DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

KOZMA FOWLER NDOE

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See instructions on reverse side before completing this form.

1. APPLICANT'S NAME AND ADDRESS

Connetics Corporation
3400 West Bayshore Road
Palo Alto, CA 94303
Contact person: Claire J. Lockey, V.P., Regulatory Affairs

2. TELEPHONE NUMBER *(include area code)*

(650) 843-2800

3. PRODUCT NAME

OLUX™ (clobetasol propionate) Foam, 0.05%

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES," CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

N/A

6. LICENSE NUMBER / NDA NUMBER

21-142

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

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

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

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT *(See Item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT *(See Item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Please DO NOT RETURN this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Claire Lockey	Vice President, Regulatory Affairs	July 16, 1999

FORM FDA 3397 (5/98)

18 0002

[16] DEBARMENT CERTIFICATION

In accordance with Section 306(k)(1) of the Federal Food, Drug, and Cosmetic Act, Connetics Corporation hereby certifies that, in connection with this application, it did not and will not knowingly use in any capacity the services of any person debarred under Section 306(a) or (b) of the Act.

Claire J. Lockey
Vice President
Regulatory Affairs

16 July 99
Date

APPEARS THIS WAY
ON ORIGINAL

[13] PATENT INFORMATION

Pursuant to 21 USC §355(b) and 21 CFR §314.53, Connetics declares that there are no patents which claim the drug substance (clobetasol proprionate) or the drug product (clobetasol propionate foam, 0.05%), or the method of use for the drug product, and with respect to which a claim of patent infringement could reasonably be asserted against anyone who engaged in the manufacture, use or sale of clobetasol propionate foam, 0.05%, for which FDA approval is sought.

Katrina Church, Esq.
Vice President
Legal Affairs and Corporate Counsel

16 July 99
Date

APPEARS THIS WAY
ON ORIGINAL

[14] 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. 4,370,322 which claimed clobetasol proprionate drug substance, drug product, and method of use, owned by Glaxo Laboratories Ltd. expired on January 27, 1991.

Katrina Church, Esq.
Vice President
Legal Affairs and Corporate Counsel

16 July 99
Date

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 21-142 SUPPL # _____

Trade Name Olux Foam Generic Name clobetasol propionate

Applicant Name Connetics Corporation HFD-540

Approval Date _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES/_X__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X__/

      If yes, what type(SE1, SE2, etc.)?

   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 /_X __/ 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.
      Clinical Data submitted to support safety (HPA Axis study) & a bioavailability study in which OLUX was not inferior to RLD.

      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:

   d) Did the applicant request exclusivity?

      YES /_X_/ NO /___/

      If the answer to (d) is "yes," how many years of exclusivity did the applicant request? **3 years**

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

YES /___/ NO /_x_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such). **(Different Dosage Form)**

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s). **Refer to attachment #1**

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

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 /_X__/

APPEARS THIS WAY
ON ORIGINAL

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 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 /X/ NO /(X)/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (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 9:**

(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: _____

(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: _____

(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:

Investigation #1, Study # CFCN, C, 002

Investigation #2, Study # _____

Investigation #3, Study # _____

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 /___/

Investigation #3 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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(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 /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(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"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

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 # _____ YES /___/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ 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: _____

_____

_____

_____

Signature of Preparer: Kalyani Bhatt /S/ Date: May 12, 2000
Title: Project Manager

Signature of Office or Division Director: /S/
Date:

cc:
Archival NDA
HFD-540 /Division File
HFD-540 /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

ANSWER TO QUESTION # 1, Part II:

Approved drug products containing the same active moiety:

Topical Crème, 0.05%	**Drug Name**	**Sponsor**
ANDA # 74087	Clobetasol propionate	Copley Pharm
# 74392	Clobetasol propionate	Fougera
# 74249	Clobetsol propionate	Taro
NDA # 19-322	Temovate	
20-340	Temovate E	

Topical Gel, 0.05%		
Temovate	NDA# 20-337	.05%

Topical Ointment, 0.05%		**Drug Name**	**Sponsor**
ANDA	74-089		Copley Pharm
ANDA	74-407		Faugera
ANDA	74-128		NMC
ANDA	74-248		Taro
ANDA	74-221	Embeline	DPT
NDA 19-323			Temovate

Topical Solution, 0.05%	**Drug Name**	**Sponsor**
ANDA 74-331	Clobetasol propionate	NMC
ANDA 74-222	Embeline	DPT
ANDA 19-966	Temovate	GW

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 hereby claims three years' exclusivity for OLUX (clobetasol propionate) Foam, 0.05%.

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. OLUX (clobetasol propionate) Foam, 0.05% contains the active moiety, clobetasol propionate. Clobetasol propionate has been previously approved under section 505(b): Glaxo Welcome's NDA #19-322 (cream) and NDA #19-323 (ointment) approved in 1985, NDA #19-966 (solution) approved in 1990, NDA #20-340 (emollient cream) approved in 1994 and NDA #20-337 (gel) approved in 1994.

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 OLUX (clobetasol propionate) Foam, 0.05%, which meet the above definition:

- comparative vasoconstrictor study (CPCD.C.001)
- comparative Phase III safety and efficacy study (CPCD.C.002)
- comparative HPA axis suppression study (CPCD.C.003)

The intent of all three of these studies was to establish the safety and efficacy of OLUX (clobetasol propionate) Foam, 0.05%. At the Pre-IND Meeting held on February 19, 1998, the Agency indicated that the intent of the vasoconstrictor study in a 505(b)(2) application is to determine potency, not comparative bioavailability. Potency, determined by vasoconstrictor assay, is a well-established surrogate marker for corticosteroid efficacy. The intent of the Phase III study was to assess the

safety and efficacy of OLUX (clobetasol propionate) Foam, 0.05% in the treatment of scalp psoriasis, and the intent of the HPA axis suppression study was to assess safety, as measured by the effect of OLUX (clobetasol propionate) Foam, 0.05%, on the adrenal axis.

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 §314.180(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 OLUX (clobetasol propionate) Foam, 0.05%, 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' ' _____ filed on April 22, 1998.

connetics®
CORPORATION

March 21, 2000

NEW

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic & Dental Drug Products
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

NC

RE: NDA #21-142 OLUX™ (clobetasol propionate) Foam, 0.05%

9.1 Financial Disclosure Statements

Dear Dr. Wilkin:

This submission is in response to the following information request that we received from the Medical Officer via facsimile on March 13, 2000:

Please submit the proper Financial Disclosure Form, and list the studies and investigators to which their disclosure statement applies.

