

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-738

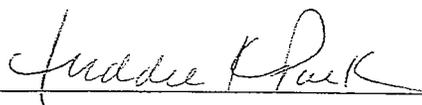
ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

1.3.5.1 PATENT INFORMATION

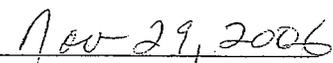
Table 1: Patent Information

Patent Number	Patent Title	Patent Expiration Date	Type of Patent	Patent Owner (name/place of business)
US 4,942,162	Topical Treatment of Seborrheic Dermatitis with Ketoconazole	11 February 2003	Method of Use	University of Tennessee Research Corporation, Knoxville, TN

The undersigned declares that US Patent No. 4,942,162 covers a method of using ketoconazole for the treatment of seborrheic dermatitis. The product described in the patent is the subject of this New Drug Application for which Connetics is seeking approval.



Freddie K. Park
Vice President, Intellectual Property



Date

1.3.5.2 Patent Certification

Paragraph II Certification

Pursuant to 21 USC §355(b)(2)(A)(ii) and 21 CFR §314.50(i), Connetics Corporation certifies to the best of its knowledge that U.S. Patent No. 4,942,162 which claims a method of treating seborrheic dermatitis by topical application of ketoconazole, owned by the University of Tennessee Research Corporation, expired on February 11, 2003.



Freddie K. Park
Vice President, Intellectual Property



Date

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

21-738

NAME OF APPLICANT / NDA HOLDER

Connetics Corporation

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Extina®

ACTIVE INGREDIENT(S)

ketoconazole

STRENGTH(S)

2%

DOSAGE FORM

Aerosol Foam

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

4,942,162

b. Issue Date of Patent

7/17/1990

c. Expiration Date of Patent

February 11, 2003

d. Name of Patent Owner

University of Tennessee Research Corporation

Address (of Patent Owner)

1534 White Avneue Suite 403

City/State

Knoxville, Tenn.

ZIP Code

37996-1527

FAX Number (if available)

865-974-2803

Telephone Number

865-974-1882

E-Mail Address (if available)

UTRC@utk.edu

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Same as above

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) 1 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)
Topical Treatment of Seborrheic Dermatitis

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed
19 April 2004



NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Katrina Church, Executive Vice President, Legal Affairs and General Counsel, Connetics Corporation

Address

3290 West Bayshore Road

City/State

Palo Alto, CA

ZIP Code

94303

Telephone Number

650.843.2843

FAX Number (if available)

650.494.0172

E-Mail Address (if available)

kchurch@connetics.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

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ATTACHMENT 1

Connetics' Complete Response to NDA 21-738 Information Request, dated 24 March 2004

1. **Agency Comment:**

A signed copy of Patent Information Form FDA 3542a (see attached)

Connetics' Response:

A signed copy of Patent Information Form FDA 3542a is enclosed.

2. **Agency Comment:**

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.

Connetics' Response:

NDA 21-738 was filed as a 505(b)(2) application and relies on clinical and nonclinical information pertaining the active pharmaceutical ingredient, ketoconazole, for which Connetics does not either own or have a right of reference. This application strategy was discussed and agreed to during the pre-IND/End of Phase 2 meeting on August 31, 2001 and supported by the established clinical bridge to the reference listed drug (Nizoral[®] Cream) in the Phase 3 clinical study.

3. **Agency Comment:**

Submit a statement as to whether the reference listed drug identified has received a period of marketing exclusivity.

Connetics Response:

To the best of Connetics' knowledge, the reference listed drug, Nizoral[®] Cream, is not currently subject to a period of marketing exclusivity.

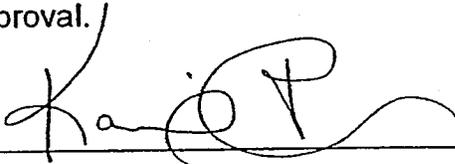
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1.3.1.1 Patent Information

Table 1: Patent Information

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The undersigned declares that Patent No. 4,942,162 covers a method of using ketoconazole for the treatment of seborrheic dermatitis. The product described in the patent is the subject of this New Drug Application for which Connetics is seeking approval.



3 June 03

Katrina J. Church
Executive Vice President
Legal Affairs and General Counsel

Date

Appears This Way
On Original

1.3.1.2 Paragraph II Patent Certification

I, Katrina J. Church, certify that Patent No. 4,942,162 has expired on 11 February 2003.



3 June 03

Katrina J. Church
Executive Vice President
Legal Affairs and General Counsel

Date

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On Original

EXCLUSIVITY SUMMARY

NDA # 21-738

SUPPL # N/A

HFD # 540

Trade Name Extina Foam, 2%

Generic Name ketoconazole

Applicant Name Stiefel Laboratories, Inc

Approval Date, If Known June 12, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	18-533, 19-927, and 19-084	Nizoral
NDA#	19-648	Nizoral Cream
NDA#	20-310 21-946	Nizoral A-D Ketoconazole Gel 2%

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

N/A

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

N/A

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

N/A

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

N/A

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

KFD.C.003, KFD.C.002, KFD.C.005, KFD.C.004, KFD.C.006, KFD.C.007

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 63,153 YES ! NO
! Explain:

Investigation #2
IND # 63,153 YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES

Explain:

!
!

