponsor stated the chemistry information request response will arrive on September 15, 2004.

Conversation ended amicably.

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

/s/

Mary Jean Kozma Fornaro
9/22/04 09:56:28 AM
CSO
Jonathan Wilkin
9/22/04 10:32:30 AM
MEDICAL OFFICER

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/

Mary Jean Kozma Fornaro
9/22/04 11:12:35 AM
CSO

Appears This Way
On Original

MEMORANDUM OF TELEPHONE CONVERSATION

DATE: September 13, 2004
DRUG: Ketoconazole Foam, 2%
NDA: 21-738
SPONSOR: Connetics Corporation:
Sharon Hall, Senior Director, Regulatory Affairs
Katy Morton, Director, Regulatory Affairs
FDA: Division of Dermatologic and Dental Drug Products:
Jonathan Wilkin, M.D., Director
Stanka Kukich, M.D., Deputy Director
Mary Jean Kozma-Fornaro, Supervisor, Project Management Staff
Subject: Review Status Update for NDA 21-738

Sponsor was contacted to inform and comment that:

- Reviewers are in final stages of closing reviews as of September 13, 2004
- We are waiting for Chemistry information request response
- It is noted that there was no Phase 2 study conducted to demonstrate how well the vehicle works
- It is noted that the response rate for the product compared to the vehicle was marginal, and there was a substantial improvement in the vehicle group.

Sponsor stated the chemistry information request response will arrive on September 15, 2004.

Conversation ended amicably.

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/

Mary Jean Kozma Fornaro
9/22/04 09:56:28 AM
CSO

Jonathan Wilkin
9/22/04 10:32:30 AM
MEDICAL OFFICER

Appears This Way
On Original



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

FACSIMILE TRANSMITTAL SHEET

DATE: 9/13/04

For Ginny Giroux

To: Sharon Hall/Katy Morton	From: Mary Jean Kozma-Fornaro Supervisor, Project Management Staff
Company: Connetics	Division of Dermatologic & Dental Drug Products
Fax number: 650 843 2802	Fax number: (301) 827-2091
Phone number: 650 843-2860	Phone number: (301) 827-2020
Subject: NDA 21-738 Ketoconazole Foam : Clinical Information Request	

Total no. of pages including cover: 2

Comments: Please provide the number and percent of subjects who developed each of the irritation scores during the induction phase of Study KFD.C.004 for each test article.

Thank you.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2020. Thank you.

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

/s/

Mary Jean Kozma Fornaro
9/13/04 04:59:30 PM
CSO

Appears This Way
On Original

4 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)



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

FACSIMILE TRANSMITTAL SHEET

DATE: September 2, 2004

To: Katy Morton	From: Mary Jean Kozma-Fornaro Supervisor, Project Management Staff
Company: Connetics	Division of Dermatologic & Dental Drug Products
Fax number: 650 843-2802	Fax number: (301) 827-2091/2075
Phone number: 650 843-2860	Phone number: (301) 827-2020

Subject: NDA 21-738 ketoconazole foam

Total no. of pages including cover: 2

Comments: 10 month user fee goal date for above application. Correction to original acknowledgment letter

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2020. Thank you.

Appears This Way
On Original



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-738

Connetics
Attention: Katy Morton
Regulatory Affairs
3290 West Bayshore Road
Palo Alto, CA 94303

Dear Mr. Democko:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ketoconazole Foam, 2%.

We also refer to our Acknowledgement Letter for this NDA, issued on March 22, 2004. Please note that the user fee goal date cited in that letter (September 24, 2004) is in error. Your NDA, dated January 23, 2004, was received on January 26, 2004. Therefore, the 10-month user fee goal date will be November 26, 2004.

If you have any questions, call Ginny Giroux, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}
Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic & Dental Drugs
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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

/s/

Mary Jean Kozma Fornaro
8/31/04 01:12:34 PM

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

/s/

Mary Jean Kozma Fornaro
8/31/04 01:12:34 PM

Appears This Way
On Original

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Predecisional Agency Information

Date: August 9, 2004

From: Sonny Saini, Pharm.D. – DDMAC
Iris Masucci, Pharm.D. – DDMAC

To: Lea Carrington

Re: Extina (ketoconazole) Foam, 2% Draft Labeling Comments
N 21-738

Mode of Action

- The sentence “~~_____~~” contains information that appears to be speculative. Is this mechanism well supported? If not, we recommend deletion. **b(4)**

Clinical Studies

- The description of the study is done in very broad terms. Can more detail be given, e.g., description of the Investigator’s Static Global Assessment tool, baseline and end of study scores, etc.?

Indications and Usage

- Are there any age limitations for Extina? If so, we recommend adding this information in this section.

Adverse Reactions

- The statement “~~_____~~” **b(4)**
~~_____~~
Is this statement accurate? If not, we

recommend deletion. Also, if any patients experienced adverse reactions and discontinued therapy we recommend including that percentage in this section.

- ~~_____~~ b(4)
- Can the adverse reactions data be presented in a table format, perhaps vs. vehicle foam? This type of presentation is the one suggested by the draft guidance on the Adverse Reactions section of labeling.
- In the first sentence, the phrase '~~_____~~', the meaning is unclear. Do they mean those occurring in at least 10% of patients? b(4)

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/

Sonny Saini
8/13/04 02:10:14 PM
DDMAC REVIEWER

Appears This Way
On Original

27 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research**

LABEL and LABELING REVIEW

DATE OF REVIEW: June 1, 2004
NDA # 21-738
NAME OF DRUG: Extina™
(Ketoconazole) Foam
2%
NDA HOLDER: Connetics Corporation

I. INTRODUCTION:

This consult was written in response to a request from the Division of Dermatologic and Dental Drug Products to review the container labels, carton, and insert labeling of Extina which were submitted to the EDR on February 26, 2004. At the time of the initial proprietary name review, DMETS provided comments and suggestions for the revision on the proposed labels and labeling of Extina (see ODS consult #03-0177) and provided several recommendations for revisions. However, a few of the recommendations were incorporated into the labels and labeling.