Pursuant to this request and in accordance with an agreement with Linda Carter (CDER), the following documents are attached:

- Form FDA 3454
- Financial disclosure statement regarding proprietary interest in clobetasol propionate foam, 0.05%
- List of clinical studies and investigators for the three clinical studies that were submitted in the above-referenced NDA

Please do not hesitate to call Dawn Parsell at (650) 843-2809 or me at (650) 843-2889 if you need any additional information regarding this submission.

Sincerely,

Max Nyggaard / for

Claire J. Lockey
Vice President
Regulatory Affairs
and Quality Assurance

DUPLICATE

3400 West Bayshore Road • Palo Alto, CA 94303 • USA • Telephone: (650) 843-2800 • Facsimile: (650) 843-2899

NEW DRUG APPLICATION #21-142

CLOBETASOL PROPIONATE FOAM, 0.05%

9.1 Financial Disclosure Statements

Duplicate

Connetics Corporation
3400 West Bayshore Road
Palo Alto, CA 94303

(650) 843-2800
Fax: (650) 857-1193

Date: March 21, 2000

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Connetics Corporation	**March 21, 2000**
TELEPHONE NO. *(Include Area Code)* **650/843-2800**	FACSIMILE (FAX) Number *(Include Area Code)* **650/843-2899**
APPLICANT ADDRESS *(Number, Street, City, State, County, and ZIP Code or Mail Code, and U.S. License number if previously issued)*: **3400 West Bayshore Road, Palo Alto, CA 94303**	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) **NDA 21-142**

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Clobetasol Propionate, USP	**OLUX™ Foam**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*: **(11β,16β)-21-chloro-9-fluoro-11-hydroxy-16-methyl-17 (1-oxopropoxy)-pregna-1,4-diene-3,20-dione**

CODE NAME *(If any)*:

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Aerosol Foam	**0.05%**	**Topical**

(PROPOSED) INDICATION(S) FOR USE:

APPLICATION INFORMATION

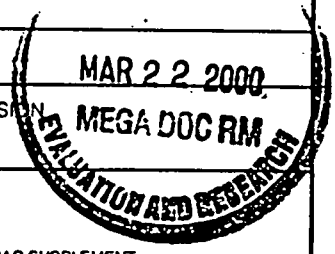
APPLICATION TYPE (check one)

X NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

☐ BIOLOGIC LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) X 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application



TYPE OF SUBMISSION (check one)

ORIGINAL APPLICATION X AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT

☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Financial Disclosure Statements

PROPOSED MARKETING STATUS (check one) X PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS X PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

(see Section 4.A.1.b); this site is ready for pre-approval inspection. Drug product is manufactured by CCL Pharmaceuticals (see Section 4.A.2.d); this site is ready for pre-approval inspection. Final product is released following approval by Connetics Corporation. The contact person for all sites is Claire J. Lockey, Vice President, Regulatory Affairs, Connetics Corporation, 3400 West Bayshore Road, Palo Alto, CA; (650) 843-2800.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA #20-934: Connetics Corporation [Luxiq™ (betamethasone valerate) foam, 0.12%], Palo Alto, CA 94303

FORM FDA 356h (4/97)

001

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) **Financial Disclosure Statements**

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211; 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610 and/or 809.
4. In the case of a prescription drug or biologic product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Mav Nygaard / for	**Claire J. Lockey** **Vice President** **Regulatory Affairs & Quality Assurance**	**3/21/00**

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
3400 West Bayshore Road, Palo Alto, CA 94303	**650/843-2800**

Public reporting burden for this collection of information is estimated to average 40 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:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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.

Please **DO NOT RETURN** this form to this address.

Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). ~~I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests.~~ I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f). (See Attachments)

Clinical Investigators		
	(See attached list)	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
John L. Higgins	Executive Vice President Finance and Administration Chief Financial Officer
FIRM/ORGANIZATION	
Connetics Corporation	
SIGNATURE	**DATE**
John L. Higgins	3-21-00

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FINANCIAL DISCLOSURE STATEMENT

Pursuant to 21 CFR §54.4, Connetics Corporation certifies that none of the investigators who participated in the three clinical studies submitted in this NDA (Protocols CPCD.C.001, CPCD.C.002, CPCD.C.003) has a proprietary interest [as defined in 21 CFR §54.2(c)] in clobetasol propionate foam, 0.05%, such as a patent, trademark, copyright, or licensing agreement.

Katrina J. Church
Vice President
Legal Affairs and Corporate Counsel

20 March 2000
Date

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

2 pages

connetics
CORPORATION

ORIGINAL

12/17/99

December 17, 1999

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic & Dental Drug Products
Food and Drug Administration, CDER
HFD-540
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: ——— – Clobetasol Propionate Foam 0.05%
Corticosteroid-Responsive Dermatoses of the Scalp
Serial No. 015

Protocol Amendment:

- New Investigators

Dear Dr. Wilkin:

We are submitting clinical documentation for the following Principal Investigators who are conducting the ongoing study entitled, "A Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Clobetasol Propionate Foam, 0.05%, in the Treatment of Non-Scalp Psoriasis" (Protocol CPCD.C.004 submitted in S:013, 9/7/99):

Gerald Krueger, M.D.
University of Utah Medical Center
Salt Lake City, UT 84132

Alan Menter, M.D.
Texas Dermatology Associates
Dallas, TX 75230

If you have any questions regarding this submission, please contact Dawn Parsell at (650) 843-2809 or me at (650) 843-2889.

Sincerely,

Claire J. Lockey
Vice President
Regulatory Affairs

3400 West Bayshore Road • Palo Alto, CA 94303 • USA • Telephone: (650) 843-2800 • Facsimile: (650) 843-2899

connetics®
CORPORATION

November 29, 1999

ORIG NEW CORRES
NC

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic & Dental Drug Products
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA #21-142 OLUX™
(clobetasol propionate) Foam, 0.05%

Four-Month Safety Update Report

Dear Dr. Wilkin:

As required by 21 CFR 314.50(d)(5)(vi)(b), the Four-Month Safety Update Report for Clobetasol Propionate Foam, 0.05% (NDA #21-142) is enclosed. There has been no new safety information since the NDA was submitted to the Agency on July 28, 1999.

