

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-738

CHEMISTRY REVIEW(S)



NDA 21-738

Extina (ketoconazole) Foam

Stiefel Laboratories, Inc.

Jane L. Chang, Ph.D.

Review Chemist

**Division of Dermatologic and Dental Drug Products
HFD-540**

Appears This Way
On Original



Table of Contents

Table of Contents2

Chemistry Review Data Sheet.....3

The Executive Summary8

I. Recommendations.....8

 A. Recommendation and Conclusion on Approvability 8

 B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable..... 8

II. Summary of Chemistry Assessments.....8

 A. Description of the Drug Product(s) and Drug Substance(s)..... 8

 B. Description of How the Drug Product is Intended to be Used..... 10

 C. Basis for Approvability or Not-Approval Recommendation 10

III. Administrative.....10

 A. Reviewer’s Signature..... 10

 B. Endorsement Block..... 10

 C. CC Block..... 10

Chemistry Assessment11

I. Deficiencies Listed in the 11/23/04 Action Letter 11

II. Addition of 10 g and 100 g Package sizes31

 A. Description and Composition of Drug Product..... 31

 B. Controls of Critical Steps and Intermediates in Manufacture..... 32

 C. Control of Drug Product 33

 D. Container Closure System..... 34

 E. Stability (including update for the 50 g Package Size)..... 35

III. Labeling and Package Insert39

 A. Package Insert 39

 B. Labels..... 42

 C. Drug Listing Data Elements (DLDE) in Structured Product Labeling (SPL)..... 45



Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 21-738
2. REVIEW #: 2
3. REVIEW DATE: 06-JUN-2007
4. REVIEWER: Jane L. Chang
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	23-Jan-2004
Amendment (BC)	10-Feb-2004
Amendment (BC)	17-Feb-2004
Amendment (BC)	23-Mar-2004
Amendment (BC)	19-Apr-2004
Amendment (BZ)	26-Apr-2004
Amendment (BC)	15-Jun-2004
Amendment (BC)	09-Jul-2004
Amendment (BC)	15-Jul-2004
Amendment (BC)	22-Jul-2004
Amendment (BL)	04-Aug-2004
Amendment (BC)	06-Aug-2004
Amendment (BC)	27-Aug-2004
Amendment (BC)	14-Sep-2004
Amendment (BC)	14-Oct-2004
CMC Review #1	20-Oct-2004
Amendment (MS)	24-Mar-2006
FDA's response to 3/24/06 Meeting Briefing Package	01-May-2006
4/25/06 Type C Meeting Minutes	22-May-2006
Protocol for post approval commitment (C)	15-Jun-2006
FDA's General Advice Letter	07-Jul-2007
FDA's Information Request	06-Oct-2006



Chemistry Review Data Sheet

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (BC)	01-Nov-2006
Amendment (AZ)	11-Dec-2006
Amendment (BL)	10-Apr-2007
Amendment (BC)	27-Apr-2007
Amendment (BL)	18-May-2007
Amendment (BC)	23-May-2007
Amendment (BL)	01-Jun-2007

7. NAME & ADDRESS OF APPLICANT:

Name: Stiefel Laboratories, Inc.
Address: 20 TW Alexander Drive
Research Triangle Park, NC 27709
Representative: Marcia Gaido, Ph.D., R.A.C.
Director, Regulatory Affairs
Telephone: Phone (919) 990-6202
Fax (919) 990-6978

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Extina
b) Non-Proprietary Name: Ketoconazole
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3 (new dosage form per MAPP 7500.3)
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Antifungal

11. DOSAGE FORM: Aerosol, Foam

12. STRENGTH/POTENCY: 2%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx OTC

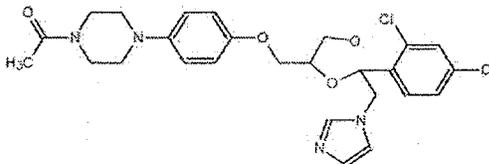
Chemistry Review Data Sheet

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Ketoconazole
 $C_{26}H_{28}Cl_2N_4O_4$ M.W.: 531.43 CAS-65277-42-1

or

b(4)