! NO

! Explain:

Investigation #2

YES

Explain:

!
!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

N/A

=====

Name of person completing form: Melinda Bauerlien

Title: Regulatory Project Manager

Date: June 7, 2007

Name of Office/Division Director signing form: Susan Walker, M.D.

Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Susan Walker

6/12/2007 01:52:08 PM

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1.3.5.3 Exclusivity Request

Claimed Exclusivity

Pursuant to sections 505(c)(3)(D)(iii) and 505(j)(4)(D)(iii) of the Food, Drug and Cosmetic (FD&C) Act and 21 CFR §314.50(j), Connetics Corporation hereby claims three years' exclusivity for Ketoconazole Foam, 2%.

This claim is made under the provisions of 21 CFR §314.108(b)(4) based on the following grounds:

1. This application is submitted under section 505(b) of the FD&C Act.
2. Ketoconazole Foam 2% contains the active moiety, ketoconazole. Ketoconazole has been previously approved under section 505(b): Janssen Pharmaceutical's NDA 19-084, Nizoral (ketoconazole 2% Cream), approved in 1985 for treatment of tinea corporis and tinea cruris; NDA 19-576, Nizoral (ketoconazole 2% Cream), approved in 1987 for the treatment of seborrheic dermatitis; NDA 19-648, Nizoral (ketoconazole 2% Cream) approved in 1987 for the treatment of cutaneous candidiasis; NDA 19-927, Nizoral (ketoconazole 2% Shampoo) approved in 1990 for the relief and symptoms of dandruff and is currently indicated for the treatment of tinea versicolor, ANDA 75-581 for Teva (ketoconazole) cream, 2% generic equivalent to Nizoral[®] Cream, approved in 2000, and ketoconazole gel, 2% (Xologel[™] gel) approved in 2006 for the treatment of seborrheic dermatitis.
3. This application contains reports of new clinical investigations (other than bioavailability studies) conducted by Connetics that are essential to the approval. This statement is supported by the following information:
 - "New clinical investigation" is defined in §314.108(a) as "an investigation in humans the results of which have not been relied upon by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied upon by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product."

This application contains reports for the following clinical studies on Ketoconazole Foam, 2%, which meet the above definition:

-- comparative bioavailability study:

KFD.C.003: Randomized, Open-Label Study to Evaluate the Comparative Bioavailability of Ketoconazole

-- comparative Phase 3 safety and efficacy studies:

KFD.C.002: A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Study of the Safety and Efficacy of Ketoconazole Foam, 2%, versus Nizoral® (ketoconazole) 2% Cream in the Treatment of Seborrheic Dermatitis

KFD.C.005: A Randomized, Double-Blind, Vehicle-Controlled Study of the Safety and Efficacy of Ketoconazole Foam 2%, versus Teva (ketoconazole) 2% Cream in the Treatment of Seborrheic Dermatitis

-- comparative dermal sensitization and photosafety studies:

KFD.C.004: A Cumulative Irritation and Skin Sensitization Study of Ketoconazole Foam, 2%

KFD.C.006: An Evaluation of the Phototoxic Potential of Ketoconazole Foam 2% in Healthy Volunteers

KFD.C.007: An Evaluation of the Photoallergy Potential of Ketoconazole Foam 2% in Healthy Volunteers

The intent of all of these studies was to establish the safety and efficacy of Ketoconazole Foam, 2%. The intent of the Phase 3 studies was to assess the safety and efficacy of Ketoconazole Foam, 2% in the treatment of seborrheic dermatitis. The Phase 3 study, Bioavailability Study, Dermal/Sensitization Study, and Phototox and Photoallergy Studies provide safety assessment on the Ketoconazole Foam, 2%

Connetics certifies that to the best of its knowledge, these studies meet the definition of "new clinical investigation" and have not been submitted to or relied upon by FDA to demonstrate efficacy or safety of a previously approved drug product.

- "Essential to approval" per §314.80(a) means that "there are no other data available that could support approval of the application."

Connetics certifies that a thorough search of the scientific literature has been performed and no published studies or publicly available reports of clinical investigations with Ketoconazole Foam, 2% were found. Therefore, it is Connetics' opinion that there are no publicly available reports that provide a sufficient basis for the approval of the conditions for which Connetics is seeking approval without reference to the new clinical investigations in this application.

- "Conducted or sponsored by" per §314.180(a) means "that before or during the investigation, the applicant was named in Form FDA-1571 filed with FDA as the sponsor of the investigational new drug application under which the investigation was conducted, or the applicant or the applicant's predecessor in interest, provided substantial support for the investigation."

Connetics was the sponsor of the new clinical investigations submitted in this application. The clinical investigations were conducted under Connetics' IND No. 63-153, filed on 24 August 2001.