Please do not hesitate to call Dawn Parsell at (650) 843-2809 or me at (650) 843-2889 if you need any additional information.

Sincerely,

Claire J. Lockey
Vice President
Regulatory Affairs

ORIGINAL

3400 West Bayshore Road • Palo Alto, CA 94303 • USA • Telephone: (650) 843-2800 • Facsimile: (650) 843-2899

ATTACHMENT 1

COPY OF LABELING CONSULT REPORTS FROM OPDRA AND DDMAC

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: January 28, 2000	DUE DATE: May 29, 2000	OPDRA CONSULT #: 00-0029

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

THROUGH: Kalyani Bhatt, Project Manager
HFD-540

PRODUCT NAME: Olux (clobetasol propionate foam, 0.05%) NDA #: 21-142	MANUFACTURER: Connetics Corporation 3400 West Bayshore Road Palo Alto, CA 94303

SAFETY EVALUATOR: Carol Pamer, R.Ph.

SUMMARY: In response to a consult from the Division of Dermatologic and Dental Drug Products (HFD-540), OPDRA conducted a review of the proposed proprietary name "Olux" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: From a safety perspective, OPDRA has no objections to the use of the name Olux". We have made recommendations for labeling revisions, which are consistent with a previous consult completed for NDA 20-934, Luxiq (betamethasone valerate foam, 0.12%)

/S/ 3/28/2000

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/ 3/29/00

Peter Honig, M.D.
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Postmarketing Drug Risk Assessment (OPDRA)

HFD-400; Parklawn Building Room 15B-03

FDA Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: March 23, 2000

NDA NUMBER: 21-142

NAME OF DRUG: Olux (clobetasol propionate foam, 0.05%)

NDA HOLDER: Connetics Corporation
3400 West Bayshore Road
Palo Alto, CA 94303

I. INTRODUCTION

This consult was written in response to a request from the Division of Dermatologic and Dental Drug Products (HFD-540) for assessment of the proprietary name Olux.

Olux (clobetasol propionate foam, 0.05%) is a topical corticosteroid product. This product is indicated for the short-term treatment of inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses of the scalp. Treatment should be limited to 2 weeks or less and with use of no more than 50 grams per week. Use in children under 12 years of age is not recommended. The usual dosage is twice daily application, once in the morning and once at night. The foam is supplied in a 100-gram aerosol can.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which sound alike or look alike to Olux to a degree where potential confusion between drug names could

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[i] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[ii] American Drug index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.

[iii] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[iv] Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-99, and the electronic online version of the FDA Orange Book.

occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[v]. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three (3) prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

A group discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name Olux. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

With regard to Olux, there were no product names identified that had significant look-alike or sound-alike properties to this name. However, as with a previous review concerning another Connetics topical foam product (Luxiq, NDA 20-934, dated 2/10/2000), there was a concern raised regarding the use of the nomenclature " " for the following reasons:

" *sounds and looks like the drug product name Vioform™*, an OTC product currently marketed by Novartis. Vioform is an antifungal cream and ointment with the active ingredient of 3% Clioquinol (iodochlorhydroxyquin). In accordance with 21 CFR 201.10 (c) (5), the labeling of a drug may be misleading if the proprietary name, designating a drug or ingredient, is similar in spelling or pronunciation of another proprietary name. In addition, 201.10(c)(4) states that the featuring in the labeling of inert or inactive ingredients in a manner that creates an impression of value greater than their true functional role in the formulation may be misleading.

B. STUDY CONDUCTED BY OPDRA

1. Methodology

A study was conducted within FDA employing a total of 91 health care professionals (nurses, pharmacists, physicians) to determine the degree of confusion of Olux with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote inpatient orders and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for (see below). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

[v] WWW location http://www.uspto.gov/tmdb/index.html.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTIONS
Outpatient: Olux, Apply to scalp QD, #1, No refills	*Outpatient*: Olux, apply to scalp everyday. Dispense one, no refills.
Inpatient: Discharge pt home today Olux Apply to scalp QD	

2. Results

Results of this exercise are summarized below:

Study	No. of participants	# of responses (%)	"Olux" response	Other response
Written: Outpatient	31	19 (61%)	17 (89%)	2 (11%)
Inpatient	31	16 (52%)	15 (94%)	1 (6%)
Verbal: Outpatient	29	12 (41%)	9 (75%)	3 (25%)
Total	91	47 (52%)	41 (87%)	6 (13%)

Among participants in the two written prescription studies, the majority of the respondents (91%) provided the correct spelling of the drug name. The other responses were generally phonetic variations of the name "Olux".

Among the verbal prescription study participants, the majority of the respondents (75%) interpreted the name correctly. The other name interpretations were generally phonetic variations of "Olux".

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Olux", the primary concerns raised were related to the use of the drug vehicle name, [redacted] which has strong look-alike and sound-alike properties as compared with Vioform, a currently marketed OTC antifungal product.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the container label, carton labeling, and draft package insert for Olux, OPDRA has attempted to focus on safety issues relating to possible medication errors, but we have also completed a regulatory review of the labeling. We have identified several areas of possible improvement, in the interest of minimizing potential user error.

A. GENERAL COMMENT

OPDRA has some safety concerns surrounding the use of the term [redacted] and a currently marketed OTC product named "Vioform" (see comments above).

B. CONTAINER LABEL

1. Please note that the "ASHP Guidelines on Preventing Medication Errors in Hospitals", Am J Hosp. Pharm, Vol. 50, Feb 1993, notes that important information such as drug name and strength should have the greatest prominence. *"Olux" and the established name* should be relocated to appear more central on the label and its prominence should be increased.

2. 21 CFR 201.10 states "the established name shall be in letters that are at least ½ as large as the

letters comprising the proprietary name and shall have a prominence with such proprietary name". Although it would appear that the established name meets this requirement, we recommend the *prominence of the established name,* and especially the phrase "foam 0.05%", be increased and revised to appear in the same font and appearance as Olux on all labels and labeling.

3. The " [redacted] " which appears over the majority of the primary panel may be confused with a Controlled Substance Symbol (C) which is overlayed on scheduled drugs as required by the DEA.

4. The *"Rx Only"* statement should be moved to the primary display panel, because there is plenty of room and that is the Agency preference.

5. In accordance with 21 CFR 201.100(b)(1) all *inactive ingredient names* must be listed on the label if the product is not for oral use. The firm should be advised to list them on the label in alphabetical order.