Appears This Way
On Original

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
					Adequate	23-Apr-2007	Reviewed by J. Chang
					NA	30-Sep-2004	Reviewed by A. Fenselau
					NA	30-Sep-2004	Reviewed by A. Fenselau
					NA	NA	Adequate information provided in NDA

b(4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	Description
IND	63,153	Ketoconazole Foam 2%
Patent	4,942,162	Topical treatment of seborrheic dermatitis with ketoconazole

Appears This Way
On Original



Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	3/28/2007	S. Ferguson
Pharm/Tox	N/A		
Biopharm	N/A		
Methods Validation	N/A, according to the current ONDC policy		
Office of Drug Safety	Acceptable	6/1/2007	W. Fava
EA	Categorical exclusion (see review)	6/6/2007	J. Chang
Microbiology	N/A		

Appears This Way
On Original

The Chemistry Review for NDA 21-738

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry, manufacturing, and controls review perspective, this NDA may be approved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The applicant is committed to address _____

b(4)

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Product

Ketoconazole Foam, 2% is delivered in a quick-breaking, temperature-sensitive, patented foam vehicle platform. The manufacture of drug product involves _____

b(4)

The proposed drug product specifications are acceptable to ensure product quality. The drug product specifications include testing for appearance, absorbance at _____ (measured from a _____ minimum fill, pressure, leakage, ketoconazole identity (release only), content of ketoconazole and related substances, microbial limits, apparent pH, ethanol content, weight loss (stability

b(4)

Executive Summary Section

only), product/packaging interactions (stability only), dispensing rate, and delivered amount. Acceptable acceptance criteria have been established for these tests except those for dispensing rate and delivered amount. The acceptance criteria for dispensing rate and delivered amount will be established when sufficient data become available (from commercial lots or within one year of NDA approval).

The proposed acceptance criterion of _____ has not been adequately justified. As the correlation between the absorbance and quantity has not been established, it is unclear whether the _____ the ICH Q3B qualification threshold. In order to resolve these issues, this reviewer recommended _____ based on data from the _____ clinical batches. However, the applicant maintained their proposal based on their manufacturing capability.

b(4)

The concern with _____ has been brought to the attention of the Pharm/tox reviewer, Dr. K. Mainigi and the Pharm/tox team leader, Dr. P. Brown. Since neither Dr. Mainigi nor Dr. Brown expressed any safety concern (see Dr. Brown's review on 6/1/2007), the _____ is not deemed to be a safety concern. It is believed that the _____ would have little impact on the safety and efficacy of the drug product unless either the toxicology team or the clinical team has any reservation. Therefore, from the CMC perspective, the _____ is considered to be acceptable based on the manufacturing capability.

b(4)

The drug product will be packaged in two commercial package sizes, 50 g and 100 g cans, and a physician's sample, 10 g cans. The CMC information for the 10 g and 100 g cans, provided in the 11/1/2006 amendment, was adequate to support the addition of these two packaging sizes.

b(4)

Stability data on _____ of each fill size of Ketoconazole Foam, 2% were provided, ranging from _____ months of long-term and _____ of accelerated conditions. The data showed increasing trends for absorbance at 490 nm and total related substances. The stability data support the proposed 12 months expiry for the 10 g professional sample size and 24 months for the 50 g and 100 g fill sizes when stored at controlled room temperature.

(2) Drug Substance

Ketoconazole is currently approved in the United States for use in three different prescription topical dosage forms (all at a concentration of 2%): Xolegel (NDA 21-

Executive Summary Section

946, approved in 2006), Nizoral Cream (NDAs 19-576 and 19-648, both approved in 1987) and Ketoconazole shampoo (NDA 19-927, approved in 1990). A nonprescription formulation of 1% Ketoconazole shampoo (NDA 20-310) was also approved in 1997.