Appears This Way
On Original

1.3.1.8 Statements of Claimed Exclusivity and Associated Certifications

Claimed Exclusivity

Pursuant to sections 505(c)(3)(D)(iii) and 505(j)(4)(D)(iii) of the Food, Drug and Cosmetic (FD&C) Act and 21 CFR §314.50(j), Connetics Corporation hereby claims three years' exclusivity for Ketoconazole Foam, 2%.

This claim is made under the provisions of 21 CFR §314.108(b)(4) based on the following grounds:

1. This application is submitted under section 505(b) of the FD&C Act.
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3. This application contains reports of new clinical investigations (other than bioavailability studies) conducted by Connetics that are essential to the approval. This statement is supported by the following information:
 - "New clinical investigation" is defined in §314.108(a) as "an investigation in humans the results of which have not been relied upon by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied upon by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product."

This application contains reports for the following three clinical studies on Ketoconazole Foam, 2%, which meet the above definition:

- comparative bioavailability study KFD.C.003
- comparative Phase III safety and efficacy study (KFD.C.002)
- comparative dermal/sensitization study (KFD.C.004)

The intent of all three of these studies was to establish the safety and efficacy of Ketoconazole Foam, 2%. At the Guidance Meeting of 9 April 2001 and Pre-IND/End of Phase 2 Meeting of 30 July 2001, the Agency indicated that phototoxicity and photoallergenicity may be waived if the drug product does not show significant absorbance in the _____ region. Connetics performed the UV and visible spectroscopy study. Results indicated the Ketoconazole Foam, 2% has similar absorbance spectrum as the active drug substance ketoconazole and both demonstrated minimal absorbance in the UVA, UVB and visible wavelengths. Based on these results, phototoxicity and photoallergenicity patient studies are not required for the Ketoconazole Foam, 2%. The intent of the Phase III study was to assess the safety and efficacy of Ketoconazole Foam, 2% in the treatment of seborrheic dermatitis. The Phase III study, Bioavailability Study, and Dermal/Sensitization Study provides safety assessment on the Ketoconazole Foam, 2%

b(4)

Connetics certifies that to the best of its knowledge, these studies meet the definition of "new clinical investigation" and have not been submitted to or relied upon by FDA to demonstrate efficacy or safety of a previously approved drug product.

- "Essential to approval" per §314.80(a) means that "there are no other data available that could support approval of the application."

Connetics certifies that a thorough search of the scientific literature has been performed and no published studies or publicly available reports of clinical investigations with Ketoconazole Foam 2% were found. Therefore, it is Connetics' opinion that there are no publicly available reports that provide a sufficient basis for the approval of the conditions for which Connetics is seeking approval without reference to the new clinical investigations in this application.

- "Conducted or sponsored by" per §314.180(a) means "that before or during the investigation, the applicant was named in Form FDA-1571 filed with FDA as the sponsor of the investigational new drug application under which the investigation was conducted, or the applicant or the applicant's predecessor in interest, provided substantial support for the investigation."

Connetics was the sponsor of the new clinical investigations submitted in this application. The clinical investigations were conducted under Connetics' IND #63-153, filed on 24 August 2001.

Request for Waiver of Pediatric Studies

NDA#21-738

Sponsor: Connetics Corporation

Indication(s): Seborrheic Dermatitis

1. What age ranges are included in your waiver request?

Connetics is requesting a waiver of pediatric studies for seborrheic dermatitis in children under 12 years of age.

2. Reasons for waiving pediatric studies:

The waiving of pediatric studies is based on agreements with the Food and Drug Administration, Division of Dermatologic & Dental Drug Products.

3. Justification for waiver:

In two meetings with the Agency, a Pre-IND/End of Phase 2 Meeting on 20 July 2001, and a Pre-NDA Meeting on 30 May 2003, the Division concurred on both occasions that for the indication of seborrheic dermatitis, the inclusion of subjects younger than 12 was not required (Meeting minutes can be found in Module 1, Section 1.3.5 Agreements).

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-738 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: December 12, 2006 PDUFA Goal Date: June 12, 2007

HFD-540 _____ Trade and generic names/dosage form: Extina (ketoconazole) Foam, 2%

Applicant: Stiefel Laboratories Therapeutic Class: 3

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): N/A

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: treatment of seborrheic dermatitis

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
 No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
 Disease/condition does not exist in children
 Too few children with disease to study
 There are safety concerns
 Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. 0 yr. 0 Tanner Stage _____
Max _____ kg _____ mo. 0 yr. 12 Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. 0 yr. 12 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. less than 18 Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

NDA 22-076

Page 3

{See appended electronic signature page}

Melinda Bauerlien, M.S.
Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STAFF at 301-796-0700**

(Revised: 10/10/2006)

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/s/

Brenda Carr
6/4/2007 01:12:23 PM

Jill Lindstrom
6/4/2007 06:31:54 PM

Susan Walker
6/11/2007 12:58:07 PM

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PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-738 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: January 26, 2004 Action Date: November 26, 2004

HFD 540 Trade and generic names/dosage form: Extina (ketoconazole) Foam, 2%

Applicant: Connectics Corporation Therapeutic Class: 3S

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of seborrheic dermatitis

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived: 0 to 12 years

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies: 12 to 18 years

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Grace Carmouze
(revised 12-22-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

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Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Grace Carmouze
(revised 10-14-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

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/s/

Phyllis Huene
6/7/04 01:47:27 PM

Markham Luke
6/10/04 04:55:49 PM
Concur with partial waiver of the <12 pediatric patient
population for the seborrheic dermatitis indication.