PRODUCT INFORMATION

Extina (Ketoconazole) contains the broad spectrum synthetic antifungal agent, ketoconazole. It is indicated for the topical treatment of seborrheic dermatitis. Extina will be supplied as a foam containing 2% ketoconazole supplied in 50 gram aluminum cans. Extina is applied to the affected areas of the skin twice daily for four weeks or until clinical clearing. Patients should dispense a small amount of Extina directly onto the affected area(s), or onto a saucer or other cool surface, taking care to avoid contact with the eyes. The foam will begin to melt upon contact with warm skin. Patients should be instructed to gently massage the foam into the affected areas until the foam disappears. Extina is for external, topical use only.

**Appears This Way
On Original**

2. Reorder the third point, "~~_____~~ to be the first instruction provided. b(4)
3. ~~_____~~
4. Please clarify the statement "~~_____~~ to include the amount of time necessary or some guidance to enable the patient to know when the product is ready. b(4)
5. It is noted ~~_____~~ DMETS questions ~~_____~~ would cause the product to immediately liquefy or melt since it was previously mentioned that the product would melt on contact with warm skin.
6. Please address if shaking the can is permitted or not advised.
7. Please address what effect refrigeration will have on the product. Due to the need for the can to feel cool, patients may refrigerate the product which prompts the necessary knowledge of how this will affect the chemical efficacy and/or delivery mechanism.

III. DMETS RECOMMENDATIONS:

DMETS recommends implementation of the labeling revisions outlined in Section II of this review.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Felicia Duffy, RN
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Felicia Duffy
7/20/04 08:19:50 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
7/20/04 09:52:23 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/20/04 10:34:06 AM
DRUG SAFETY OFFICE REVIEWER

Appears This Way
On Original



connetics®
Connecting Science, Skin and Lives™

ORIGINAL

03 June 2004

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

RECEIVED

JUN 07 2004

MEGA/CDER

**RE: NDA 21-738/Amendment 011, Ketoconazole Foam, 2%
Four-Month Safety Update Report**

Attention: Lea Carrington, Regulatory Project Manager

21-738(SU)
CRIG AMENDMENT

Dear Ms. Carrington:

Connetics Corporation (Connetics) is providing the Four-Month Safety Update per 21 CFR 314.50(d)(5)(vi)(b) for Ketoconazole Foam, 2%, NDA 21-738.

There has been no new safety information for Ketoconazole Foam, 2% since submission of the NDA to the Agency. Connetics has not conducted additional nonclinical or clinical studies with Ketoconazole Foam, 2%. All studies were reported in the NDA. Connetics is not aware of any nonclinical or clinical studies being conducted with the product.

There is no new information in the literature concerning the safety of topical administration of ketoconazole (nonclinical or clinical) from the date of NDA submission to the present date.

If you have questions concerning this amendment, please contact me at (650) 843-2858 or Darlene O'Banion, Senior Manager, Regulatory Affairs, at (650) 843-2829. The Regulatory Affairs facsimile number is (650) 843-2802.

Sincerely,

Sharon L. Hall
Senior Director, Regulatory Affairs

Carrington, Leonthena

From: CDERDocAdmin
Sent: Friday, May 28, 2004 4:19 PM
: CARRINGTONL@cder.fda.gov; BESTJ@cder.fda.gov; PIAZZAHEPPT@cder.fda.gov;
DALPANG@cder.fda.gov; STEPHENSL@cder.fda.gov; WILKINJ@cder.fda.gov
Subject: DFS Email - N 021738 N 000 23-Jan-2004 - Review

Follow Up Flag: Follow up
Flag Status: Flagged



090014648042 090014648042
65cf.drl (185 B)5cf.pdf (197 KB)

Document room close out the following assignments:

	Personnel Code	Sup-Concur	St
N 021738 N 000 23-Jan-2004	88V	28-May-2004	CM

Document Type: Review
Submission Description: ODS/DSRCS Review of Patient Instructions
PM activity: PM activity required

Author(s)/Discipline(s)

1. Jeanine Best, DRUG SAFETY OFFICE REVIEWER

Signer(s)

1. Jeanine Best
27-May-2004
Toni Piazza Hepp
for Gerald Dal Pan
28-May-2004

Appears This Way
On Original

1 Page(s) Withheld

 Trade Secret / Confidential (b4)

 ✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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

/s/

Jeanine Best
5/27/04 02:52:11 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
5/28/04 04:17:36 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

Appears This Way
On Original

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # **21-738** Supplement # **N/A** SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: **Extina**
Generic Name: **(ketoconazole)**
Strengths: **2%**

Applicant: **Connetics Corporation**

Date of Application: **January 23, 2004**

Date of Receipt: **January 26, 2004**

Date clock started after UN:

Date of Filing Meeting: **March 15, 2004**

Filing Date: **March 26, 2004**

Action Goal Date (optional):

User Fee Goal Date: **November 26, 2004**

Indication(s) requested: **Treatment of seborrheic dermatitis**

Type of Original NDA: (b)(1) _____ (b)(2) **X**
OR

Type of Supplement: (b)(1) _____ (b)(2) _____

NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S **X** _____ P _____
Resubmission after withdrawal? _____ Resubmission after refuse to file? _____
Chemical Classification: (1,2,3 etc.) **3** _____
Other (orphan, OTC, etc.) _____

User Fee Status: Paid _____ Exempt (orphan, government) _____
Waived (e.g., small business, public health) **X** _____

Form 3397 (User Fee Cover Sheet) submitted: **X** YES NO

User Fee ID # _____

Clinical data? YES _____ NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES NO **X**

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? YES NO **X**

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

X N/A YES NO

Is the application affected by the Application Integrity Policy (AIP)? YES NO **X**

If yes, explain.