The CMC information pertaining to _____ of the drug substance is referred to DMF _____ from the _____. The DMF has been reviewed by this reviewer and found to be adequate to support this NDA _____

b(4)

B. Description of How the Drug Product is Intended to be Used

Ketoconazole Foam, 2% is intended to be applied to the affected area(s) twice daily for four weeks, or as directed by a physician for topical treatment of seborrheic dermatitis in immunocompetent patients 12 years of age and older. Seborrheic dermatitis is a common, inflammatory skin condition that causes flaky, white to yellowish scales to form on oily or greasy areas such as the scalp, creases of the nose, or inside the ear.

Ketoconazole Foam, 2% is to be stored at controlled room temperature 68-77°F (20-25°C). When stored under the specified conditions, an expiration dating period of 12, 24, and 24 months can be supported for the 10 g, 50 g, and 100 g cans, respectively. The drug product should not be exposed to heat or stored at temperature above 120°F (49 °C), or stored under refrigerated conditions. The contents are flammable. Cautions should be taken to avoid fire, flame, and/or smoking during and immediately following application.

C. Basis for Approvability or Not-Approval Recommendation

From the CMC perspective, all the CMC issues were resolved adequately to ensure the drug product's identity, strength, quality, purity, potency, and stability. All manufacturing and testing facilities were found to be acceptable by the Office of Compliance. Therefore, from a CMC standpoint, this new drug application may be approved.

III. Administrative

- A. **Reviewer's Signature:** electronically signed in DFS
- B. **Endorsement Block:** electronically signed in DFS
- C. **CC Block:** entered electronically in DFS

35 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/

Jane Chang
6/6/2007 03:27:40 PM
CHEMIST

Moo-Jhong Rhee
6/6/2007 03:31:23 PM
CHEMIST
Chief, Branch III

NDA 21-738

**EXTINA™
(ketoconazole)
Foam, 2%**

Connetics Corporation

**Allan Fenselau, Ph.D.
Division of Dermatologic and Dental Drug Products
(HFD-540)**

Table of Contents

CHEMISTRY REVIEW DATA SHEET.....	4
EXECUTIVE SUMMARY	8
I. Recommendations.....	8
A. Recommendation and Conclusion on Approvability.....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments	8
A. Description of the Drug Product.....	8
B. Intended Use of the Drug Product.....	11
C. Justification of Recommendation.....	12
III. Administrative.....	12
A. Reviewer's Signature.....	12
B. Endorsement Block.....	12
C. CC Block.....	12
CHEMISTRY ASSESSMENT.....	13
I. <u>Review of Common Technical Document—Quality [CTD-Q] Module 3.2: Body of Data</u>	
S. DRUG SUBSTANCE.....	13
S.1 General Information.....	13
S.1.1-2 Nomenclature and Structure.....	13
S.1.3 General Properties.....	14
S.2 Manufacture.....	14
S.2.1 Manufacturers.....	14
S.2.2 Description of Manufacturing Process and Process Controls.....	14
S.2.3 Control of Materials.....	14
S.2.4 Controls of Critical Steps and Intermediates.....	14
S.2.5 Process Validation and/or Evaluation.....	14
S.2.6 Manufacturing Process Development.....	14
S.3 Characterization.....	14
S.3.1 Elucidation of Structure and other Characteristics.....	14
S.3.2 Impurities.....	14
S.4 Control of Drug Substance.....	14
S.4.1 Specification.....	14
S.4.2-3 Analytical Procedures and Validation of Analytical Procedures.....	16
S.4.4 Batch Analyses.....	16
S.4.5 Justification of Specification.....	16
S.5 Reference Standards or Materials.....	16
S.6 Container Closure System.....	16
S.7 Stability.....	16
S.7.1 Stability Summary and Conclusions.....	16
S.7.2 Post-approval Stability Protocol and Stability Commitment.....	16
S.7.3 Stability Data.....	16