Jonathan Wilkin
7/26/04 05:29:22 PM

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1.3.3 Debarment Certification

Clinical

This is to verify that Connetics Corporation has not and will not use, in any capacity, the services of any person debarred under subsections (a) and (b) [Section 306 (a) or (b)], in connection with this Ketoconazole Foam, 2% New Drug Application (NDA).

Signed by:

Mark W Davis

Title:

Senior Director, Clinical Operations

Date:

29 November 2006

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Nonclinical

This is to verify that Connetics Corporation has not and will not use, in any capacity, the services of any person debarred under subsections (a) and (b) [Section 306 (a) or (b)], in connection with this Ketoconazole Foam, 2% New Drug Application (NDA).

Signed by: Stephen Ansell

Title: Toxicology Specialist

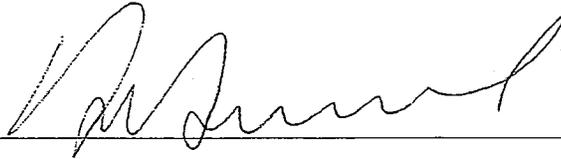
Date: 29 Nov 2006

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Quality

This is to verify that Connetics Corporation has not and will not use, in any capacity, the services of any person debarred under subsections (a) and (b) [Section 306 (a) or (b)], in connection with this Ketoconazole Foam, 2% New Drug Application (NDA).

Signed by:



Title:

VP Quality & Compliance

Date:

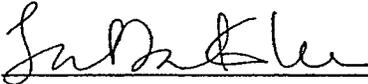
11/29/06

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1.3.1.3 Debarment Certification

Clinical

This is to verify that Connetics Corporation has not and will not use, in any capacity, the services of any person debarred under subsections (a) and (b) [Section 306 (a) or (b)], in connection with this New Drug Application (NDA).

Signed by: 
Title: Senior Director, Clinical Operations

Date: 12 June 2003

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Nonclinical

This is to verify that Connetics Corporation has not and will not use, in any capacity, the services of any person debarred under subsections (a) and (b) [Section 306 (a) or (b)], in connection with this New Drug Application (NDA).

Signed by: 

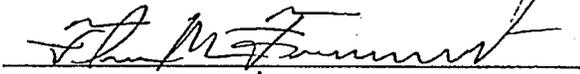
Title: Jr. Director

Date: 6/12/02

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Quality

This is to verify that Connetics Corporation has not and will not use, in any capacity, the services of any person debarred under subsections (a) and (b) [Section 306 (a) or (b)], in connection with this New Drug Application (NDA)

Signed by: 
Title: Associate Director, Contract Manufacturing

Date: 6/24/03

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 12, 2007

To: Marcia Gaido	From: Linda Mullins Athey
Company: Stiefel Laboratories	Office of New Drug Quality Assessment
Fax number: 919-990-6978	Fax number: 301-796-9850
Phone number:	Phone number: 301-796-2096

Subject: NDA 21-738 Release specification for the drug product

Total no. of pages including cover: 3

Document to be mailed: YES NO

The acceptance criterion for absorbance at _____ will remain at NMT _____

b(4)

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/s/

Linda D Mullins-Athey
6/12/2007 12:24:41 PM
PROJECT MANAGER FOR QUALITY

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

FACSIMILE TRANSMITTAL SHEET

DATE: June 11, 2007

To: Marcia Gaido	From: Melinda Bauerlien, M.S. Project Manager
Company: Stiefel Laboratories	Division of Dermatology & Dental Products
Fax number: (919) 990-6978	Fax number: (301) 796-9895
Phone number: ()	Phone number: (301) 796-2110
Subject: NDA 21-738 Information request	

Total no. of pages including cover: 2

Comments: Please make the following changes to the carton/container labeling

The lot number and expiration date should be included on the carton labels.
The letter "I" for ketoconazole should not be bolded.

Please provide revised carton/container labeling by COB today

Document to be mailed: YES NO

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/s/

Melinda Bauerlien
6/11/2007 02:31:08 PM
CSO

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STIEFEL LABORATORIES, INC., 20 TW ALEXANDER DRIVE, RESEARCH TRIANGLE PARK, NC 27709 * TEL. 919-990-6000 * FAX 919-990-6001

Sent by Courier

June 7, 2007

Susan Walker, M.D.
Director, Division of Dermatology and Dental Products (HFD-540)
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
CENTRAL DOCUMENT ROOM
5901-B Ammendale Road
Beltsville, MD 20705-1266
Fax: 301-796-9895

RE: NDA 21-738, Ketoconazole Foam 2%
Amendment 048

Attention: Melinda Bauerlien, Project Manager

Dear Dr. Walker:

Reference is made to an FDA fax dated June 7, 2007 containing two Phase 4 requests. Listed below are Stiefel's commitments to perform these studies as requested.