- | | | | |
|---|---|---|--|
| If yes, has OC/DMPQ been notified of the submission? | <input checked="" type="checkbox"/> N/A | YES | NO |
| • Does the submission contain an accurate comprehensive index? | | <input checked="" type="checkbox"/> YES | NO |
| • Was form 356h included with an authorized signature?
If foreign applicant, both the applicant and the U.S. agent must sign. | | <input checked="" type="checkbox"/> YES | NO |
| • Submission complete as required under 21 CFR 314.50?
If no, explain: | | <input checked="" type="checkbox"/> YES | NO |
| • If an electronic NDA, does it follow the Guidance?
If an electronic NDA, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format? | <input checked="" type="checkbox"/> N/A | YES | NO |
| Additional comments: | | | |
| • If in Common Technical Document format, does it follow the guidance? | N/A | <input checked="" type="checkbox"/> YES | NO |
| • Is it an electronic CTD?
If an electronic CTD, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format? | N/A | YES | <input checked="" type="checkbox"/> NO |
| Additional comments: | | | |
| • Patent information submitted on form FDA 3542a? | | <input checked="" type="checkbox"/> YES | NO |
| • Exclusivity requested?
Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required. | | YES, <u> 3 </u> years | NO |
| • Correctly worded Debarment Certification included with authorized signature?
If foreign applicant, both the applicant and the U.S. Agent must sign the certification. | | <input checked="" type="checkbox"/> YES | NO |
| NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,
“[Name of applicant] 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 this application.” Applicant may not use wording such as “To the best of my knowledge” | | | |
| • Financial Disclosure forms included with authorized signature?
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.) | | <input checked="" type="checkbox"/> YES | NO |
| • Field Copy Certification (that it is a true copy of the CMC technical section)? | | <input checked="" type="checkbox"/> YES | NO |
| Refer to 21 CFR 314.101(d) for Filing Requirements | | | |
| • PDUFA and Action Goal dates correct in COMIS? | | <input checked="" type="checkbox"/> YES | NO |

If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
- List referenced IND numbers: **63,153**
- End-of-Phase 2 Meeting(s)? Date(s) **July 30, 2001** NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) **May 30, 2003** NO
If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **X YES** NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? **X YES** NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES **X NO**
*Note: No PPI or MedGuide provided with application.
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? **X N/A** YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? **X N/A** YES NO
- Has DOTCDP been notified of the OTC switch application? **X N/A** YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? **X N/A** YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? **X YES** NO
If no, did applicant submit a complete environmental assessment? **X N/A** YES NO
If EA submitted, consulted to Nancy Sager (HFD-357)? **X N/A** YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? **X YES** NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? **X N/A** YES NO

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #: **Nizoral (ketoconazole) Cream, 2%, NDA 19-576, NDA 19-084, NDA 19-640, Nizoral (ketoconazole) Shampoo, 2%, NDA 19-927.**
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

This application provides for a new application modality for the active pharmaceutical ingredient ketoconazole. Ketoconazole Foam, 2% is a change in dosage form in the reference listed drug, Nizoral Cream, 2%.

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

YES X NO

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

YES X NO

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

YES X NO

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

___ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

X 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

___ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

___ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

___ 21 CFR 314.50(i)(1)(ii): No relevant patents.

___ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

___ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

• Did the applicant:

• Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference? X YES NO

• Submit a statement as to whether the reference listed drug(s) identified has received a period of marketing exclusivity? X YES NO

• Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug? N/A X YES NO

• Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv)).?
Seeking exact indication as the reference listed drug. X N/A YES NO

• If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

• Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a). X YES NO

• A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval. YES X NO

Applicant certifies that a thorough search was conducted and no published studies or publicly available reports of clinical investigations with ketoconazole foam 2% were found.

• EITHER
The number of the applicant's IND under which the studies essential to approval were conducted.

IND # 63,153 NO

OR

A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

X N/A YES NO

• Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

X YES NO

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

/s/

Leonthena Carrington
5/25/04 03:44:27 PM
CSO

Mary Jean Kozma Fornaro
5/25/04 03:55:44 PM
CSO

Appears This Way
On Original



Food and Drug Administration
Center for Drug Evaluation and Research

Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: May 20, 2004

To: Charles Democko, Vice President Regulatory Affairs	From: Lea Carrington Regulatory Project Manager
Company: Connetics Corporation	Division of Dermatologic & Dental Drug Products
Fax number: (650) 843-2802	Fax number: (301) 827-2091 or 2075
Phone number: (650) 739-2930	Phone number: (301) 827-2020
Subject: NDA 21-738	

Total no. of pages including cover: **3**

Comments: Information Request – Pharmacology/Toxicology

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2020. Thank you.

Appears This Way
On Original

FDA FAX MEMORANDUM

Date: May 20, 2004

To: Charles Democko, Vice President, Regulatory Affairs

Applicant: Connetics Corporation

Subject: NDA 21-738 Information Request

We refer to your submission of New Drug Application (NDA) 21-738, Extina (ketoconazole) Foam, 2%. The Pharmacology/Toxicology Reviewer has requested additional information to proceed with review of your application. Please provide the expected maximum quantity per application of the drug product.

