

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-013

CHEMISTRY REVIEW(S)

NDA 22-013

Primolux™ (clobetasol propionate) Foam, 0.05%

Connetics Corporation

**Rao Puttagunta, Ph.D.
Branch III/Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research**

**Reviewed for
Division of Dermatology and Dental Products (HFD-540)**

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Chemistry Review Data Sheet

1. NDA #: 22-013
2. REVIEW #: 1
3. REVIEW DATE: 16-NOV-2006
4. REVIEWER: Rao Puttagunta
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	14-MAR-2006
Amendment (SU)	14-JUL-2006
Amendment (BL)	05-SEP-2006
Amendment (BL)	22-SEP-2006
Amendment (BC)	05-OCT-2006
Amendment (BC)	20-OCT-2006
Amendment (BC)	30-OCT-2006
Amendment (BC)	08-NOV-2006
Amendment (BC)	16-NOV-2006
Amendment (BC)	21-NOV-2006

7. NAME & ADDRESS OF APPLICANT:

Name: Connetics Corporation
Address: 360 Porter Drive
Palo Alto, CA 94304
Representative: Michael S. Eison, Ph.D.
Vice President, Regulatory Affairs
Telephone: 650-739-2614

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Primolux™
- b) Non-Proprietary Name (USAN): Clobetasol Propionate Foam, 0.05%
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):

CHEMISTRY REVIEW

Chemistry Review Data Sheet

- Chem. Type: 5
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Corticosteroid

11. DOSAGE FORM: Foam, Aerosol

12. STRENGTH/POTENCY: 0.05% clobetasol propionate

13. ROUTE OF ADMINISTRATION: Topical

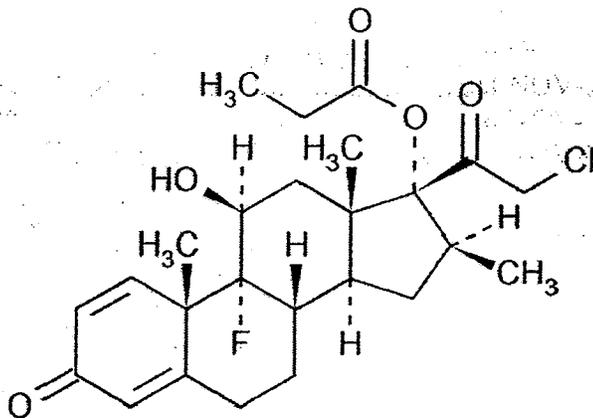
14. Rx/OTC DISPENSED: Rx OTC

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:



Chemical Name: 21-Chloro-9-fluoro-11 β ,17-dihydroxy-16 β -methylpregna-1,4-diene-3,20-dione 17-propionate

Molecular Formula: C₂₅H₃₂ClFO₅

Molecular Weight: 466.97

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
1	1	L	L	1	Adequate	11/01/06 (R. Puttagunta)	---
2	1	L	L	1	Adequate	11/07/02 (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
IND	67,818	Ethanol Free Clobetasol Propionate Foam, 0.05%

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Chemistry Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A per new ONDC policy		
DMETS	Acceptable	9/22/06	Tselaine Jones-Smith
DDMAC	N/A		
EA	Categorical Exclusion		Rao Puttagunta
Microbiology	N/A		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

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The Chemistry Review for NDA

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC standpoint this NDA is recommended as approvable pending satisfactory EES recommendation from the Office of Compliance.

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

N/A

II. Summary of Chemistry Assessments

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

1. Drug Substance

Clobetasol propionate is manufactured by [redacted]. The CMC information on clobetasol propionate was referenced to DMF [redacted]. The DMF has been reviewed and found to be adequate. Since the drug substance is a compendial item it is tested according to the USP specification. The supplier also tests the drug substance for [redacted] residual solvents and additional impurities.

2. Drug Product:

The drug product Primolux (clobetasol propionate) Foam, 0.05%, is a petrolatum based emulsion aerosol foam. Each gram of the foam contains 0.5 mg of clobetasol propionate.