6. The *net quantity statement* should not have greater prominence than the product strength. We recommend that the prominence of the product strength be increased and that the net quantity not be highlighted.

B. CARTON AND PACKAGE INSERT LABELING

See comments above, as applicable.

APPEARS THIS WAY
ON ORIGINAL

IV. RECOMMENDATIONS

A. From a safety perspective, OPDRA has no objections to the use of the proprietary name "Olux". However, we do not recommend the use of ' [redacted] ' nomenclature and offer recommendations on labeling revisions.

B. OPDRA recommends the above labeling revisions that might lead to the safer use of the product.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Carol Pamer, R.Ph. at 301-827-3245.

[redacted]

Carol Pamer, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

/S/ 3/28/2000

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

cc: NDA 21-142
HFD-540; Division Files/Kalyani Bhatt, Project Manager
HFD-540; Jonathan Wilkin, Division Director
HFD-040; Mark Askine, Senior Regulatory Review Officer, DDMAC
HFD-430; Marilyn Pitts, Safety Evaluator, OPDRA
HFD-400; Carol Pamer, Safety Evaluator, OPDRA
HFD-400; Peter Honig, Director, OPDRA (electronic copy)
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-002; Murray Lumpkin, Deputy Center Director for Review Management (electronic copy)

ATTACHMENT 2

ESTABLISHMENT EVALUATION REPORT

COPY OF THE 483 CITATION ISSUED TO CCL PHARMACEUTICAL

APPEARS THIS WAY
ON ORIGINAL

FDA, Dallas District Office

U. S. Activities Branch, HFR-SW150
3310 Live Oak Street, Dallas, Texas 75204
(214) 655-5310 phone
(214) 655-5200 fax

Fax Cover Sheet

Date:	4/19/00
To:	Dr. Turnjman - Chemist Reviewer
Fax #:	(301) 827-2075
From:	Thomas J. Frisby
Ext:	527
Total number of pages/cover sheet:	18

☑ As discussed ☐ FYI ☐ Urgent ☐ As requested ☐ Confidential

Comments: If you have any questions or comments, please feel free to call.

S

ATTACHMENT 3

ESTABLISHMENT EVALUATION REPORT

COPY OF SUMMARY REPORT

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21142/000
Stamp: 29-JUL-1999 Regulatory Due: 29-MAY-2000
Applicant: CONNETICS
3400 WEST BAYSHORE RD
PALO ALTO, CA 94303

Priority: S Org Code: 540
Action Goal: District Goal: 30-MAR-2000
Brand Name: OLUX FOAM 0.05% (CLOBETASOL PROPIONATE)
Established Name:
Generic Name: CLOBETASOL PROPIONATE
Dosage Form: ———
Strength: 0.05%

FDA Contacts:

K. BHATT	(HFD-540)	301-827-2020	, Project Manager
S. TURUJMAN	(HFD-540)	301-827-2085	, Review Chemist
W. DECAMP II	(HFD-540)	301-827-2041	, Team Leader

Overall Recommendation:

ACCEPTABLE on 18-MAY-2000 by P. ALCOCK (HFD-324) 301-827-0062

Establishment: 9611933
CCL INDUSTRIES LTD
WA7 1NU
RUNCORN, CHESHIRE, UK

DMF No: ———
AADA No:

Profile: ADM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 18-MAY-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Establishment: ———
———

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 30-MAR-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities:

Establishment: ———
———

DMF No: ———
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 31-AUG-1999

Responsibilities: ———
———

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

DRUG SUBSTANCE STABILITY TESTER

Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT 4

ESTABLISHMENT EVALUATION REPORT

COPY OF COMMENTS OF DISTRICT OFFICE AND OFFICE OF COMPLIANCE

APPEARS THIS WAY
ON ORIGINAL

1ENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: May 11, 2000

To: NDA 21-142

From: Saleh A. Turujman, Ph.D.
Review Chemist, HFD-540

Through: Wilson H. DeCamp, Ph.D.
Chemistry Team Leader, HFD-540

Subject: Addendum # 2 to Chemistry Rev # 2

The following issues were identified in the labeling meeting of May 8, 2000:

1. The section in "DOSAGE AND ADMINISTRATION" fails to clarify how the patient would ascertain that the recommended dosage (3.5 g) was dispensed from the can in the absence of an analytical balance. The applicant should be requested to propose a simple way for the patient to determine when the recommended dosage is dispensed. One possibility would be by the volume of foam dispensed. In such a case the amount could be approximated by an easily recognized object, such as the size of a golf ball.

2. The proposed color and pattern on the carton and container (can) of Olux foam are identical to those of Luxiq foam, which might cause inadvertent mix ups if the two products were stored side-by-side. The applicant should be requested to provide a distinguishing feature that would avert such a mix-up.

/S/ 5/11/00
Saleh A. Turujman, Ph.D.
Review Chemist

cc: Orig. NDA 21-142
HFD-540/Division File
HFD-540/DivDir/JWilkin
HFD-540/SATurujman/5/11/00
HFD-540/MO/MOkun
HFD-540/Pharm/PBrown
HFD-540/Micro/DReiley
HFD-540/PM/KBhatt
HFD-540/ChemTmLdr/WHDeCamp WHDC 5/11/00

C:\DATA\TURUJMAN\REVIEWS\NDA\ADDENDUM TO 21142 REV #2..DOC

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: May 2, 2000

MAY 2 2000

To: NDA 20-934/SLR-001 (Luxiq Foam) file; NDA 21-142 (Olux Foam) file

From: Wilson H. DeCamp, Ph.D.
Chemistry Team Leader, HFD-540

Subject: Consistency of labels and labeling

This memorandum provides expansion and clarification for NDA 20-934/SLR-001 (chemist's review #1, dated 12/17/1999, and addendum dated 2/8/2000) and NDA 21-142 (chemist's review #2, dated 4/20/2000).

Dr. Turujman, Mr. Pappas, and I have reviewed the carton, container label, and package insert for the above products for consistency. With a minor change, as follows, the Description and How Supplied sections of the package insert are now consistently worded between the products:

1. the phrase "for topical dermatologic use" should be restored to the first sentence of Description

The cartons and container labels (as submitted on 2/7/2000 for Olux Foam, and 11/5/199 and 1/11/2000 for Luxiq Foam) should be further revised to eliminate the word ——— from the icon at the bottom of the carton and label. We concur with the 2/15/2000 consult from OPDRA, which states that the use of this word is potentially misleading.