If you have any questions or need further clarification, please contact me at (301) 827-2020.

Respectfully,

Lea Carrington
Regulatory 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/

Leonthena Carrington
5/20/04 11:27:44 AM
CSO
Faxed to Applicant 5/20/04.

Appears This Way
On Original

BIOPHARMACEUTICS	FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	_____
• Biopharm. inspection needed:			YES	<input checked="" type="checkbox"/> NO
PHARMACOLOGY	NA	_____	FILE	<input checked="" type="checkbox"/>
			REFUSE TO FILE	_____
• GLP inspection needed:			YES	<input checked="" type="checkbox"/> NO
CHEMISTRY	FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	_____
• Establishment(s) ready for inspection?			<input checked="" type="checkbox"/> YES	NO
• Microbiology		<input checked="" type="checkbox"/> N/A	YES	NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

_____ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ No filing issues have been identified.

Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

Document filing issues conveyed to applicant by Day 74, April 9, 2004. The 74-day letter was faxed to the applicant on April 7, 2004.

Regulatory Project Manager, HFD-540

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/

Jonathan Wilkin
5/19/04 04:12:20 PM

Appears This Way
On Original



Division of Dermatologic and
Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-540
Rockville, MD 20857

FACSIMILE TRANSMISSION RECORD

DATE: APRIL 8, 2004 Pages (including cover) 13
TO: MICHAEL BRONY
COMPANY: DDMAC
ADDRESS: _____
FAX PHONE#: 301-594-6771 Our Fax # (301) 827-2075
Voice # (301) 827-2020

MESSAGE:

NDA 21-738 Extina (Ketoconazole) Foam, 2%
Draft label, carton and container.

NOTE: We are providing the attached information via telephone facsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: LEA CARRINGTON
TITLE: PROJECT MANAGER
TELEPHONE: 301-827-2072

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

REQUEST FOR CONSULTATION

TO (Division/Office):
**Div. of Drug Marketing, Advertising and Communications
(DDMAC)
HFD-042, PKLWN/Room 17B17**

FROM:
HFD-540, Div. of Dermatologic and Dental Drug Products
(DDDDP)
Lea Carrington, Regulatory Project Manager

DATE:
April 8, 2004

IND NO.

NDA NO.:
21-738

TYPE OF DOCUMENT

DATE OF DOCUMENT:
January 23, 2004

NAME OF DRUG:
Extina (ketoconazole) Foam, 2%

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG:
3S

DESIRED COMPLETION DATE:
August 2004

NAME OF FIRM: Connetics Corporation

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

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
 BIOAVAILABILITY 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
 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Extina (ketoconazole) Foam, 2%, is proposed for the indication of seborrheic dermatitis. The applicant is Connetics Corporation. The Applicant's proposed label, and carton & container labels are attached. An end of review labeling is scheduled for September 2004. Please provide comments in sufficient time prior to labeling meeting. If you have any questions or need additional information, please contact me at 301-827-2072, or email me at carringtonl@cdcr.fda.gov. The PDUFA goal date is November 26, 2004.

Thank you,
Lea

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)
 MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

10 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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

/s/

Leonthena Carrington
4/8/04 04:01:54 PM

Appears This Way
On Original

REQUEST FOR CONSULTATION

TO (Division/Office):

**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
PKLN Rm. 6-34**

FROM:

HFD-540, Div. of Dermatologic and Dental Drug Products
(DDDDP)
Lea Carrington, Regulatory Project Manager

DATE:
April 8, 2004

IND NO.

NDA NO.:
21-738

TYPE OF DOCUMENT

DATE OF DOCUMENT:
January 23, 2004

NAME OF DRUG:
Extina (ketoconazole) Foam, 2%

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG
3S

DESIRED COMPLETION DATE
August 2004

NAME OF FIRM: Connetics Corporation

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

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
 BIOAVAILABILITY 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
 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

Extina (ketoconazole) Foam, 2%, is proposed for the indication of seborrheic dermatitis. The applicant is Connetics Corporation. The Applicant's proposed label, and carton & container labels are attached. An end of review labeling is scheduled for September 2004. Please provide comments in sufficient time prior to labeling meeting. If you have any questions or need additional information, please contact me at 301-827-2072, or email me at carringtonl@cder.fda.gov. The PDUFA goal date is November 26, 2004.

Thank you,
Lea

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)
 MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

10 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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

/s/

Leonthena Carrington
4/8/04 03:23:02 PM

Appears This Way
On Original

REQUEST FOR CONSULTATION

TO (Division/Office):

Office of Drug Safety

Mail: ODS (Room 15B-08, PKLN Bldg.)

FROM:

HFD-540, Div. of Dermatologic and Dental Drug Products
(DDDDP)

Lea Carrington, Regulatory Project Manager

DATE:
April 8, 2004

IND NO.

NDA NO:
21-738

TYPE OF DOCUMENT

DATE OF DOCUMENT:
January 23, 2004

NAME OF DRUG:
Extina (ketoconazole) Foam, 2%

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG:
3S

DESIRED COMPLETION DATE:
August 2004

NAME OF FIRM: Connetics Corporation

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- | | |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Extina (ketoconazole) Foam, 2%, is proposed for the indication of seborrheic dermatitis. The applicant is Connetics Corporation. The Applicant's proposed label, and carton & container labels are attached. An end of review labeling is scheduled for September 2004. Please provide comments in sufficient time prior to labeling meeting. If you have any questions or need additional information, please contact me at 301-827-2072, or email me at carringtonl@cdcr.fda.gov. The PDUFA goal date is November 26, 2004.