Stiefel will conduct a study to assess the long-term safety of Extina per the ICH E1A guidelines. As requested, the protocol will be submitted prior to December 23, 2007, with a commitment to start the study by June 2, 2008 and to submit the final study report to FDA by June 30, 2011.

Stiefel is committed to address _____

b(4)

Please contact Marcia Gaido at 919-990-6202 or 919-599-3630 for any questions regarding this submission or any other information needed in support of Extina (ketoconazole foam, 2%).

Regards,

Marcia Gaido, PhD, RAC
Director, Regulatory Affairs



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 7, 2007

To: Marcia Gaido	From: Melinda Bauerlien, M.S. Project Manager
Company: Stiefel Laboratories	Division of Dermatology & Dental Products
Fax number: (919) 990-6978	Fax number: (301) 796-9895
Phone number: ()	Phone number: (301) 796-2110
Subject: NDA 21-738 Phase 4 commitment	

Total no. of pages including cover: 3

Comments: Please submit officially to your NDA and by fax, your commitment to conduct the following Phase 4 commitments to include the protocol submission, study initiation and completion and final report submission dates as outlined above.

Document to be mailed: YES NO

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NDA 21-738

Phase 4 request

1. The applicant should conduct a study in which the long-term safety of their product is assessed, as per the ICH E1A guidelines.

Protocol Submission:	by December 28, 2007
Study Start:	by June 2, 2008
Final Report Submission:	by June 30, 2011

Please also commit to conducting the following additional CMC study request:

The applicant is committed to address the

~~_____~~

b(4)

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/s/

Melinda Bauerlien
6/7/2007 10:44:23 AM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: June 5, 2007

To: Marcia Gaido	From: Melinda Bauerlien, M.S. Project Manager
Company: Stiefel Laboratories	Division of Dermatology & Dental Products
Fax number: (919) 990-6978	Fax number: (301) 796-9895
Phone number: ()	Phone number: (301) 796-2110
Subject: NDA 21-738 Phase 4 commitments	

Total no. of pages including cover: 3

Comments: Please submit officially to your NDA and by fax, your commitment to conduct the following Phase 4 commitments to include the protocol submission, study initiation and completion and final report submission dates as outlined above.

Document to be mailed: YES NO

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NDA 21-738

Phase 4 request

1. The applicant is committed _____

b(4)

2. The applicant should conduct a study in which the long-term safety of their product is assessed, as per the ICH E1A guidelines.

Protocol Submission:	by December 28, 2007
Study Start:	by June 2, 2008
Final Report Submission:	by June 30, 2011

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/s/

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

FACSIMILE TRANSMITTAL SHEET

DATE: June 5, 2007

To: Marcia Gaido	From: Melinda Bauerlien, M.S. Project Manager
Company: Stiefel Laboratories	Division of Dermatology & Dental Products
Fax number: (919) 990-6978	Fax number: (301) 796-9895
Phone number: ()	Phone number: (301) 796-2110
Subject: NDA 21-738	

Total no. of pages including cover: 3

Comments: revisions to carton/container. Please respond by COB June 6, 2007

Document to be mailed: YES NO

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NDA 21-738
labeling.

Please make the following revisions to the carton/container

A. GENERAL COMMENTS

1. Delete the graphic incorporated into the letter “e” of the proprietary “extina”. The graphic is distracting and distorts the presentation of the proprietary name.
2. Use the same color font for each letter of the proprietary name, to increase clarity and readability of the proprietary name.

B. CARTON LABEL

1. See General Comments.
2. Differentiate the trade dress proposed for Extina to make it readily distinguishable from other topical foam products marketed by Connetics. It appears the currently proposed colors and graphics used for the label and labeling of Extina, are very similar to another topical foam product, Evoclin (clindamycin phosphate) foam, 1%, as demonstrated in the side by side graphic of the two product carton labels (see below). It is likely that topical products from Connetics such as Extina and Evoclin may be stored in close proximity to each other on the pharmacy shelf, and the look-alike container label/carton labeling may increase the potential for product selection errors to occur. Furthermore, postmarketing surveillance has shown that similar labeling across manufacturers’ product lines may increase the potential for product selection errors due to similarity in appearance.

C. CONTAINER LABEL

1. See General Comments.
2. Relocate the route of administration statement “For Topical Use Only” to the primary display panel.