P.	DRUG PRODUCT	17
P.1	Description and Composition of the Drug Product	17
P.2	Pharmaceutical Development	17
P.2.1	Components of the Drug Product	18
P.2.1.1	Drug Substance	18
P.2.1.2	Excipients	18
P.2.2	Drug Product	23
P.2.2.1	Formulation Development	23
P.2.2.2	Overages	24
P.2.2.3	Physicochemical and Biological Properties	24
P.2.3	Manufacturing Process Development	24
P.2.4	Container Closure System	25
P.2.5	Microbiological Attributes	25
P.2.6	Compatibility	25
P.3	Manufacture	25
P.3.1	Manufacturers	25
P.3.2	Batch Formula	26
P.3.3	Description of Manufacturing Process and Process Controls	26
P.3.4	Controls of Critical Steps and Intermediates	29
P.3.5	Process Validation and/or Evaluation	29
P.4	Control of Excipients	30
P.4.1	Specifications	30
P.4.2	Analytical Procedures	31
P.4.3	Validation of Analytical Procedures	31
P.4.4	Justification of Specifications	32
P.4.5	Excipients of Human or Animal Origin	32
P.4.6	Novel Excipients	32
P.5	Control of Drug Product	32
P.5.1	Specification(s)	32
P.5.2	Analytical Procedures	38
P.5.3	Validation of Analytical Procedures	38
P.5.4	Batch Analyses	46
P.5.5	Characterization of Impurities	47
P.5.5.1	Inquiry into Product Discoloration	52
P.5.6	Justification of Specification(s)	76
P.6	Reference Standards or Materials	79
P.7	Container Closure System	79
P.7.1	Specifications and Analytical Methods	81
P.7.1.1	Specifications of Packaging Components	82
P.8	Stability	83
P.8.1	Stability Summary and Conclusion	83
P.8.1.1	Stress Testing	84
P.8.2	Post-approval Stability Protocol and Stability Commitment	87
P.8.3	Stability Data	89

CHEMISTRY REVIEW

A. APPENDICES..... 91

A.1 Facilities and Equipment (biotech only)..... Not Applicable

A.2 Adventitious Agents Safety Evaluation..... Not Applicable

A.3 Novel Excipients..... Not Applicable

R. REGIONAL INFORMATION..... 91

R.1 Executed Batch Records..... 91

R.2 Comparability Protocols..... 91

R.3 Methods Validation Package..... 91

II. REVIEW of COMMON TECHNICAL DOCUMENT QUALITY MODULE 1..... 92

A. Labeling and Package Insert..... 92

B. Environmental Assessment of Claim of Categorical Exclusion..... 94

C. Establishment Inspections..... 95

C.1 Establishment Evaluation Report..... 95

III. DRAFT DEFICIENCY LETTER..... 99

Appears This Way
On Original



Chemistry Review Data Sheet

1. **NDA 21-738**
2. **REVIEW: # 1**
3. **REVIEW DATE: 19-OCT-2004**
4. **REVIEWER: Allan Fenselau**
5. **PREVIOUS DOCUMENTS: None**
6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Original	23-JAN-2004
Amendment (BC)	10-FEB-2004
Amendment (BC)	17-FEB-2004
Amendment (BC)	23-MAR-2004
Amendment (BC)	19-APR-2004
Amendment (BZ)	26-APR-2004
Amendment (BC)	15-JUN-2004
Amendment (BC)	09-JUL-2004
Amendment (BC)	15-JUL-2004
Amendment (BC)	22-JUL-2004
Amendment (BL)	04-AUG-2004
Amendment (BC)	06-AUG-2004
Amendment (BC)	27-AUG-2004
Amendment (BC)	14-SEP-2004
Amendment (BC)	14-OCT-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Connetics Corporation
Address:	3290 West Bayshore Road Palo Alto, CA 94303
Representative:	Charles Democko, VP, Regulatory Affairs
Telephone:	650-739-2930/Fax: 650-843-2802

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) **Proprietary Name:** EXTINA™ Foam
- b) **Non-Proprietary Name (USAN):** Ketoconazole
- c) **Code Name/# (ONDC only):** NA