Thank you,
Lea

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)
 MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

10 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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

/s/

Leonthena Carrington
4/8/04 03:16:29 PM

Appears This Way
On Original

Carrington, Leonthena

From: CDERDocAdmin
Sent: Monday, April 05, 2004 4:05 PM
TEMPLE@cder.fda.gov; CARRINGTONL@cder.fda.gov; HUENE@cder.fda.gov;
MAINIGIK@cder.fda.gov; FENSELAUA@cder.fda.gov; GHOSHT@cder.fda.gov;
FRITSCHK@cder.fda.gov; SCHMUFFN@cder.fda.gov; KOZMAFORNARO@cder.fda.gov;
CHILDSS@cder.fda.gov; LUKEM@cder.fda.gov; BROWNP@cder.fda.gov;
BASHAW@cder.fda.gov; ALOSHM@cder.fda.gov
Subject: DFS Email - N 021738 N 000 FG 23-Jan-2004 - NDA Letters



09001464803f 09001464803f
e27d.drl (229 B) 27d.pdf (128 KB)

Document room update the following:

	Decision Date	Decision Code
N 021738 N 000 FG 23-Jan-2004	05-Apr-2004	FI:FILING ISSUES IDENTIFIED

Mail paper copy to

DISTRICT OFFICE

Document Type: NDA Letters
Letter Group: Filing Letters
Letter Name: Filing Communication - Issues Identified
Submission Description: 74-day Filing Review Letter

Author(s)/Discipline(s)

Leonthena Carrington, CSO

Signer(s)

- 1. Leonthena Carrington
05-Apr-2004
2. Jonathan Wilkin
05-Apr-2004

Supervisory Signer(s)

- 1. Jonathan Wilkin
05-Apr-2004

Appears This Way
On Original



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

FACSIMILE TRANSMITTAL SHEET

DATE: April 7, 2004

To: Charles Democko, Vice President Regulatory Affairs	From: Lea Carrington Regulatory Project Manager
Company: Connetics Corporation	Division of Dermatologic & Dental Drug Products
Fax number: (650) 843-2802	Fax number: (301) 827-2091 or 2075
Phone number: (650) 739-2930	Phone number: (301) 827-2020
Subject: NDA 21-738	

Total no. of pages including cover: 6

Comments: Filing Review Letter

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2020. Thank you.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-738

Connetics Corporation
Attention: Charles Democko,
Vice President, Regulatory Affairs
3290 West Bayshore Road
Palo Alto, CA 94303

Dear Mr. Democko:

Please refer to your January 23, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Extina (ketoconazole) Foam, 2%.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on April 9, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Clinical:

1. There do not appear to be adequate numbers of patients in the 12 to 18 year age range.
2. As was stated in the pre-NDA meeting, there is risk with an NDA submission in which a clear demonstration of superiority of the drug product over the vehicle is lacking.

Clinical Microbiology:

1. The microbiology reviewer recommends that the statement _____ be deleted from the label.

b(4)

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

Chemistry, Manufacturing and Controls:

We refer to the Agency's facsimile dated March 26, 2004, requesting additional CMC information:

1.

b(4)

2.

3.

b(4)

4.

Pharmacology/Toxicology:

We note that the product contains the toxic denaturant, brucine sulfate. There appears to be no benefit gained by having this compound in the drug product. Please provide a toxicologic rationale as to why it is acceptable to have brucine sulfate in the drug product.

Biopharmaceutics:

1. Provide a full analytical validation report with detailed methodology and chromatograms.
2. Provide a detailed pharmacokinetic (PK) analysis with estimation of PK parameters (e.g., AUC, C_{max}, t_{max}, T_{1/2}, CL, etc.).

3. Provide the percentage of Body Surface Area (BSA) involved for each patient at least at the beginning of the study.

Clinical:

1. Absorption spectra which show no absorption of the complete product in the _____ nm range should be submitted. If these have been submitted, please specify the location in the application.

b(4)

Biostatistics

We refer to the Agency's facsimile dated March 17, 2004, requesting additional Biostatistics information:

1. Submit an electronic analysis data set in SAS transport format for Study KFD.C.002 with (at minimum) the following variables. Adequately define any variables and codes within variables that are not immediately obvious.

Patient #

Center #

Pooled Center #

Treatment

Race

Sex

Age

Visit (provide an explanation for codes, especially those > 4)

Visit date

Extent of body involvement

Investigator's Static Global Assessment

Pruritus severity

Target area size

Lesion location

Erythema

Scaling

Induration

Subject's Global Assessment

ISGA success (ISGA=0 or 1, unless baseline=2 then ISGA=0 only)

Imputed ISGA success using LOCF (with flag identifying imputed observations)

Sum of erythema, scaling, and induration

Percent change from baseline of sum of erythema, scaling, and induration

Per protocol population status

2. Provide a more detailed description of the following variables and their codes from the datasets for Study KFD.C.002

PGSTATUS (What is pgstatus=3?)
VISIT (What are visit=9 and visit=10?)

3. Provide explanation for the following subjects in Study KFD.C.002
 - a. Subject 016-185 – why are three visits listed as Visit 1?
 - b. Subject 022-228 – why are there two Visit 4s with different efficacy assessments from the same date?