We also recommend that consideration be given to whether the use of identical size, background color, and general design for the cartons may contribute to the potential for product confusion in dispensing.

/S/

cc:
NDA 20-934/SLR-001
NDA 20-142
HFD-540/Division file (NDA 20-934/SLR-001; NDA 20-142)
HFD-540/Wilkin
HFD-540/Pappas EDP 5/2/00
HFD-540/Turujman SAT 5/2/00
HFD-540/Walker
HFD-540/Okun
HFD-540/Jacobs
HFD-540/Bashaw
HFD-540/Bhatt
HFD-540/Cintron
HFD-540/Huene
HFD-540/Brown

IENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: April 24, 2000

To: NDA 21-142

APR 24 2000

From: Saleh A. Turujman, Ph.D.
Review Chemist, HFD-540

Through: Wilson H. DeCamp, Ph.D.
Chemistry Team Leader, HFD-540

Subject: Addendum to Chemistry Rev # 2

Attachments 1, 2 and 3 in chemistry review #2 (NDA 21-142 OLUX Foam) were the version of the labeling provided on a floppy disk in the original submission dated July 28, 1999, and not the modified version provided in the amendment dated February 4, 200. As stated under "Consults" on page 2 of Chemistry Review # 2, the applicant had withdrawn the icon in the amendment. All other comments apply. A copy of the modified labeling is attached

/S/ 4/24/00

Saleh A. Turujman, Ph.D.
Review Chemist

cc: Orig. NDA 21-142
HFD-540/Division File
HFD-540/DivDir/JWilkin
HFD-540/SATurujman/4/24/00
HFD-540/MO/MOkun
HFD-540/Pharm/PBrown
HFD-540/Micro/DHussong
HFD-540/PM/KBhatt
HFD-540/ChemTmLdr/WHDecamp WD 4/24/00

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Number of Pages Redacted 6

❖❖❖

Draft Labeling
(not releasable

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21142/000
Stamp: 29-JUL-1999 Regulatory Due: 29-MAY-2000
Applicant: CONNETICS
3400 WEST BAYSHORE RD
PALO ALTO, CA 94303

Priority:
Org Code: 540
Action Goal:
District Goal: 30-MAR-2000
Brand Name: OLUX FOAM 0.05% (CLOBETASOL PROPIONATE)
Established Name:
Generic Name: CLOBETASOL PROPIONATE
Dosage Form: ———
Strength: 0.05%

FDA Contacts:			
K. BHATT	(HFD-540)	301-827-2020	, Project Manager
S. TURUJMAN	(HFD-540)	301-827-2085	, Review Chemist
W. DECAMP II	(HFD-540)	301-827-2041	, Team Leader

Overall Recommendation:

Establishment: 9611933
CCL INDUSTRIES LTD
9 ARKWRIGHT RD WA7 1NU
RUNCORN, CHESHIRE, UK

DMF No: ———
AADA No:

Profile: NEC OAI Status: NONE
Last Milestone: SUBMITTED TO OC
Milestone Date: 31-AUG-1999

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Establishment: ———
———

DMF No: ———
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: SUBMITTED TO OC
Milestone Date: 31-AUG-1999

Responsibilities: ———
———
———

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION

(Division/Office)			FROM:	
HFD-160 Peter Cooney			Kalyani Bhatt HFD-540	
DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
8-11-99		21-142	New NDA	July 29, 1999
NAME OF DRUG		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Clobetasol Propionate Foam		—		
NAME OF FIRM				
Connetics				

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☑ OTHER *(Specify below)*
  New NDA

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL– BIOPHARMACEUTICS
- ☐ IN–VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)*
- ☐ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*

Please review for filability purpose. The filing meeting will be on August 31, 1999 @ 10:00AM (Rm N225) Cooperate Office. Please let me know who will be the reviewer of this NDA.

SIGNATURE OF REQUESTER S	METHOD OF DELIVERY *(Check one)* ☑ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

connetics® CORPORATION

ORIGINAL

NEW CORRESP
NC

October 29, 1999

Ms. Kalyani Bhatt
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products
9201 Corporate Boulevard, HFD – 540
Rockville, MD 20850

Re: NDA #21-142 (Clobetasol Propionate Foam, 0.05%)
Clinical Site Audits

Dear Kalyani:

Pursuant to the advice of Dr. Jose Carreras in the Division of Scientific Investigations, attached is a copy of the cover letter from the submission we sent to him regarding the clinical site audits for the above-mentioned NDA. Dr. Carreras advised us to send the submission directly to him (without going through Document Control) and to send a copy of the cover letter to our NDA file.

Please do not hesitate to call me at (650) 843-2809 if you have any questions regarding this submission.

Sincerely,

Dawn Parsell

Dawn Parsell, Ph.D.
Associate Director
Regulatory Affairs

Enc.

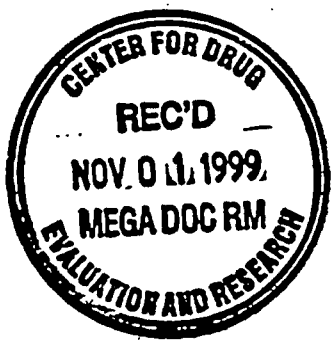
3400 West Bayshore Road • Palo Alto, CA 94303 • USA • Telephone: (650) 843-2800 • Facsimile: (650) 843-2899

Connetics® CORPORATION

ORIGINAL

ORIG AMENDMENT
BC

October 27, 1999



Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic & Dental Drug Products
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA #21-142 OLUX™
(clobetasol propionate) Foam, 0.05%

Correction of Clerical Errors in Stability and Validation Reports

Dear Dr. Wilkin:

Since the submission of the referenced NDA on July 28, 1999, several clerical errors have been corrected in the stability report data tables presented in Section 4.A.2.i (6) (pages 04-0329 to 04-0429) and three analytical method validation reports presented in Section 4.A.2.h (3) (pages 04-0271 to 04-0328). The following information is provided to the NDA for completeness and clarity.

Stability report data tables (Section 4.A.2.i (6))

The revised data tables with the corrections highlighted and bolded are provided in Attachment 1. Only the tables with corrections are included. All other tables are correct as submitted in the NDA. None of the corrections alter any of the conclusions of the report.

Since corrections were made to the data that are used in the regression analyses for Clobetasol Propionate Content (Table 10) (page 04-0358), the analyses were repeated. The revised graphs are also provided in Attachment 1. The re-analyses did not alter the conclusions.