CHEMISTRY REVIEW

Chemistry Assessment Section

d) Chem. Type/Submission Priority: 3/S

9. LEGAL BASIS FOR SUBMISSION: Not Applicable

10. PHARMACOLOGICAL CATEGORY: Antifungal

11. DOSAGE FORM: Foam

12. STRENGTH/POTENCY: 2% w/w

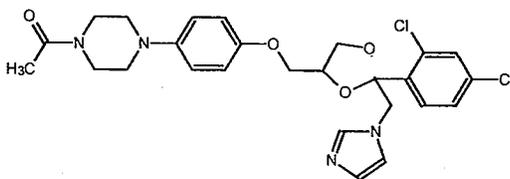
13. ROUTE OF ADMINISTRATION: Topical

14. R_x/OTC DISPENSED: X R_x ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

___ SPOTS product – Form Completed
X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



C₂₆H₂₈Cl₂N₄O₄

KETOCONAZOLE

M.W.: 531.43

CAS-65277-42-1

Appears This Way
On Original



CHEMISTRY REVIEW



Chemistry Assessment Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF No.	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENT
					A	08-OCT-2004	Adequate info.
					NA	30-SEP-2004	Adequate info. provided in NDA
					NA	30-SEP-2004	Adequate info. provided in NDA
					NA	NA	Adequate info. provided in NDA

b(4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – No revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under “Comments”)

² Adequate, Inadequate, or NA (i.e., there is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Documents	Document Date
IND: 63,153	Filed 24-AUG-2001
Patent: 4,942,162	expired 11-FEB-2003

18. STATUS: ONDC

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	08-APR-2004	S.Ferguson
Plfarm/Tox	Acceptable	06-AUG-2004	K.Mainigi
Methods Validation	To be submitted to FDA lab.	----	----
DMETS/DDMAC	Acceptable	28-SEP-2004	L.Kim-Jung
EA	Acceptable	08-OCT-2004	A.Fenselau

Appears This Way
On Original



EXECUTIVE SUMMARY

Chemistry Review for NDA 21-738

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 21-738 for EXTINA (ketoconazole) Foam, 2% is Approvable and will require satisfactory resolution of the safety issues that relate to _____ before receiving a recommendation for Approval.

b(4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable Not Applicable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance: Ketoconazole is currently approved in the US for use in six products [NDAs 18-533, 19-084, 19-576, 19-648, 19-927, and 20-310]. Detailed CMC information pertaining to _____ of the drug substance is provided by reference in the _____ Drug Master File _____ from the _____. There are no pending deficiencies for this DMF, which is considered Adequate to support the subject NDA.

b(4)

_____ The structure of ketoconazole, as drawn in the Package Insert for the various approved products, indicates _____, which will be revised by the sponsor in the product labeling.

Drug Product: Ketoconazole Foam, 2% is delivered in a quick-breaking, temperature-sensitive, patented foam vehicle platform. This topical drug product contains ketoconazole, USP, specially denatured alcohol _____ cetyl alcohol, citric acid, polysorbate 60, potassium citrate, propylene glycol, purified water, and stearyl alcohol pressurized in a _____ with a hydrocarbon (propane/butane) propellant. With the exception of the denatured alcohol _____ all of the excipients are USP or NF grade. Control of these latter excipients is established adequately. Acceptance testing of the propane/butane propellant also indicates adequate control. However, use of the denatured alcohol posed several problems.

b(4)

The denatured alcohol consists of absolute alcohol plus the additives *tert*-butyl alcohol and brucine sulfate, a potentially toxic alkaloid of the strychnine class. The absolute alcohol is manufactured _____

_____ Based on the _____ formulation for _____ each 50g can of Ketoconazole Foam, 2% should contain approximately _____ brucine sulfate. The opinion of the Pharmacology/Toxicology reviewer is that this level presents no safety concerns. Two CMC actions have been taken to better assure safe use of the product: 1) revising the specification for the denatured alcohol _____ and 2) stating the composition of the denatured alcohol in the Package Insert. The revised _____ specification will list the content of brucine sulfate as determined by _____

b(4)



CHEMISTRY REVIEW



Chemistry Assessment Section

_____ (based on a content of _____ mg brucine sulfate/mL alcohol calculated from the _____ formulation). The Package Insert will specify the two additives in the absolute alcohol—*tert*-butyl alcohol and brucine sulfate—as opposed to merely stating that “_____” is present in the formulation.

b(4)

The manufacture of drug product involves the _____

b(4)

_____ The manufacturing operations are well described in the batch record; adequate in-process testing is performed to assure batch-to-batch uniformity and product quality.