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Lea Carrington, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

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

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/

Jonathan Wilkin
4/5/04 04:04:07 PM

Appears This Way
On Original

4 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)



Food and Drug Administration
Center for Drug Evaluation and Research

Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: March 24, 2004

To: Charles Democko, Vice President Regulatory Affairs	From: Lea Carrington Regulatory Project Manager
Company: Connetics Corporation	Division of Dermatologic & Dental Drug Products
Fax number: (650) 843-2802	Fax number: (301) 827-2091 or 2075
Phone number: (650) 739-2930	Phone number: (301) 827-2020

Subject: NDA 21-738

Total no. of pages including cover: 3

Comments: Information Request – Regulatory

Document to be mailed: • YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2020. Thank you.

FDA Fax Memorandum

Date: March 24, 2004

To: Charles Democko, Vice President, Regulatory Affairs

Applicant: Connetics Corporation

Subject: NDA 21-738 Information Request

We refer to your submission of New Drug Application (NDA) 21-738 Extina (ketoconazole) Foam, 2%. Please provide the following information in an official submission to your NDA:

1. A signed copy of Patent Information Form FDA 3542a (see attached).
2. Identify which parts of the application rely on information Connetics does not own or to which the applicant does not have a right of reference.
3. Submit a statement as to whether the reference listed drug identified has received a period of marketing exclusivity.

If you have any questions, please contact me at (301) 827-2020.

Respectfully,

Lea Carrington
Regulatory 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/

Leonthena Carrington
3/24/04 02:42:38 PM
CSO
Faxed to Applicant 3/24/04.

Appears This Way
On Original



Food and Drug Administration
Center for Drug Evaluation and Research

Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: March 24, 2004

To: Charles Democko, Vice President Regulatory Affairs	From: Lea Carrington Regulatory Project Manager
Company: Connetics Corporation	Division of Dermatologic & Dental Drug Products
Fax number: (650) 843-2802	Fax number: (301) 827-2091 or 2075
Phone number: (650) 739-2930	Phone number: (301) 827-2020

Subject: NDA 21-738

Total no. of pages including cover: 5

Comments: Information Request - Regulatory - Form FDA 3542 a.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2020. Thank you.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-738

Connetics
Attention: Charles Democko
Vice President, Regulatory Affairs
3290 West Bayshore Road
Palo Alto, CA 94303

Dear Mr. Democko:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Ketoconazole Foam, 2%

Review Priority Classification: Standard

Date of Application: January 23, 2004

Date of Receipt: January 26, 2004

Our Reference Number: NDA 21-738

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 26, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 24, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the waiver granted in the Pre-NDA meeting minutes held on May 30, 2003 for the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

NDA 21-738

Page 2

U.S. Postal Service:

Center for Drug Evaluation and Research
Division of Dermatologic & Dental Drugs
HFD-540
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic & Dental Drugs
HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

If you have any questions, call Lea Carrington, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic & Dental Drugs
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/

Leonthena Carrington
3/22/04 11:15:21 AM
Signed for Mary Jean Kozma-Fornaro.

Appears This Way
On Original



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

FACSIMILE TRANSMITTAL SHEET

DATE: 3/17/2004

To: Charles Democko Vice President, Regulatory Affairs	From: Lea Carrington Regulatory Project Manager
Company: Connetics Corporation	Division of Dermatologic and Dental Drug Products
Fax number: (650) 843-2802	Fax number: (301) 827-2091
Phone number: (650) 739-2930	Phone number: (301) 827-2020
Subject: NDA 21-738 Information Request - Biostatistics	

Total no. of pages including cover: 4

Comments: Biostatistics Information Request, 3/17/04.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-827-2020. Thank you.

Appears This Way
On Original

FDA Fax Memorandum

Date: March 17, 2004

To: Charles Democko, Vice President, Regulatory Affairs

Applicant: Connetics Corporation

Subject: NDA 21-738 Biostatistics Information Request

Dear Mr. Democko,

The Biostatistics reviewer has requested the additional information to facilitate review of New Drug Application (NDA) 21-738, Extina (ketoconazole) Foam, 2%. Please submit the following documentation to the Central Document Room as an official submission to your NDA:

1. Submit an electronic analysis data set in SAS transport format for Study KFD.C.002 with (at minimum) the following variables. Adequately define any variables and codes within variables that are not immediately obvious.

Patient #

Center #

Pooled Center #

Treatment

Race

Sex

Age

Visit (provide an explanation for codes, especially those > 4)

Visit date

Extent of body involvement

Investigator's Static Global Assessment

Pruritus severity

Target area size

Lesion location

Erythema

Scaling

Induration

Subject's Global Assessment

ISGA success (ISGA=0 or 1, unless baseline=2 then ISGA=0 only)

Imputed ISGA success using LOCF (with flag identifying imputed observations)

Sum of erythema, scaling, and induration

Percent change from baseline of sum of erythema, scaling, and induration

Per protocol population status

2. Provide a more detailed description of the following variables and their codes from the datasets for Study KFD.C.002

PGSTATUS (What is pgstatus=3?)

VISIT (What are visit=9 and visit=10?)

3. Provide explanation for the following subjects in Study KFD.C.002
 - a. Subject 016-185 – why are three visits listed as Visit 1?
 - b. Subject 022-228 – why are there two Visit 4s with different efficacy assessments from the same date?

If you have any questions, please contact me at (301) 827-2020.

Respectfully,

Lea Carrington
Regulatory 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/

Leonthena Carrington
3/17/04 01:16:49 PM
CSO
Faxed to Applicant 3/17/04.