Analytical method validation reports (Section 4.A.2.h (3))

Clerical errors were also found in three validation reports:

- Validation report for the HPLC assay of clobetasol-17-propionate
- Validation report for the HPLC assay of the related substances of clobetasol-17-propionate
- Cross validation report for the determination of ethanol content in clobetasol foam mousse

Attachment 2 provides the amended reports, with the specific corrections noted on the first page of each report (Reason for Amendment). The corrections do not alter any of the conclusions of the validation reports.

(650) 843-2800 • Facsimile: (650) 843-2899

4.1
10/27/99
FORM FDA 356h
ATTACHMENT 1
ATTACHMENT 2

If you have any questions regarding this submission, please contact Dawn Parsell at (650) 843-2809 or me at (650) 843-2889.

Sincerely,

Claire J. Lockey
Vice President
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: October 20, 1999

Number of Pages (including cover sheet) - 2

TO: Claire J. Lockey/Dawn Parsell
COMPANY: Connetics Corporation
FAX #: 1-650-8432899

MESSAGE: Please find information request from the Biopharmaceutic Reviewer for your original NDA 21-142 Olux Foam (clobetasol propionate) submitted July 29, 1999.

FROM: Kalyani Bhatt,
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

Please find comments as follows:

1.) In our review of study CPCD.C.003 (i.e. the HPA axis suppression study) in NDA 21-142 we have come to realize that you have not supplied the individual plasma cortisol levels (pre- and post-stimulation) but only the differences in pre- and post-stimulation (i.e., the "deltas").

2.) Please provide the individual pre- and post-stimulation cortisol levels from both study entry and study exit, upon which you base your study conclusions. This information should be provided as soon as possible as it has a direct impact on the approvability of this application.

connetics

FACSIMILE TRANSMISSION SHEET

Date: October 20, 1999

To: Kaylani Bhatt
Division of Dermatologic & Dental Drug Products

Fax: (301) 827-2075

From: Dawn Parsell

Subj: Clobetasol Propionate Foam, 0.05% (NDA #21-142)

No. of pgs. (3) including transmission sheet

Dear Kalyani,

As requested by Dr. Bashaw, here are copies of pages 08-1887 and 08-1888 of our NDA #21-142. If you have any further questions regarding this data, please do not hesitate to contact me at (650)843-2809.

Best Regards,

Dawn

Dawn Parsell, Ph.D.
Associate Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

3400 W. Bayshore Road, Palo Alto, CA 94303. Telephone (650) 843-2800. Fax (650) 843-2899.

Number of Pages Redacted 2

❖❖❖

Confidential,
Commercial Information

connetics

FACSIMILE TRANSMISSION SHEET

Date: October 4, 1999

To: Kaylani Bhatt
Division of Dermatologic & Dental Drug Products

Fax: (301) 827-2075

From: Dawn Parsell

Subj: Clobetasol Propionate Foam, 0.05% (NDA #21-142)
Copy of Financial Disclosure Information Submitted in Amendment 3.1 (9/27/99)

No. of pgs. (7) including transmission sheet

Dear Kalyani,

The following is a copy of the cover letter and Attachment 1 of our September 27, 1999 submission to NDA 21-142, containing the information requested by the Agency regarding financial disclosure of investigators. Please call me if you have any further questions about this submission.

Best Regards,

Dawn Parsell

Dawn Parsell, Ph.D.
Associate Director, Regulatory Affairs

3400 W. Bayshore Road, Palo Alto, CA 94303. Telephone (650) 843-2800. Fax (650) 843-2899.

connetics®
CORPORATION

September 27, 1999

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic & Dental Drug Products
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

CMC AMENDMENT
BS

RE: NDA #21-142 OLUX™
(clobetasol propionate) Foam, 0.05%

Response to Agency's Request for Information

- **Administrative**
- **Transfer of Data**

Dear Dr. Wilkin:

The following is Connetics' response to the Agency's request (dated September 2, 1999) for the following two items:

1. Administrative information regarding the financial disclosure of the clinical investigators who participated in the clinical studies that were submitted to the above-mentioned NDA.

2. Transfer of data from the Phase III study (Protocol CPCD.C.002).

1. <u>Administrative:</u> (For ease of review, the Agency's comments are in bold and our response follows.)

Financial Disclosure:

Please report proprietary interests and compensation affected by the outcome of the clinical studies. The Sponsor is referred to page 72173 of the December 31, 1998, amendment to the rule, for requirements for investigators participating in clinical studies, whether they are ongoing or completed, if the studies are to be used to support applications that are submitted on or after February 2, 1999.

Pursuant to a discussion with Linda Carter, Associate Director, Regulatory Affairs, Office of Drug Evaluation I, appended in Attachment 1 are financial disclosure statements regarding the following:

- compensation affected by the outcome of the clinical studies;
- proprietary interests in clobetasol propionate foam, 0.05%.

2. **Transfer of Data:** (Request from FDA Division of Biometrics)

Appended in Attachment 2 is an electronic copy (two diskettes) of the reformatted data from the Phase III study (Protocol CPCD.C.002). As agreed to with the Agency, the data presented in our Demographics and Efficacy data sets have been merged to create a new data set (1), and the data presented in our Adverse Event and Vital Signs data sets have been merged to create a new data set (2). No laboratory results are included in the Safety data set. Hard copies of the User's Guides, Contents Procedures, Description of Datasets, Data Formats, and List of SAS Programs are also included in Attachment 2.

If you have any questions regarding this submission, please contact Dawn Parsell at (650) 843-2809 or me at (650) 843-2889.

Sincerely,

Claire J. Lockey
Vice President
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

New Drug Application #21-142

Connetics Corporation

Clobetasol Propionate Foam, 0.05%

FINANCIAL DISCLOSURE STATEMENT

Pursuant to 21 CFR §54.4, I hereby certify that it is the policy of Connetics Corporation that no clinical investigator will be granted financial compensation [as defined in 21 CFR §54.2(a)] whereby the value of the compensation could be influenced by the outcome of the study, such as compensation that is explicitly greater for a favorable result or compensation to the investigator in the form of an equity interest in Connetics Corporation or in the form of compensation tied to sales of the product, such as a royalty interest.