The container closure system is designed to dispense foam from an upright canister (unlike the firm’s other approved foam products OLUX and Luxiq). The specifications for the canister and its component parts are presented in sufficient detail. _____

_____ the container closure was subjected to thorough extractable/leachable testing. Extraction conditions for the can and valve assemblies were in accord with those described by the current USP/NF Physicochemical Testing of Extracts and 21 CFR §175.300 Testing. The results of these tests on cans from the _____ proposed suppliers were well within the established limits _____

b(4)

_____ Based on these results, no additional analyses were applied to obtain further information as to the chemical nature of certain sets of extractables.

The drug product specification includes testing for Appearance, Minimum Fill, Pressure, Leakage, Ketoconazole Identity (Release only), Content of Ketoconazole and Related Substances, Microbial Limits, Apparent pH, Ethanol Content, Weight Loss (Stability only), and Product/Packaging Interactions (Stability only). With the exceptions of the determination of ketoconazole content and Product/Packaging Interactions test, the listed tests and acceptance criteria were acceptable. The method for determining ethanol content has been satisfactorily validated.

The acceptance criteria were set using data from testing of the product for related substances, an adjustment to the 99% confidence interval, and consideration of the drug substance specification (see above). The related substances with RRT values of _____ have been included as well as any single unidentified or unspecified related substance. The total related substances cannot exceed _____ of the ketoconazole label claim. The acceptance criteria for ketoconazole and its related substances were revised to reflect the capabilities of the test methods for obtaining data to three significant figures. The proposed testing and acceptance criteria for the specified related substances are acceptable.

b(4)

Deficiencies, however, were found in testing for ketoconazole-related substances and product/packaging interactions. These problems were associated with the sponsor’s finding that _____ All _____ registration lots showed _____

b(4)



CHEMISTRY REVIEW



Chemistry Assessment Section

b(4)

Consequently, a test for absorbance has been included in the product specification, and an acceptance criterion of _____ absorbance unit [AU] has been established based on analysis of limited data. Another test missing in the specification is a determination of spray rate, which would assure dispensation of a uniform amount of foam from the can. The sponsor will include this test in the product specification in order to comply with USP <601> for pressurized topical aerosols. An acceptance criterion will be set when sufficient data become available (from _____ commercial lots or within one year of NDA approval).

b(4)

become issues of concern.

b(4)

These revised procedures for testing product/packaging interactions have been incorporated into the product specification.

Possibly relevant information on the biological safety of product containing the _____ ketoconazole-related substance may be found in the results from the studies on irritation/sensitization, comparative bioavailability, and Phase 3 safety and efficacy.

These findings permit a tentative conclusion

b(4)

_____ batches of Ketoconazole Foam, 2% have been manufactured in the 50-gram product size: _____ of these lots (SCFC-C and SCFH-C) had a batch size of _____ and were used in clinical studies and stability testing. Lot SCFL-C had a batch size of _____

CHEMISTRY REVIEW

Chemistry Assessment Section

_____ and was used for stability testing. The batch analyses demonstrated that the chemical, physical, and microbiological characteristics of all _____ batches met their respective product release specifications.