Appears This Way
On Original

4 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)



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

FACSIMILE TRANSMITTAL SHEET

DATE: 3/2/2004

To: Charles Democko Vice President, Regulatory Affairs	From: Lea Carrington Regulatory Project Manager
Company: Connetics Corporation	Division of Dermatologic and Dental Drug Products
Fax number: (650) 843-2802	Fax number: (301) 827-2091
Phone number: (650) 739-2930	Phone number: (301) 827-2020

Subject: NDA 21-738 Tradename review status.

Total no. of pages including cover: 3

Comments: Response to Applicant's 2/27/04 Tradename review inquiry NDA 21-738.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-827-2020. Thank you.

Appears This Way
On Original

FDA Fax Memorandum

Date: March 2, 2004

To: Charles Democko
Vice President, Regulatory Affairs

Applicant: Connetics Corporation

Subject: NDA 21-738 Tradename Review Status

Dear Mr. Democko,

The memo is in response to a February 27, 2004 telephone inquiry from Connetics Corporation Regulatory Affairs Manager, Jeff Stegall, regarding the status of the tradename review for Extina (ketoconazole) Foam, 2%, NDA 21-738.

The Filing Review is pending however, we would like to convey the following comments:

1. An applicant's proposed tradename and its associated labels and labeling must be re-evaluated upon submission of the NDA and 90 days prior to the expected approval of the NDA.
2. The tradename, Extina, was determined to be acceptable, however this decision is tentative. Re-evaluation of the tradename will rule out any objections based upon other applicants who proposed and were approved for the established tradename.

Please let me know if you have any additional questions.

Respectfully,

Lea Carrington
Regulatory 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/

Leonthena Carrington
3/2/04 04:49:21 PM
CSO
Faxed to Applicant 3/2/04.

Appears This Way
On Original

Carrington, Leonthena

From: Shawar, Ribhi
Sent: Tuesday, March 02, 2004 2:01 PM
Carrington, Leonthena
Sheldon, Albert T
Subject: MDA 21738 Ketoconazole foam draft label

Dear Lea,

I am new reviewer in ODE IV. My team leader, Al Sheldon had assigned this label review to me. I have the following questions based on information provided in the request for consultation:

1. You indicate that no Microbiology volumes were submitted with the NDA. Is this still the case and if so, what other available material could I use? I searched the EDR under this NDA # but could not find anything electronically.
2. In the "desired completed date" box you indicate March 15 as the filing meeting date and TBD for the review completion date. If I do not have a lot of other material to refer back to, it is reasonable for me to complete the review prior to the set meeting. Please let me know, so that we can decide on a mutually agreeable completion date.

Thanks.

Ribhi Shawar, Ph.D., ABMM

Clinical Microbiology Review Officer
Division of Anti-infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration
01 Corporate Blvd, HFD-520, Room S-316
Rockville, MD 20850

Tel (301)827 2149
Fax (301)827 2325
shawarr@cder.fda.gov

Appears This Way
On Original

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Frances LeSane Supervisory Project Manager DAIDP, HFD-520		FROM: Lea Carrington, Regulatory Project Manager HFD-540, Div. of Dermatologic and Dental Drug Products		
DATE February 26, 2004	IND NO.	NDA NO. 21-738	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT January 23, 2004
NAME OF DRUG Extina (ketoconazole) Foam, 2%	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG 3S, anti-seborrheic	DESIRED COMPLETION DATE Filing meeting on 3/15/04; review completion date TBD.
NAME OF FIRM: Connetics Corporation				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input checked="" type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input checked="" type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Please assess the Microbiology section of the proposed draft labeling for this NDA. If possible, please forward comments to me before the filing meeting on March 15, 2004. I apologize for the short notice, however, no Microbiology volumes were submitted with the NDA, and consult requirement had to be determined. I will bring up a hard copy of the draft labeling for your review. Thank you.				
SIGNATURE OF REQUESTER Lea Carrington, RPM 01-827-2072		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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

/s/

Frances LeSane,
2/27/04 10:19:30 AM

Appears This Way
On Original

6 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

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/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

Connetics Corporation
3290 West Bayshore Road
Palo Alto, CA 94303

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
21-738

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
 YES 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:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA.)

2. TELEPHONE NUMBER (Include Area Code)

(650) 843.2800

3. PRODUCT NAME

Ketoconazole Foam, 2%

6. USER FEE I.D. NUMBER
NA

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

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)

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.)

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?

Per Mr. Michael Jones, ORP, on 2 December 2003, NDA 21-738

YES NO

qualifies for exclusion from a User Fee assessment (see cover letter) (See Item 8, reverse side if answered YES)

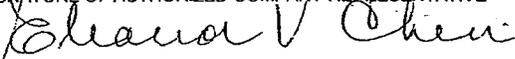
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments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

Director, Regulatory Affairs

DATE

23 January 2004

Carrington, Leonthena

From: Cross Jr, Frank H
Sent: Friday, November 14, 2003 3:26 PM
Carrington, Leonthena
Subject: FW: DFS Email - I 063153 N 000 24-Aug-2001 - Review



090014648039 090014648039
5735.drl (185 B/735.pdf (139 KB

Hi Lea,

Should make a copy of review and have in NDA action package after NDA arrives and pays user fee.

Will need to have another Tradename consult after NDA arrives per ODS, i.e., <http://cdernet.cder.fda.gov/pmcc/default.htm> as ODS reviews their databases for new information since their last review.

With new consult, should reference old review as a reminder.

