CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-978

CHEMISTRY REVIEW(S)

NDA 21-978

[redacted]™ (desonide) Foam, 0.05%

Connetics Corporation

Division of Dermatology and Dental Products

Gene W. Holbert, Ph.D.
Division of Premarketing Assessment II

Brian D. Rogers, Ph.D.
Division of Manufacturing Science

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Chemistry Review Data Sheet

1. NDA 21-978

2. REVIEW #: 1

3. REVIEW DATE: August 21, 2006

4. REVIEWER: Gene W. Holbert, Ph.D. and Brian D. Rogers, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	November 18, 2005
Amendment (BC)	March 15, 2006
Amendment (BC)	May 2, 2006
Amendment (BC)	May 24, 2006
Amendment (BZ)	July 18, 2006
Amendment (BC)	August 29, 2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Connetics Corporation
Address:	3160 Porter Drive
	Palo Alto, CA 94304
Representative:	Michael S. Eison, Ph.D.
Telephone:	(650) 739-2614

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: [redacted] (alternate Verdeso)
b) Non-Proprietary Name (USAN): Desonide
c) Code Name/# (ONDQA only): Desilux
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Anti-inflammatory (Glucocorticoid)

11. DOSAGE FORM: Aerosol, Foam Code: 800

12. STRENGTH/POTENCY: 0.05%

13. ROUTE OF ADMINISTRATION: Topical Code: 011

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

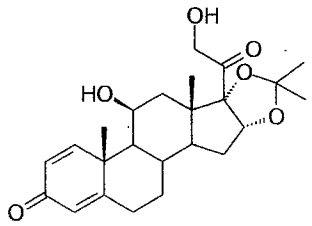
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

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

(11β,16α)-11,21-Dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregna-1,4-diene-3,20-dione



Molecular Formula: $C_{24}H_{32}O_6$ Molecular Weight: 416.51 CAS: 638-94-8

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	1	Adequate	30-JAN-2006	
[redacted]	III	[redacted]	[redacted]	3	Adequate	12-NOV-2002	E. Pappas

[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
Applications	NDA 17-010, [redacted]	Desonide Cream, 0.05%
Applications	NDA 17-426, [redacted]	Desonide Ointment, 0.05%

18. STATUS:

ONDQA:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	18-JAN-2006	J. D'Ambrogio
Pharm/Tox	N/A		
Biopharm	Approvable	13-JUL-2006	B. Hill
DMETS	Pending		
DDMAC	Comments	18-AUG-2006	A. Haffer
EA	Categorical exclusion	21-AUG-2006	G. Holbert
Microbiology	N/A		

The Chemistry Review for NDA 21-978

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls perspective, this application may be approved.

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

N/A. See review notes.

II. Summary of Chemistry Assessments

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

The drug substance, desonide, is a low potency anti-inflammatory corticosteroid typically applied topically. Information on the preparation of desonide is found in DMF [redacted].

The drug product, [redacted]™ (desonide) Foam, 0.05%, is a petrolatum-based emulsion aerosol foam. Each gram of the foam contains 0.5 mg desonide. The foam also contains Citric Acid USP, Cetyl Alcohol NF, Cyclomethicone NF, Isopropyl Myristate NF, Light Mineral Oil NF, White Petrolatum USP, Polyoxyl 20 Cetostearyl Ether NF, Potassium Citrate USP, Propylene Glycol USP, Purified Water USP, Sorbitan Monolaurate NF, and Phenoxyethanol NF as a preservative. Each container contains 100 g of foam.

The product is dispensed from an aluminum can pressurized with a hydrocarbon (propane/butane) propellant. The container consists of a [redacted]. The can is fitted with an [redacted] or [redacted], and a non product contacting [redacted]. The [redacted] does not control the dispensed dose. The can size is [redacted] to accommodate 100 grams of product.

The product is labeled for storage at controlled room temperature of 68-77°F (20-25°C). Based on the stability data submitted (18 months at 25°C/60% RH and 6 months at 40°C/75% RH), an expiration date of 24 months is appropriate.

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

[redacted]. Foam is indicated for the treatment of mild to moderate atopic dermatitis in patients 3 months of age or older. A thin layer of [redacted] Foam is applied to the affected area(s) twice daily. The can is labeled to be shaken before use. The can is inverted and sufficient foam is dispensed to cover the affected area with a thin layer.

Treatment is limited to 4 consecutive weeks, however, patients are to be instructed to use desonide foam for the minimum time necessary to achieve the desired results. If no improvement is noted within 2 weeks, a reassessment of the diagnosis may be in order.

Since the product contains a hydrocarbon propellant, the product is flammable. Patients are warned against smoking and to avoid fire or flame during and immediately following application. Patients are cautioned not to puncture or incinerate or to expose or store the product above 120°F (49°C).

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments ultimately provided adequate information on the chemistry, manufacturing and controls for the production of [redacted]™ (desonide) Foam. During the review a number of issues, including the following, were resolved:

- Clarification of the commercial batch size;
- Comparison of the equipment used to manufacture the clinical and stability batches;
- Clarification of some of the details in the analytical methods;
- Clarification of the reason for shaking before use (the applicant states that it is to [redacted] on standing);
- Clarification of the location of the lot number and expiry dates on the primary and secondary packaging;
- Provided data to indicate that proposed minimum propellant pressure at release (not less than [redacted] was sufficient to dispense the entire contents of the container;
- Changed the acceptance criterion for propellant pressure at release and stability from not less than [redacted] to not less than [redacted] to better reflect manufacturing capability and product used in the clinical trials;
- Clarification of several items in the master batch record;
- Clarification of in-process controls;
- Established a minimum water bath immersion time for leak testing;
- Provided unit failure rate data from in-line weight checking; and
- Provided data concerning the unit-to unit variability in canister pressure.

In addition, several commitments were made in the Amendment dated 24-MAY-2006, as listed below:

- To gather assay data from multiple units of product from three [redacted] batches that will be manufactured for process validation prior to commercialization and to submit these data to the NDA within 6 months post-approval.
- To provide the agency with analysis of can pressure data at the end of the manufacturing process following completion of 10 lots of manufacturing of the [redacted] size product to demonstrate that can pressure is adequately controlled.
- To collect additional data, during initial commercial manufacturing, on the physical characteristics of the Desonide Foam emulsion and submit the resulting data to the NDA within one year post-approval.

As amended, all methods and acceptance criteria were found satisfactory for the drug product.

DMETS review of the proposed trade name is pending.

The applicant has also submitted comparability protocols which provide for an alternate manufacturing site, and [redacted]

III. Administrative

A. Reviewer's Signature

Signed electronically in DFS.

B. Endorsement Block

Chemist Name/Date:	Gene W. Holbert, Ph.D. Brian D. Rogers, Ph.D.
Branch Chief Name/Date:	Moo-Jhong Rhee, Ph.D.

C. CC Block

HFD-540/DD: Stanka Kukich
HFD-540/MTL: Markham Luke
HFD-540/MO: Denise Cook
HFD-540/PM: Melinda Bauerlien
ONDQA/PM: Linda Athey
ONDQA/PAL: Shulin Ding

77 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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

/s/

Gene Holbert
9/7/2006 12:19:38 PM
CHEMIST

Brian Rogers
9/7/2006 01:33:32 PM
CHEMIST

Moo-Jhong Rhee
9/7/2006 02:10:09 PM
CHEMIST
Chief, Branch III