The results of the stability studies were reported for storage at 40°C/75% RH for _____ and at 25°C/60% RH for _____. The data show little or no change over time and little or no variability when the _____ lots of 50 gram product are stored under either long-term or accelerated conditions or in an _____ orientation. All test parameters comply with the specification after _____ of recommended storage with no apparent _____ of the ketoconazole. Consequently, Connetics has proposed an expiration dating period of _____ for the 50-gram product size of Ketoconazole Foam, 2%. A shelflife of _____ is unacceptable based on the data contained in the submission and subsequent amendments.

b(4)

These stability data do not permit full evaluation of product stability and expiry dating. Limitations in testing and analysis are responsible for the lack of information on the content of the product's most apparent _____

b(4)

Drug product stress testing was carried out using standard conditions (treatment with acid, base, peroxide, heat, and light exposure). Unlike the results of the standard stability studies, _____

_____ The study established the utility of the HPLC method as a stability-indicating method.

The proposed post-approval stability protocol and stability commitment are standard statements and are acceptable with modification (based on revisions to be made to the product specification). Product labeling is acceptable with incorporation of the changes cited earlier (regarding representation of the ketoconazole structure and inclusion of the components of the denatured alcohol). The claim for the environmental impact indicates the amount of ketoconazole introduced into the aquatic environment falls within acceptable limits; the amount, however, appears to be miscalculated. All manufacturing and testing sites for drug substance and drug product have been recommended for Approval by the Office of Compliance [OC].

B. Intended Use of the Drug Product

Connetics developed Ketoconazole Foam, 2% as a convenient-to-use formulation of the established active pharmaceutical ingredient ketoconazole for topical use in the treatment of seborrheic dermatitis. Seborrheic dermatitis is an extremely common and recurrent dermatosis, which occurs primarily on the face and scalp. This disease is characterized by redness and scaling, with occasional papule and plaque formation. The yeasts *Pityrosporon ovale* or *Pityrosporon orbiculare* (*Malassezia furfur*) are believed to play a role in the pathogenesis of seborrheic



dermatitis and are susceptible to treatment with antifungal agents. Ketoconazole is a broad-spectrum, synthetic antifungal drug, whose therapeutic effect has been postulated to be due to its ability to impair fungal synthesis of ergosterol, producing deficient fungal cell membranes.

The treatment of relapsing seborrheic dermatitis requires a safe topical preparation. Ketoconazole is currently approved for prescription use in the United States in two different prescription topical dosage forms (both at a concentration of 2%): Nizoral Cream and Ketoconazole shampoo. Nizoral Cream was first approved in 1985 initially for the treatment of tinea corporis, tinea cruris, and tinea pedis, but subsequently for the treatment of seborrheic dermatitis, cutaneous candidiasis, and tinea versicolor. Ketoconazole shampoo, 2% was approved in 1990 and is currently indicated for the treatment of tinea versicolor. [A nonprescription formulation of 1% ketoconazole shampoo for flaking, scaling, and itching associated with dandruff was also approved for marketing in the United States in 1997.] Over ~~the~~ topical treatment courses of ketoconazole have been prescribed worldwide, the majority using a 2% formulation. Connetics Ketoconazole Foam, 2% differs from these approved products in that it employs VersaFoam—a quick-breaking, temperature-sensitive patented foam vehicle platform that, when applied to the skin, breaks down due to body heat and deposits the active ingredient directly on the lesion. Better patient compliance is expected with the foam formulation because of the localized application, longer contact time (compared to the shampoo), and the improved cosmetic aspects (compared to the cream).

C. Justification of Recommendation

Three serious concerns about the possible effects of ketoconazole foam discoloration on product safety and quality were identified: 1) ~~the~~, 2) ~~the~~ and 3) ~~the~~

b(4)

~~_____~~ The sponsor needs to address these issues in order to provide greater assurance on product quality and safety.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

A.FENSELAU/08-OCT-2004: Same date as draft review

N.SCHMUFF/Date:

V.GIROUX/Date:

C. CC Block

HFD-830

D.LIN/Date:

N.SCHMUFF/Date:

86 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/

Allan Fenselau
10/19/04 10:54:15 AM
CHEMIST

Norman Schmuff
10/20/04 03:09:07 PM
CHEMIST

**Appears This Way
On Original**

NDA FILEABILITY CHECKLIST

NDA Number: 21-738

Applicant: Connetics Corp.