The product is dispensed from a one-piece seamless aluminum can lined with a [redacted]. The can is fitted with an [redacted] valve, an [redacted] and a non-product-contacting [redacted] cap. Each can contains 100 grams of the product.

The drug product is labeled for storage at controlled room temperature of 68 – 77°F (20-25°C).

Executive Summary Section

All ingredients in the drug product are of USP/NF grade except for the propellant, and are tested according to their respective monographs. The specification for the propellant was provided. The same propellant is also used in currently approved products of the same dosage form.

Appropriate in-process, release, and stability acceptance criteria have been established for the drug product to ensure consistency in quality. The in-process specification and the drug product specification were considered adequate as revised.

The _____ was referenced to DMF _____. The DMF was reviewed previously and found to be adequate.

The submitted drug product stability data for up to 30 months conform to the established acceptance criteria. The submitted stability data was considered adequate to support the proposed 24-month expiration dating period.

The submitted revised master batch record by including the detailed instruction for visual inspections, and incorporating the hand-written changes from the executed batch record was considered adequate.

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

Primolux (clobetasol propionate) Foam, 0.05%, is indicated for the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 12 years or older. Primolux Foam is applied to the affected area(s) twice daily. The treatment is limited to 2 consecutive weeks, and amounts greater than 100 g in a 2 week period should not be used.

The product contains hydrocarbon (butane/propane) propellant, and is labeled as flammable. A warning is included to avoid fire, flame or smoking during and immediately following application. It is also warned not to puncture, incinerate, expose to heat, or store the product at temperatures above 120°F (49°C).

C. Basis for Approvability or Not-Approval Recommendation

The NDA original submission and amendments provided adequate CMC information for Primolux™ (clobetasol propionate) Foam and the following conclusions were made.

- The referenced DMFs for drug substance and _____ are adequate.
- The submitted raw material controls are adequate.
- The manufacturing process and process controls are robust to ensure consistent product quality in conformance with the established specification.
- The drug product specification as revised is adequate.

Executive Summary Section

- The submitted stability data is adequate to support the proposed expiration dating period.
- The packaging information is adequate to ensure the product quality during storage, transportation, and use.
- The submitted labeling as revised is acceptable from the CMC standpoint.

The NDA 22-013 is recommended as approvable pending satisfactory EES recommendation from the Office of Compliance.

III. Administrative

A. Reviewer's Signature

Rao Puttagunta {electronic signature}

B. Endorsement Block

Moo-Jhong Rhee {electronic signature}
Branch Chief, Branch III, DPA II, ONDQA

C. CC Block

N/A

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§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

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/s/

Rao Puttagunta
12/11/2006 03:19:34 PM
CHEMIST

Moo-Jhong Rhee
12/11/2006 03:33:06 PM
CHEMIST
Chief, Branch III

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NDA #: 22-013

Applicant: Connetics Corporation

Drug Product: Primolux™ (clobetasol propionate) Foam, 0.05%

Addendum to CMC Review #1

In the CMC Review #1, at the top of page 7 (Executive Summary), the NDA number appears as _____ The correct NDA number is 22-013.

Rao Puttagunta, Ph.D.
Review Chemist

12/13/06
Date

Moo-Jhong Rhee, Ph.D.
Branch Chief

Date

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Rao Puttagunta
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CHEMIST

Moo-Jhong Rhee
12/13/2006 12:12:26 PM
CHEMIST
Chief, Branch III.

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NDA 22-013

Primolux™ (clobetasol propionate) Foam, 0.05%

Connetics Corporation

Rao Puttagunta, Ph.D.