Frank

-----Original Message-----

From: CDERDocAdmin [mailto:CDERDocAdmin]
Sent: Wednesday, November 12, 2003 2:39 PM
To: CARRINGTONL@cder.fda.gov; CROSSF@cder.fda.gov; WILKINJ@cder.fda.gov;
GUINNP@cder.fda.gov; MAHMUDA@cder.fda.gov; BEAMS@cder.fda.gov; ROSELLEN@cder.fda.gov
Subject: DFS Email - I 063153 N 000 24-Aug-2001 - Review

Document room close out the following assignments:

	Personnel Code	Sup-Concur	St
I 063153 N 000 24-Aug-2001	34P	12-Nov-2003	CM

Document Type: Review
Submission Description: Extina-Tradename Acceptable
PM activity: PM activity required

Author(s)/Discipline(s)

1. Nora L. Roselle, DRUG SAFETY OFFICE REVIEWER

Signer(s)

1. Nora L. Roselle
12-Nov-2003
2. Alina Mahmud
12-Nov-2003
3. Carol Holquist
12-Nov-2003
4. Jerry Phillips
12-Nov-2003

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information

NDA 21-738	Efficacy Supplement Type SE- N/A	Supplement Number N/A
Drug: Extina (ketoconazole) Foam, 2%		Applicant: Connetics Corporation
RPM: Lea Carrington	HFD-540	Phone # (301) 827-2020
Application Type: () 505(b)(1) (X) 505(b)(2)	Reference Listed Drug (NDA #, Drug name): Nizoral (ketoconazole) Cream, 2%	
❖ Application Classifications:		
• Review priority	(X) Standard () Priority	
• Chem class (NDAs only)	3S	
• Other (e.g., orphan, OTC)	N/A	
❖ User Fee Goal Dates		November 26, 2004
❖ Special programs (indicate all that apply)		(X) None Subpart H () 21 CFR 314.510 (accelerated approval) () 21 CFR 314.520 (restricted distribution) () Fast Track () Rolling Review () CMA Pilot 1 () CMA Pilot 2
User Fee Information		
• User Fee	() Paid	
• User Fee waiver	() Small business () Public health () Barrier-to-Innovation () Other	
• User Fee exception	() Orphan designation () No-fee 505(b)(2) (X) Other: Label change	
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP	() Yes (X) No	
• This application is on the AIP	() Yes (X) 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 & certifications from foreign applicants are cosigned by US agent.		(X) Verified
❖ Patent		
• Information: Verify that form FDA-3542a was submitted.	(X) Verified	
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.	21 CFR 314.50(i)(1)(i)(A) () I () II () III () IV	
	21 CFR 314.50(i)(1) () (ii) () (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).	() Verified	

patent claim #1 (4.2)

❖ Exclusivity (approvals only)		
<ul style="list-style-type: none"> Exclusivity summary Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification! 		() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		
General Information		
❖ Actions		
<ul style="list-style-type: none"> Proposed action 		() AP () TA () AE (X) NA
<ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) 		
<ul style="list-style-type: none"> Status of advertising (approvals only) 		() Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications		
<ul style="list-style-type: none"> Press Office notified of action (approval only) 		() Yes (X) Not applicable
<ul style="list-style-type: none"> 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))		
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) 		N/A
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 		January 23, 2004
<ul style="list-style-type: none"> Original applicant-proposed labeling 		January 23, 2004
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings) 		DDMAC DMETS DSRCS (May 28, 2004)
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 		
❖ Labels (immediate container & carton labels)		
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 		
<ul style="list-style-type: none"> Applicant proposed 		January 23, 2004
<ul style="list-style-type: none"> Reviews 		
❖ Post-marketing commitments		
<ul style="list-style-type: none"> Agency request for post-marketing commitments 		NA
<ul style="list-style-type: none"> Documentation of discussions and/or agreements relating to post-marketing commitments 		
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)		X
❖ Memoranda and Telecons		X
❖ Minutes of Meetings		
<ul style="list-style-type: none"> EOP2 meeting (indicate date) 		July 30, 2001
<ul style="list-style-type: none"> Pre-NDA meeting (indicate date) 		May 30, 2003
<ul style="list-style-type: none"> Pre-Approval Safety Conference (indicate date; approvals only) 		NA
<ul style="list-style-type: none"> Other 		NA

❖ Advisory Committee Meeting		
• Date of Meeting		NA
• 48-hour alert		NA
❖ Federal Register Notices, DESI documents, NAS/NRC reports,(if applicable)		
Summary Application Review		
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)		
Clinical Information		
❖ Clinical review(s) (indicate date for each review)		Oct. 2004 ✓
❖ Microbiology (efficacy) review(s) (indicate date for each review)		March 12, 2004
❖ Safety Update review(s) (indicate date or location if incorporated in another review)		June - 3, 2004
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)		NA
❖ Pediatric Page(separate page for each indication addressing status of all age groups)		July 26, 2004
❖ Demographic Worksheet (NME approvals only)		NA
❖ Statistical review(s) (indicate date for each review)		Sept 8, 2004
❖ Biopharmaceutical review(s) (indicate date for each review)		OCT 22, 2004
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)		NA
❖ Clinical Inspection Review Summary (DSI)		
• Clinical studies		NA
• Bioequivalence studies		NA
CMC Information		
❖ CMC review(s) (indicate date for each review)		10/20/04
❖ Environmental Assessment		
• Categorical Exclusion (indicate review date)		10/20/04
• Review & FONSI (indicate date of review)		
• Review & Environmental Impact Statement (indicate date of each review)		10/20/04
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)		NA
❖ Facilities inspection (provide EER report)		Date completed: 4/5/04 (X) Acceptable () Withhold recommendation
❖ Methods validation		() Completed (X) Requested pending () Not yet requested
Nonclinical Pharm/Tox Information		
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)		8/16/04
❖ Nonclinical inspection review summary		NA
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)		NA
❖ CAC/ECAC report		NA