Stamp Date: 28-JAN-2004

Drug Name: EXTINA™ (ketoconazole) Foam, 2%

Letter Date: 26-JAN-2004

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

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

	Parameter	Yes/ No	Comment
1	On its face, is the section organized adequately?	Y	
2	Is the section indexed and paginated adequately?	Y	CMC Pagination is non-sequential. Location is given as pg.no. in subsection, e.g., "General Information." Referencing in review the location of data in the submission is difficult/awkward.
3	On its face, is the section legible?	Y	
4	Are all of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	Y	DS: OK DP: OK
5	Is a statement provided that all facilities are ready for GMP inspection?	Y	DS: Yes DP: Yes
6	Has an environmental assessment report or categorical exclusion been provided?	Y	Module 1.3.6: "Environmental Impact"
7	Does the section contain controls for the drug substance [DS]?	NA	DS information is contained in DMF _____ (for which a Letter of Authorization has been received).
8	Does the section contain controls for the drug product [DP]?	Y	Modules 3.2.P.4 and 3.2.P.5.
9	Has stability data and analysis been provided to support the requested expiration date?	N	DP: Module 3.2.P.8. Only _____ data have been submitted to support a _____ expiration date.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	Y	The sponsor appears to discuss all relevant FDA guidance in Module 2.3 ("Quality Overall Summary")
11	Have draft container labels been provided?	Y	Module 1.3.2.2: "Draft Immediate and Carton Label"
12	Has the draft package insert been provided?	Y	Module 1.3.2.1: "Draft Package Insert"
13	Has an Investigational Formulations section been provided?	Y	Module 3.2.P.2.
14	Is there a Methods Validation package?	Y	Submitted separately
15	Is a separate microbiological section included?	NA	DP Specification includes appropriate Microbial Limit Tests.

b(4)

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

Reviewing Chemist:

Date:

Allan Fenselau

Team Leader (Acting)

Date:

Norman Schmuff

cc:

Original NDA 21-738
HFD-540/Division File

HFD-540/Chem/A.Fenselau
HFD-830/DivDir(Acting)/D.Lin

HFD-540/PM/L.Carrington



CHEMISTRY REVIEW



Chemistry Assessment Section

NDA Number: 21-738

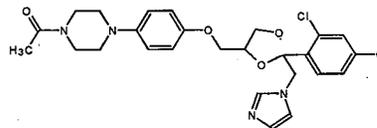
Applicant: Connetics Corp.

Drug Name: EXTINA™ (ketoconazole) Foam, 2%

KETOCONAZOLE CAS-65277-42-1

C₂₆H₂₈Cl₂N₄O₄

M.W.: 531.43



or

b(4)

LISTING of MANUFACTURING and TESTING SITES USED in the MANUFACTURE of the DRUG PRODUCT, EXTINA FOAM

DMF NO./ TYPE	CFN	HOLDER	DESCRIPTION	LOA	Insp. Ready	Insp. Status	ADDRESS
KETOCONAZOLE							
				Yes	Yes	AC	
EXTINA Foam							
				---	Yes	AC	
				---	Yes	AC	
				---	Yes	PN	
				---	Yes	AC	

b(4)

Abbreviations used: DS, Drug Substance; DP, Drug Product; AC, Acceptable; PN, Pending.

1 The CFN nos. provided by the sponsor do not agree with the CFN nos. of the sites reviewed by the Office of Compliance.

SUPPORTING DOCUMENTS:

DMF No.	TYPE	HOLDER	ITEM REFERENCED	LOA ¹ DATE	DATE of LAST REVIEW
				Y 24-JUN-2003	29-MAR-2000
				Y 24-MAR-2003	07-NOV-2002
				Y 17-MAR-2003	No Review ³
				Y	NA ⁴
				Lists GRAS items	

b(4)

1 LOA = Letter of Authorization; Included Yes/No [Y/N]; LOA Date

2

3 No review listed in "DMFReviews"

4 NA = Not Applicable

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/

Allan Fenselau

6/15/04 03:42:48 PM

CHEMIST

For some reason this list did not get placed
in DFS at the time of the Fileability
Meeting. Everything was OK for filing.

Norman Schmuff

6/18/04 09:51:20 AM

CHEMIST

Appears This Way
On Original