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/s/

Melinda Bauerlien
6/5/2007 01:31:40 PM
CSO

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MEMORANDUM

To: Melinda Bauerlein
Division of Dermatology and Dental Products

From: Iris Masucci, PharmD, BCPS
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: May 25, 2007

Re: Comments on draft labeling for Extina (ketoconazole) Foam
NDA 21-738

We have reviewed the proposed label for Extina Foam (FDA version dated 5/21/07) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

GENERAL COMMENTS

- In Contents and in the Full Prescribing Information (FPI), there should not be periods after the main section numbers (e.g., "1 Indications and Usage" instead of "1. Indications and Usage").
 - Will the patient package insert be attached to the label as one long document or will it accompany the label? Either way is acceptable under the PLR. If it will be attached, then it should be given a subsection number (e.g., 17.3) and be listed in Contents. If it will be separate, then it should not be listed in Contents and the first line under "17 Patient Counseling Information" should refer the reader to the PPI, but without a subsection number in parentheses.
-

HIGHLIGHTS

- ~~_____~~

This line at the beginning of Highlights should be deleted.

b(4)

- ~~_____~~

The initial U.S. approval date here should be the first time any product was approved containing this molecular entity (ketoconazole), regardless of the dosage form. It should not be _____

b(4)

Indications and Usage

• [

b(4)

The phrase "_____ " should be deleted from this sentence. If the drug is part of an established pharmacologic class, the class would be presented here, not the generic name.

We suggest, however, that consideration be given to _____
_____ It would be misleading to classify this as an "antifungal" and then say below and throughout the label that it doesn't treat fungal infections and the contribution of its antifungal activity in seborrheic dermatitis is unknown. The recently publicized draft guidance on Pharmacologic Classifications for labeling says that the pharmacologic class should be "known and relevant to the indication under review." While ketoconazole's class is indeed known, would you consider it relevant to this indication? For further discussion, please contact Lilliam Rosario or Bill Pierce of the SEALD team.

b(4)

- **"Safety and efficacy of Extina Foam for treatment of fungal infections have not been established."**

This sentence should not be in bolded type. In Highlights, bolded type is reserved for section headings and specific lines are required by the regulations.

Dosage and Administration

- We suggest moving the bullets over to the left so they are justified with the left margin, not indented.

• [

b(4)

Contraindications

• [

b(4)

As in Highlights, this text should not be in bolded type.

4 Contraindications

- ~~_____~~

b(4)

5.1 ~~_____~~

- In PLR labeling, we are discouraging the use of broad section headings like this one. Instead, we recommend that each distinct warning/precaution have its own titled subsection, rather than lumping them together.

6 Adverse Reactions

- *"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug,..."*

We suggest that this paragraph appear under 6.1 instead of directly under the main section heading. Section 6.1 is where clinical trial data are presented. In the future, there may also be another subsection for Postmarketing Experience, further supporting the moving of this paragraph.

8.1 Pregnancy

b(4)

- *"No reproductive studies in animals have been performed with Extina Foam. There are no adequate and well-controlled studies of Extina Foam in pregnant women."*

These statements are inconsistent with the pregnancy labeling regulations under CFR 201.57. The regulations state,

If there are no animal reproduction studies and no adequate and well-controlled studies in humans, the labeling must state: "Pregnancy Category C. Animal reproduction studies have not been conducted with (name of drug). It is also not known whether (name of drug) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (Name of drug) should be given to a pregnant woman only if clearly needed." The labeling must contain a description of any available data on the effect of the drug on the later growth, development, and functional maturation of the child.

Please revise this section accordingly.

• [redacted]

b(4)

12.1 Mechanism of Action

• [redacted]

[redacted]

For other antimicrobial products, the statement under 12.1 would read, "DrugX is an antifungal (or antibacterial/antiviral/antiprotozoal) agent. [See *Clinical Pharmacology* (12.4)]."

b(4)

12.2 Pharmacodynamics

• [redacted]

b(4)

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

• "In oral carcinogenicity studies in mice (18-months) and rats (24-months) at dose levels of 5, 20 and 80 mg/kg/day ketoconazole was not carcinogenic."

Is the term "oral carcinogenicity studies" common? It seems awkward. Shouldn't "oral" appear somewhere else within the sentence?

• "At oral dose levels of 75 mg/kg/day (4.5 times the expected topical human dose in mg/m²), ketoconazole impaired reproductive performance and fertility when administered to male rats (increased abnormal sperm—decreased sperm mobility and decreased pregnancy in mated females)."

Shouldn't we say "abnormal sperm" instead of "[redacted]"

b(4)

16 How Supplied/Storage and Handling

- *"Do not expose containers to heat, and/or store at temperatures above 120oF (49oC)."*

We suggest that this sentence be moved up to accompany the earlier sentence about proper storage temperature.

- We suggest that the last few lines in this section not be in bolded text unless truly necessary for emphasis.

17 Patient Counseling Information

- Please ensure that this section is numbered "17" and the subsections also numbered accordingly.

17.1 Instructions for Use

- *"AVOID FIRE, FLAME AND/OR SMOKING DURING AND IMMEDIATELY FOLLOWING APPLICATION."*

We suggest that this sentence be in mixed case lettering, not all capital letters.