Thomas G. Wiggans
President and Chief Executive Officer

9/16/99
Date

APPEARS THIS WAY
ON ORIGINAL

New Drug Application #21-142

Connetics Corporation

Clobetasol Propionate Foam, 0.05%

FINANCIAL DISCLOSURE STATEMENT

Pursuant to 21 CFR §54.4, Connetics Corporation certifies to the best of its knowledge that none of the investigators who participated in the three clinical studies submitted in this NDA have a proprietary interest [as defined in 21 CFR §54.2(c)] in clobetasol propionate foam, 0.05%, such as a patent, trademark, copyright, or licensing agreement.

Katrina J. Church
Vice President
Legal Affairs and Corporate Counsel

17 Sept 99
Date

APPEARS THIS WAY
ON ORIGINAL

NEW DRUG APPLICATION #21-142

CLOBETASOL PROPIONATE FOAM, 0.05%

3.1 Response to Request for Information

Connetics Corporation
3400 West Bayshore Road
Palo Alto, CA 94303

(650) 843-2800
Fax: (650) 843-2899

Date: September 27, 1999

Attachment 1

Financial Disclosure of Clinical Investigators:

Pursuant to the December 31, 1998, Federal Register amendment to the rule, the following two financial disclosure statements are attached:

- a statement regarding compensation affected by the outcome of the clinical studies; and
- a statement regarding the proprietary interests in clobetasol propionate foam, 0.05%.

APPEARS THIS WAY
ON ORIGINAL

FINANCIAL DISCLOSURE STATEMENT

Pursuant to 21 CFR §54.4, I hereby certify that it is the policy of Connetics Corporation that no clinical investigator will be granted financial compensation [as defined in 21 CFR §54.2(a)] whereby the value of the compensation could be influenced by the outcome of the study, such as compensation that is explicitly greater for a favorable result or compensation to the investigator in the form of an equity interest in Connetics Corporation or in the form of compensation tied to sales of the product, such as a royalty interest.

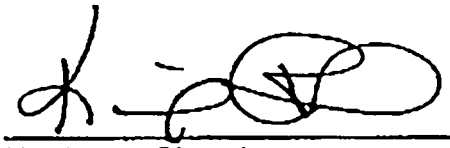
Thomas G. Wiggans
President and Chief Executive Officer

9/16/99
Date

APPEARS THIS WAY
ON ORIGINAL

FINANCIAL DISCLOSURE STATEMENT

Pursuant to 21 CFR §54.4, Connetics Corporation certifies to the best of its knowledge that none of the investigators who participated in the three clinical studies submitted in this NDA have a proprietary interest [as defined in 21 CFR §54.2(c)] in clobetasol propionate foam, 0.05%, such as a patent, trademark, copyright, or licensing agreement.



17 Sept 99

Katrina J. Church
Vice President
Legal Affairs and Corporate Counsel

Date

APPEARS THIS WAY
ON ORIGINAL

Attachment 2

Appended are two diskettes containing the reformatted data from the Phase III efficacy and safety study on clobetasol propionate foam, 0.05% (Protocol CPCD.C.002).

Diskette #1 –

- Word Documents.zip contains 8 MS Word documents:
  1. User's Guide to Raw SAS Database.doc [describes how to convert SAS transport files to.sd2 files]
  2. PROC_CONTENTS_RAW.doc
  3. User's Guide to Analysis SAS Database.doc [describes how to convert SAS transport files to sd.2 files]
  4. PROC_CONTENTS_ANAL.doc
  5. Analysis Files to FDA.doc
  6. Additional Analysis Files.doc
  7. Data Formats.doc [describes the SAS format library file]
  8. List of SAS Programs.doc
- SAS Programs.zip contains all SAS Programs [Refer to List of SAS Programs.doc as a guide]

Diskette #2 –

- SASDATA_002.zip – contains the raw .sd2 SAS data and formats .sc2 files
- RAW Transport.zip – contains the SAS transport file (SASDATA.xpt) of the raw data [Refer to User's Guide to Raw SAS Database.doc as a guide]
- ANALDATA_002.zip – contains the analysis .sd2 SAS data and formats .sc2 files
- ANAL Transport.zip – contains the SAS transport file (ANALDATA.xpt) of the analysis datasets [Refer to User's Guide to Analysis SAS Database.doc as a guide]

Also appended are hard copies of the following:

1. User's Guide to Raw SAS Database
2. PROC_CONTENTS_RAW
3. User's Guide to Analysis SAS Database
4. PROC_CONTENTS_ANAL
5. Description of Datasets for FDA Requested Analysis Files(DEMO_EFF and SAFETY)
6. Description of Datasets of Additional Analysis File (LABS_AN)
7. Data Formats
8. List of SAS Programs (Ref

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 21-142 Supplement # ________ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade (generic) name/dosage form: clobetasol propionate Action: AP AE NA

Applicant Connetics Corp. Therapeutic Class 3S

Indication(s) previously approved ________

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application Short-term topical treatment of the inflammatory & pruritic manifestations of moderate to severe corticosteroid responsive dermatoses of the scalp.

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing.

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed. under the age of 12 years of age for short-term topical treatment of the inflammatory & pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses of the scalp. (see attached [illegible])

___ 4. EXPLAIN. If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

/S/

Signature of Preparer and Title (PM, CSO, MO, other) 5-23-00 Date

cc: Orig NDA/PLA # 21-142 Please Refer to Addendum to M.O. Review dated 5-15-

HFD-540 /Div File

NDA/PLA Action Package

HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling) /S/ 5/24/

NOTE: A new Pediatric Page must be completed at the time of each action even though one was

21 CFR §314.50(d)(7) and 21 CFR §314.55 - Pediatric Study Requirement (Effective 4/1/99)

Connetics requests a full waiver, per 21 CFR §314.55(c)(2), of the requirement that this application contain data that are adequate to assess the safety and efficacy of clobetasol propionate foam, 0.05% (Clobetasol foam) for the treatment of moderate to severe corticosteroid-responsive dermatoses of the scalp in all relevant pediatric sub-populations, and to support dosing and administration for each pediatric sub-population for which the drug is safe and effective. This request for full waiver of the pediatric assessment [21 CFR §314.55(a)], is pursuant to 21 CFR §314.55(c)(2)(i) in that Clobetasol foam, a) does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients; and b) is not likely to be used in a substantial number of pediatric patients.

a) Clobetasol Foam Does Not Represent a Meaningful Therapeutic Benefit Over Existing Treatments for Pediatric Patients

Treatment of moderate to severe dermatoses of the scalp usually involves the use of super-high-potency corticosteroids. Currently, there are three corticosteroids classified as super-potent: halobetasol propionate, bethametasone dipropionate and clobetasol propionate. All three compounds are marketed in both cream and ointment formulations. Additionally, betamethasone dipropionate and clobetasol propionate are marketed in gel and lotion form, and clobetasol propionate as an emollient cream. Except for halobetasol propionate, numerous generic versions of these products are also available commercially. All of these products are labeled for use in children 12 years of age or older; use in children under the age of 12 years is not recommended. Therefore, when faced with treatment of pediatric patients with stubborn dermatoses not effectively controlled by steroids of lower potency, a practitioner has access to at least 11 super-high-potency corticosteroid products that are already labeled for use in children 12 years or older.

