CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-801

CHEMISTRY REVIEW(S)

NDA 21-709

Evoclin (clindamycin phosphate) Foam, 1%

Connetics Corporation

Saleh A. Turujman, Ph.D.
Division of Dermatologic and Dental Drug Products
HFD-540/830

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-709

2. REVIEW #: 1

3. REVIEW DATE: 18 October 2004

4. REVIEWER: Saleh A. Turujman, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original submission NDA 21-709	December 24, 2003
21-709/N-000 BL	5 May 2004
21-709/N-000 BL	6 August 2004
21-709/N-000 BL	13 September 2004
21-709/N-000 BL	17 September 2004
21-709/N-000 BL	20 September 2004
21-709/N-000(BC)	13 October 2004
21-709/N-000(BC)	14 October 2004
21-709/N-000(BC)	15 October 2004
21-709/N-000 BL	18 October 2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission NDA 21-709	December 24, 2003
21-709/N-000 BL	5 May 2004
21-709/N-000 BL	6 August 2004
21-709/N-000 BL	13 September 2004
21-709/N-000 BL	17 September 2004
21-709/N-000 BL	20 September 2004
21-709/N-000(BC)	13 October 2004
21-709/N-000(BC)	14 October 2004
21-709/N-000(BC)	15 October 2004
21-709/N-000 BL	18 October 2004

Chemistry Review Data Sheet
NDA 21-709

7. NAME & ADDRESS OF APPLICANT:

Name:	Connetics Corporation
Address:	3290 West Bayshore Road Palo Alto, CA 94303
Representative:	Sharon Hall,Senior Director, Regulatory Affairs
Telephone:	(650) 843-2860

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Evoclin Foam (proposed names: Evoclin is acceptable, no DMETS decision on Luclere to date, see table under item 18 below)
b) Non-Proprietary Name (USAN): Clindamycin phosphate Foam
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) application; 21 CFR 314.54; Listed drug: Clindagel® (clindamycin phosphate gel).

10. PHARMACOL. CATEGORY: Antibiotic

11. DOSAGE FORM: Foam

12. STRENGTH/POTENCY: 1%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

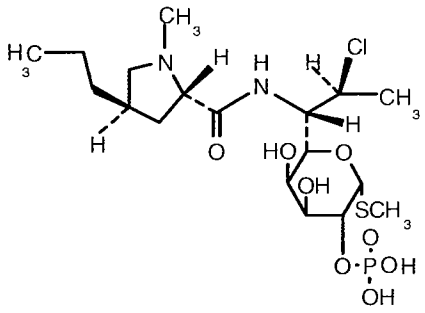
__X__Not a SPOTS product

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

The chemical name is methyl-7-chloro-6,7,8-trideoxy-6-(1-methyl-4-*trans*-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*threo*-α-D-*galacto*-octopyranoside 2-(dihydrogen phosphate)

Chemistry Review Data Sheet
NDA 21-709

Molecular Formula: $C_{18}H_{34}ClN_2O_8P_8S$
Molecular Weight: 504.97
CAS number: 24729-96-2.
The chemical structure is shown below.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	September 8, 2003	
	III			3	Adequate	November 7, 2002	

[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 TYPE	APPLICATION NUMBER	HOLDER	DESCRIPTION
IND	64,577	Connetics Corporation	Clindamycin Phosphate Foam, 1%
NDA	21-142	Connetics Corporation	Clobetasol Propionate Foam, 0.05%
NDA	20-934	Connetics Corporation	Betamethasone Valerate Foam, 0.12%

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES* (Drug substance: Clindamycin Phosphate Manufacturer/Packager/ Tester:)	Acceptable	20 February 2004	J. D'Ambrogio
EES* (Drug Product Manufacturer/Packager:)	Acceptable	27 January 2004	J. D'Ambrogio
EES* (Drug Product Tester:)	Acceptable	21 January 2004	J. D'Ambrogio
EES* (Drug Product Tester:)	Acceptable	3 March 2004	J. D'Ambrogio
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Submitted, but will not be forwarded to FDA Labs.		
OPDRA	Initial proposed name: Not Acceptable Second proposed name. , Not Acceptable Evoclin: Acceptable ..... No recommendation to date	20 January 2004 13 July 2004 13 October 2004	Linda Wisniewski, Denise Toyer Linda Wisniewski Kristina C. Arnwine
EA	Categorical Exclusion	N/A	
Microbiology	N/A		

* See Appendix 1 for EES report

The Chemistry Review for NDA 21-709

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommendation for this NDA, is APPROVAL from a chemistry, manufacturing and controls standpoint. The applicant omitted the spray rate, a quality control measure, from the regulatory specification. The applicant has provided a commitment to monitor the spray rate for the first six post-approval batches and to propose an acceptance criterion for the spray rate (based on the results of the study) within a year of the date of the action letter.

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

None recommended.

II. Summary of Chemistry Assessments

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

The active pharmaceutical ingredient (API), clindamycin phosphate, is a compendial antibiotic drug substance, which is used in several formulations approved for marketing such as a sterile solution (NDA 50-441), a topical solution (NDA 50-537), a topical lotion (NDA 50-600), several topical gels (e.g., NDA 50-615, NDA 50-782), and a vaginal cream (NDA 50-680). It has also been approved for bacterial vaginosis in the vaginal suppositories (NDA 50-767). The current application provides for the treatment of acne vulgaris. All dosage forms use the same strength of 1 % clindamycin phosphate proposed by the applicant.