Branch III/Division of Pre-Marketing Assessment II

Office of New Drug Quality Assessment

Center for Drug Evaluation and Research

Reviewed for

Division of Dermatology and Dental Products (HFD-540)



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II. Summary of Chemistry Assessments.....7

 A. Description of the Drug Product(s) and Drug Substance(s) 7

 B. Description of How the Drug Product is Intended to be Used..... 8

 C. Basis for Approvability or Not-Approval Recommendation..... 8

III. Administrative..... 9

 A. Reviewer’s Signature..... 9

 B. Endorsement Block..... 9

 C. CC Block 9

Chemistry Assessment..... 10

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data... 10

 S DRUG SUBSTANCE [Name, Manufacturer]..... 10

 P DRUG PRODUCT [Name, Dosage form]..... 13

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II. Review Of Common Technical Document-Quality (Ctd-Q) Module 143

 A. Labeling & Package Insert 43

 B. Environmental Assessment Or Claim Of Categorical Exclusion 46

III. List Of Deficiencies To Be Communicated.....46

Chemistry Review Data Sheet

1. NDA #: 22-013
2. REVIEW #: 2
3. REVIEW DATE: 15-DEC-2006
4. REVIEWER: Rao Puttagunta
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	14-MAR-2006
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Amendment (BL)	22-SEP-2006
Amendment (BC)	05-OCT-2006
Amendment (BC)	20-OCT-2006
Amendment (BC)	30-OCT-2006
Amendment (BC)	08-NOV-2006
Amendment (BC)	16-NOV-2006
Amendment (BC)	21-NOV-2006

7. NAME & ADDRESS OF APPLICANT:

Name: Connetics Corporation
Address: 360 Porter Drive
Palo Alto, CA 94304
Representative: Michael S. Eison, Ph.D.
Vice President, Regulatory Affairs
Telephone: 650-739-2614

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Primolux™
- b) Non-Proprietary Name (USAN): Clobetasol Propionate Foam, 0.05%
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):

CHEMISTRY REVIEW

Chemistry Review Data Sheet

- Chem. Type: 5
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Corticosteroid

11. DOSAGE FORM: Foam, Aerosol

12. STRENGTH/POTENCY: 0.05% clobetasol propionate

13. ROUTE OF ADMINISTRATION: Topical

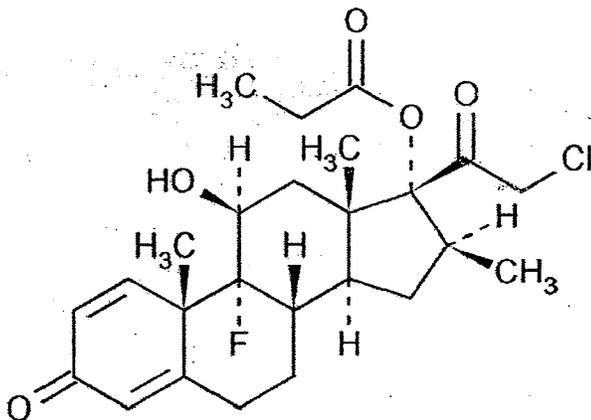
14. Rx/OTC DISPENSED: Rx OTC

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:



Chemical Name: 21-Chloro-9-fluoro-11 β ,17-dihydroxy-16 β -methylpregna-1,4-diene-3,20-dione 17-propionate

Molecular Formula: C₂₅H₃₂ClFO₅

Molecular Weight: 466.97

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
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---	---	---	---	---	Adequate	11/07/02 (E. Pappas)	---

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

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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	67,818	Ethanol Free Clobetasol Propionate Foam, 0.05%

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CHEMISTRY REVIEW

Chemistry Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	12/14/06	S. Ferguson
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A per new ONDQA policy		
DMETS	Acceptable	9/22/06	Tselaine Jones-Smith
DDMAC	N/A		
EA	Categorical Exclusion		Rao Puttagunta
Microbiology	N/A		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:

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On Original

The Chemistry Review for NDA 22-013

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC standpoint this NDA is recommended for approval.