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/s/

Iris Masucci
5/29/2007 02:30:53 PM
DDMAC REVIEWER

Laurie Burke
5/30/2007 05:43:42 PM
INTERDISCIPLINARY

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 10, 2007
TO: Dawne Hom
FROM: Linda Athey
SUBJECT: **CMC request for Teleconference**
NDA 21-738, Ketoconazole Foam, 2%

May 10, 2007, FDA contacted Dawne Hom with Connetics to schedule a teleconference to discuss their response for Item #1 in the amendment dated April 27, 2007. The Tcon was rescheduled for Friday, May 18, 2007 at 11:00 AM. May 14, 2007, Marcia Gaido contacted FDA stating that Stiefel has purchased Connetics and she will be the new contact. See emails below.

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

From: Marcia L. Gaido [<mailto:mgaido@stiefel.com>]
Sent: Monday, May 14, 2007 10:19 AM
To: Athey, Linda
Cc: Dawne Hom
Subject: CMC questions NDA 21-738

Hi Linda,

I am taking over as the lead regulatory person on NDA 21-738 since Stiefel has purchased Connetics and is moving all regulatory responsibilities to North Carolina. Dawne Hom has let us know that you requested a meeting and it is scheduled for Thursday at 11 AM. We would like to know any further information you could provide regarding the purpose of the meeting so that we can prepare ourselves for the discussion. Please direct all future communications to me at the following information:

Marcia Gaido, PhD, RAC
Director, Regulatory Affairs
Stiefel Laboratories
20 TW Alexander Dr.
Research Triangle Park, NC 27709
Phone 919-990-6202
Cell
Fax 919-990-6978

b(6)

I will call you in person as well to follow up. Thank you for your help

with this program.

Sincerely,
Marcia Gaido

From: Athey, Linda
Sent: Thursday, May 10, 2007 12:59 PM
To: 'Hom, Dawne'
Subject: NDA 21-738 Ketoconazole Foam, 2%

Hello Dawne,

This is to confirm our teleconference scheduled for Thursday, May 17, 2007 at 11:00 AM EST. The call in number is 866-714-4882 and pass code 6792431. The purpose of the meeting is to discuss their response for Item #1 in the amendment dated April 27, 2007.

Best regards,
Linda

Linda D. Athey
Regulatory Health Project Manager for Quality
FDA/CDER/OPS/ONDQA
Division Of Pre-Marketing Assessment II
10903 New Hampshire Ave., Bldg 22, Room 2483
Silver Spring, MD 20993-0002
Phone (301)796-2096
Fax (301)796-9850

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/s/

Linda D Mullins-Athey
5/24/2007 11:07:08 AM
PROJECT MANAGER FOR QUALITY

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 21, 2007

TO: Susan Walker, M.D., Director
Division of Dermatologic and Dental Products

VIA: Melinda Bauerlein, M.S., Regulatory Project Manager
Division of Dermatologic and Dental Products

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm.D., Deputy Director
Division of Surveillance, Research, and Communication Support

SUBJECT: OSE/DSRCS Review of Patient Labeling for Extina (ketoconazole)
Foam, 2%, NDA 21-738

Background and Summary

The sponsor submitted a Complete Response on December 11, 2006, in response to the November 23, 2004 Approvable Letter for Extina (ketoconazole) Foam, 2%, NDA 21-738. Submitted labeling includes Full Prescribing Information (FPI) in the PLR format and patient labeling in the form of a Patient Package Insert (PPI) including instructions for using the product.

OSE/DSRCS was consulted to review the revised patient information.

Comments and Recommendations

1. See the attached marked and clean copies of the PPI for our recommended revisions. We have made the patient information consistent with the PI, simplified language where possible, and removed unnecessary information. The sponsor submitted a consumer-friendly document written at a 7.6 grade reading level (Flesch-Kincaid). Our revisions lowered the reading slightly to a 7.4 grade reading level (Flesch-Kincaid).
2. The FPI for Extina Foam states, "~~_____~~
Patient labeling is derived from information presented in the FPI. The PPI should not contain information that is not in the FPI. Ensure that all instructions for using Extina Foam are also located in the FPI in the Dosage and Administration section or Patient Counseling Information section.

b(4)

Comments to the review division are **bolded, italicized, and underlined**. Please call us if you have any questions.

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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Jeanine Best
5/21/2007 03:54:09 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
5/21/2007 05:34:29 PM
DRUG SAFETY OFFICE REVIEWER

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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

Date: May 8, 2007

To: Melinda Bauerlien, DDDP
Brenda Carr, MD

From: Andrew Haffer, DDMAC

Re: Comments on draft PI for Extina (ketoconazole) Foam, 2%
NDA# 20-723

DDMAC has reviewed the draft version of the PI and Patient Information for Extina located in the EDR (FILE: //\\ \CDSESUB1\N21738\N 000\2006-12-11) dated 12/11/06.

DDMAC offers the following comments. Our comments are provided directly in the attached labeling.