Furthermore, the data obtained from the clinical studies presented in this NDA (Section [8]) show that Clobetasol foam is as safe and effective as other marketed clobetasol products, but does not represent a meaningful therapeutic benefit over existing treatment for pediatric patients with moderate to severe dermatoses of the scalp.

b) Clobetasol Foam is Not Likely to be Used in a Substantial Number of Pediatric Patients

The Agency has defined the following pediatric age groups:

- Neonate birth to 1 month
- Infant 1 month to 2 years
- Child 2 to 12 years
- Adolescent 12 to < 16 years

Pediatric Ages Birth to 12 Years

All marketed clobetasol propionate products are labeled for use only in individuals 12 years of age or older, with use in children under the age of 12 years not recommended. The "Precautions, Pediatric Use" section of the Clobetasol foam Package Insert will include the same restrictions.

Pediatric Ages 12 to < 16 Years

In the preamble to the Final Rule entitled, "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients" (Federal Register, December 2, 1998, pp. 66632-66672), the Agency defines a substantial number of pediatric patients as 50,000 with the disease or condition for which the drug or biological product is indicated.

We were unable to locate a direct data source to assess the number of patients, ages 12 to 16, with moderate to severe dermatoses of the scalp, but we were able to obtain, through The Physician Drug & Diagnosis Audit database, the number of patients, ages 12 through 18 who visited a physician in 1998 and were prescribed super-high-potency corticosteroids. Since super-high-potency corticosteroids are normally used to treat moderate to severe dermatoses, these numbers were interpreted to represent the population of pediatric patients with these conditions. This information is provided in Table 1.

Table 1: Estimated Number of Patients That Received Super-High-Potency Corticosteroids in 1998

Condition	Uses Age 12-18 yr
Psoriasis	13,000
Seborrheic Dermatitis	---
Atopic Dermatitis	12,000
Dermatitis NOS*	30,000
Total	55,000

*NOS is not otherwise specified.

Our information did not provide data on the site of the disease and a breakdown of pediatric patients with scalp involvement was unavailable. However, the National Psoriasis Foundation (NPF) has estimated that approximately 50% of all patients with psoriasis have some involvement of their scalp (www.psoriasis.org). Extrapolating the NPF estimate to other dermatoses, the total number of pediatric patients treated with a super-potent corticosteroid for scalp dermatoses would be 27,500; this number is below the 50,000 pediatric patients required for a waiver.

This waiver application encompasses only the pediatric population defined by the Agency as adolescents (12 to < 16 years). However, the data sources referenced above define the adolescent population as 12 to 18 years old. Therefore, our patient numbers are higher than would be represented in the Agency's defined age group.

We believe that the above information supports a full waiver of the requirement to provide safety and effectiveness data in the relevant pediatric population.

Clinical - Phyllis Huene

45 DAY MEETING CHECKLIST

NDA 21-142
Olux foam 0.05%

FILEABILITY:

On initial overview of the NDA application: ..... YES

CLINICAL:

1. On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin? ..... YES

2. Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin? ..... YES

3. On its face, is the clinical section of the NDA legible so that substantive review can begin? ..... YES

4. If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product (i.e., appropriately designed dose-ranging studies?) ..... NA

5. On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? ..... YES

Application Type: 505(b)(2).
Reference drug: Clobetasol solution

Pivotal trial: Study CPCD.C.002

Page location in NDA: as follows.

Protocol: Vol 8, page 0440
Study report: Synopsis: Vol 7, page 0035
Full report: Vol 8, page 0345

Is this an adequate multi-centered trial? ..... YES

Center	Patients enrolled
	16
	17
	14
	18
	9
	18
	18
	18
	18
	18
	12
	12
Total	188

Study Title: A Double-Blind, Active and Placebo controlled Study of the Safety and Efficacy of Clobetasol Propionate Foam in Treating Scalp Psoriasis.

Study design: Randomized, double blind, placebo controlled, multicentered.

Indication: Scalp psoriasis

Study arms:

Study CPCD.C.002		
Treatment and dosage	Duration	# pts
Clobetasol foam 0.05% Up to 3.5 gm BID	14 days	62
Clobetasol solution 0.05% Up to 3.5 ml BID	14 days	63
Vehicle foam Up to 3.5 gm BID	14 days	31
Vehicle solution Up to 3.5 ml BID	14 days	32

Efficacy endpoints: as follows.

Primary efficacy variable: Treatment Success at day 15 - defined as an Investigator's Global Assessment of clear or almost clear, a plaque thickness score of 0, a scaling score of 0 or 1 and an erythema score of 0 or 1.

Secondary efficacy variables: the changes from baseline in the scores for erythema, scaling, plaque thickness and pruritus, and the patient and investigator global assessment.

How measured: Grading scales were as follows.

Grading scale for plaque thickness	
Score	Description of response
0	No plaque elevation
1	Slight, barely perceptible elevation
2	Definite elevation, but not thick
3	Definite elevation, thick plaque with sharp edge
4	Very thick plaque with sharp edge

Grading scale for scaling	
Score	Description of response
0	No scaling
1	Sparse fine scale, lesions only partially covered
2	Coarser scales, most of lesions covered
3	Entire lesion covered with coarse scales
4	Very thick, coarse scales, possibly fissured

Grading scale for erythema	
Score	Description of response
0	No erythema
1	Faint erythema, pink to very light red
2	Definite light red erythema
3	Dark red erythema
4	Very dark red, 'beefy' erythema

Grading scale for pruritus	
Score	Description of response
0	No pruritus
1	Occasional pruritus, barely noticeable
2	More frequent pruritus, not troublesome
3	Frequent and sometimes troublesome pruritus; sleeps OK
4	Frequent, troublesome pruritus; interferes with sleep and/or other activities