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

N/A

II. Summary of Chemistry Assessments

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

1. Drug Substance

Clobetasol propionate is manufactured by _____ The CMC information on clobetasol propionate was referenced to DMF _____. The DMF has been reviewed and found to be adequate. Since the drug substance is a compendial item it is tested according to the USP specification. The supplier also tests the drug substance for residual solvents and additional impurities.

2. Drug Product:

The drug product Primolux (clobetasol propionate) Foam, 0.05%, is a petrolatum based emulsion aerosol foam. Each gram of the foam contains 0.5 mg of clobetasol propionate.

The product is dispensed from a one-piece seamless aluminum can lined with a _____ The can is fitted with an _____ valve, an _____, and a non-product-contacting _____ cap. Each can contains 100 grams of the product.

The drug product is labeled for storage at controlled room temperature of 68 – 77°F (20 – 25°C).

All ingredients in the drug product are of USP/NF grade except for the propellant, and are tested according to their respective monographs. The specification for the propellant

Executive Summary Section

was provided. The same propellant is also used in currently approved products of the same dosage form.

Appropriate in-process, release, and stability acceptance criteria have been established for the drug product to ensure consistency in quality. The in-process specification and the drug product specification were considered adequate as revised.

The _____ was referenced to DMF _____. The DMF was reviewed previously and found to be adequate.

The submitted drug product stability data for up to 30 months conform to the established acceptance criteria. The submitted stability data was considered adequate to support the proposed 24-month expiration dating period.

The submitted revised master batch record by including the detailed instruction for visual inspections, and incorporating the hand-written changes from the executed batch record was considered adequate.

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

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The product contains hydrocarbon (butane/propane) propellant, and is labeled as flammable. A warning is included to avoid fire, flame or smoking during and immediately following application. It is also warned not to puncture, incinerate, expose to heat, or store the product at temperatures above 120°F (49°C).

C. Basis for Approvability or Not-Approval Recommendation

The NDA original submission and amendments provided adequate CMC information for Primolux™ (clobetasol propionate) Foam and the following conclusions were made.

- The referenced DMFs for drug substance and _____ are adequate.
- The submitted raw material controls are adequate.
- The manufacturing process and process controls are robust to ensure consistent product quality in conformance with the established specification.
- The drug product specification as revised is adequate.
- The submitted stability data is adequate to support the proposed expiration dating period.



Executive Summary Section

- The packaging information is adequate to ensure the product quality during storage, transportation, and use.
- The submitted labeling as revised is acceptable from the CMC standpoint.
- The Office of Compliance issued an overall recommendation as “Acceptable” on 12/14/06.

The NDA 22-013 is recommended for approval based on the submitted CMC information.

III. Administrative

A. Reviewer’s Signature

Rao Puttagunta {electronic signature}

B. Endorsement Block

Moo-Jhong Rhee {electronic signature}
Branch Chief, Branch III, DPA II, ONDQA

C. CC Block

N/A

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

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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Rao Puttagunta
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CHEMIST

Moo-Jhong Rhee
12/15/2006 11:24:23 AM
CHEMIST
Chief, Branch III

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NDA #: 22-013

Applicant: Connetics Corporation

Drug product: Olux-E™ (clobetasol propionate) Foam, 0.05%

Addendum to CMC Review #2

The applicant submitted revised container and carton labels in the amendment dated 12/20/06. The main change in the labels was a change of the proprietary name to Olux-E™ from Primolux™. The remaining parts of the labels remain essentially unchanged; except that the USP/NF designation was included for each of the ingredients.

The Division of Medical Errors and Technical Support (DMETS) found the proprietary name, Olux-E™ acceptable (see Ms. Kimberly Pedersen's review dated 1/10/06 in DFS).

*Evaluation: The submitted container and carton labels as revised are **acceptable** from the CMC standpoint.*

Rao Puttagunta, Ph.D.
Review Chemist

1/11/07
Date

Moo-Jhong Rhee, Ph.D.
Branch Chief

Date

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/s/

Rao Puttagunta
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CHEMIST

Moo-Jhong Rhee
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CHEMIST
Chief, Branch III

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