If you have any questions about these comments or would like the Word version of the document please do not hesitate to call.

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Extina – Carton and Container labeling review

DDMAC recommends that all carton and container labeling be revised so that each letter of the tradename is presented in the same color. We also recommend that the dots surrounding the left side of the “e” be removed.

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✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Andrew Haffer
5/8/2007 01:25:34 PM
DDMAC REVIEWER

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

FACSIMILE TRANSMITTAL SHEET

DATE: May 3, 2007

To: Marcia Gaido	From: Melinda Bauerlien, M.S. Project Manager
Company: Stiefel Laboratories	Division of Dermatology & Dental Products
Fax number: (919) 990-6978	Fax number: (301) 796-9895
Phone number: ()	Phone number: (301) 796-2110
Subject: NDA 21-738 Information request	

Total no. of pages including cover: 2

Comments: Please submit a patent certification and Form 3542 for the generic Teva.

Document to be mailed: YES NO

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/s/

Melinda Bauerlien
5/3/2007 01:00:09 PM
CSO

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REQUEST FOR CONSULTATION

TO (Office/Division): Frances LeSane
Supervisory Project Manager
DAIDP,

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

DATE
May 3, 2007

IND NO.

NDA NO.
21-738

TYPE OF DOCUMENT
NDA

DATE OF DOCUMENT
December 11, 2006

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"/> 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 2a MEETING
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY / EFFICACY
<input checked="" 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 type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|--|---|

II. BIOMETRICS

- | | |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input 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 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

IV. DRUG SAFETY

- | | |
|---|---|
| <input type="checkbox"/> PHASE 4 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"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: The sponsor's product is ketoconazole foam, proposed for treatment of seborrheic dermatitis; they are not seeking an antimicrobial claim. We are seeking your opinion on the wording proposed for the Microbiology section, which differs somewhat from the wording in the Nizoral cream and Teva cream labels (both products contain ketoconazole; the former is no longer marketed; however, the sponsor compared their proposed wording to the labels for both Nizoral and Teva) It appears that the sponsor inserted a clause (and slightly modified the wording) from the mode of action section Nizoral and Teva into the Microbiology section of their proposed label (mechanism of action section in the PLR format).

Label is attached. Please let me know if you have any questions.

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

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 EMAIL
 MAIL
 HAND

Melinda Bauerlien, M.S. Project Manager 9-0906	
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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

FACSIMILE TRANSMITTAL SHEET

DATE: April 23, 2007

To: Marcia Gaido	From: Melinda Bauerlien, M.S. Project Manager
Company: Stiefel Laboratories	Division of Dermatology & Dental Products
Fax number: (919) 990-6978	Fax number: (301) 796-9895
Phone number: ()	Phone number: (301) 796-2110

Subject:

Total no. of pages including cover: 3

Comments: CMC request for information

Document to be mailed: YES NO

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1. Please tighten the acceptance criterion for Absorbance at ~~_____~~ in the drug product specification to ~~_____~~. The recommended limit is derived from ~~_____~~ based on the ~~_____~~ long term stability data of the ~~_____~~ primary stability batches (Table 9 on Page 82 in the 11/1/2006 amendment). The acceptance criterion may be broadened pending on the outcome of the post approval commitment. **b(4)**
2. Revise the immediate and carton labels for the following items:
 - a. Provide lot number and expiration date on the immediate container and carton labels per 21 CFR 201.17 and 201.18.
 - b. Provide the storage condition on the carton label for 10 g package size.

Please provide a desk copy for the reviewer and respond by April 30, 2007.

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/s/

Melinda Bauerlien
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REQUEST FOR CONSULTATION

TO (Office/Division): **Frances LeSane**
Supervisory Project Manager
DAIDP,

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

DATE
April 23, 2007

IND NO.

NDA NO.
21-738

TYPE OF DOCUMENT
NDA RS

DATE OF DOCUMENT
December 17, 2006

NAME OF DRUG
Extina (ketoconazole) Foam

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 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: The sponsor's product is ketoconazole foam, proposed for treatment of seborrheic dermatitis; they are not seeking an antimicrobial claim. We are seeking your opinion on the wording proposed for the Microbiology section, which differs somewhat from the wording in the Nizoral cream and Teva cream labels (both products contain ketoconazole; the former is no longer marketed; however, the sponsor compared their proposed wording to the labels for both Nizoral and Teva). It appears that the sponsor inserted a clause (and slightly modified the wording) from the mode of action section of the Nizoral and Teva labels into the Microbiology section of their proposed label (mechanism of action section in the PLR format). If you have any questions or need additional information, please contact me at x9-0906. Label is attached.

SIGNATURE OF REQUESTOR
Melinda Bauerlien, M.S.

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

Project Manager 9-0906	
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

FACSIMILE TRANSMITTAL SHEET

DATE: April 9, 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: 3

Comments: request for SPL revision

Document to be mailed: YES NO

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NDA 21-738

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Melinda Bauerlien
4/9/2007 11:52:57 AM
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