Prescription topical treatments indicated for acne vulgaris include clindamycin (gel, solution, lotion, swab), erythromycin (gel, ointment, solution, swab), azelaic acid cream, benzoyl peroxide gel, benzoyl peroxide and erythromycin gel, benzoyl peroxide and clindamycin gel, tretinoin (gel, cream, solution), adapalene (gel and cream) and tazarotene (gel and cream).

Clindamycin phosphate, a lincosamide, is a synthetic derivative of lincomycin and belongs to the pharmacologic class of acne products. The foam vehicle is a new dosage form for this API. The foam is to be applied once daily to the affected area in patients 12 years of age and older. The applicant proposed the trade names [redacted] but neither was found to be acceptable. The applicant has proposed two additional trade names, [redacted] and Evoclin. Evoclin is acceptable. Consultation with the Division of Drug Medication Errors and Technical Support (DMETS) on the suitability of Luclere is pending at the time of completion of this review.

The applicant, Connetics Corporation, does not own manufacturing or testing facilities. Manufacture, packaging and testing of the drug substance is contracted out to [redacted] and for the drug product to [redacted] The applicant refers most of the chemistry, manufacturing and controls (CMC) information regarding clindamycin phosphate, to Type II DMF [redacted] held by [redacted] Ample CMC information on the drug product is provided in the submission.

Clindamycin Phosphate Foam contains clindamycin phosphate, cetyl alcohol, dehydrated alcohol, polysorbate 60, potassium hydroxide, propylene glycol, purified water, and stearyl alcohol pressurized [redacted] container with a hydrocarbon (propane/butane) propellant. All the excipients are compendial.

Essentially the same foam formulation (vehicle) is used in the proposed clindamycin phosphate drug product as the LUXIQ Foam (betamethasone valerate foam, 0.12%; NDA 20-934) and OLUX Foam (clobetasol propionate Foam, 0.05%; NDA 21-142), both of which are marketed by the applicant. The only difference in formulation (other than the API) is that potassium hydroxide is used as the pH adjuster in the proposed drug product, while citric acid/potassium citrate is used as a buffer (pH adjuster) in both the previously approved foam drug products. The reason of this substitution of pH adjuster is that stability studies conducted by the applicant had indicated that the clindamycin phosphate was unstable in the presence of the potassium citrate/citric acid buffer. By a series of experiments (by varying the amount of potassium hydroxide), it was determined that the product was stable at an apparent pH of 4.5 to 5.5. The formulation target chosen was an apparent pH of 5.

Water functions both as a solvent and moisturizer in this formulation. It dissolves the clindamycin phosphate and the potassium hydroxide, which controls the pH. Anhydrous alcohol (ethanol) is the solvent for the organic phase, which is composed of cetyl alcohol, stearyl alcohol, polysorbate 60 and propylene glycol. Cetyl alcohol maintains the foam characteristics below 15 °C, while stearyl alcohol maintains the foam characteristics above 20 °C. Polysorbate 60 enhances the solubility of cetyl and stearyl alcohols, and enhances foam formation, while propylene glycol acts as moisturizer/humectant. Propylene glycol is also a skin penetrant (a property not mentioned by the applicant in the submission).

The propellant in the proposed drug product is identical to the two marketed drug products. Similarly, the proposed 50 g container/closure system in the current submission is the same in construction, materials and function as the 50 g container/closure system in both marketed drug products, except that the can for the proposed drug product has a liner (see P.2 Pharmaceutical Development for more details). Appropriate extraction studies were conducted to ascertain the suitability of the liner of the can for use with the proposed drug product

[redacted] the proposed drug product manufacturer in this submission, is the approved alternate manufacturer and drug release tester for both marketed drug products.

[redacted]

The submission did not contain a commitment that any production batch that has failed the drug product specification would be withdrawn from the market and reported to the Agency. In response to the Agency's request (Fax on October 12, 2004), the applicant provided the requested commitment (October 13, 2004).

The post approval stability protocol in the submission did not contain a test for ethanol content. The applicant intended to have the ethanol content test conducted only as a release test. However, in common with both approved foam products with the same formulation, LUXIQ Foam and OLUX Foam, both of which are owned by Connetics

Corporation, the ethanol content in clindamycin phosphate foam is, as stated above, a critical component in the foam formulation, and should be monitored through the shelf life of the drug product. The applicant was requested to provide a commitment to include the test for ethanol content in the drug product in the postapproval stability protocol. The applicant provided the requested commitment (October 15, 2004).

The post approval stability protocol and commitments, as amended, were found to be acceptable.

The drug product acquires a slightly yellowish hue to a slight decomposition of polysorbate 60 in the ethanolic phase. This discoloration does not increase on stability and has no apparent effect on the efficacy of the drug product. There are no associated safety concerns.

The sponsor submitted an acceptable claim for categorical exclusion.

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

Clindamycin Phosphate Foam, 1% is a topical antibiotic acne product in an aerosol foam vehicle intended for once daily application for the treatment of acne vulgaris in patients 12 years of age and older. Clindamycin phosphate is the water-soluble ester of clindamycin and phosphoric acid. It has little or no antibacterial effect in vitro, but it is rapidly hydrolyzed both *in vitro* and *in vivo*, to the active compound, clindamycin. The efficacy of clindamycin in the treatment of acne is postulated to lie in its ability to inhibit the growth of *Propionibacterium. acnes*. Overgrowth of *P. acnes* and the ensuing host inflammatory response are believed to be important in the pathogenesis of acne. According to the clinical reviewer, the applicant demonstrated the efficacy of Clindamycin Phosphate Foam, 1%, for the treatment of acne in subjects 12 years of age and older.

The container closure system is designed to dispense the foam from the can in the upright position (unlike Connetics' other approved foam products, OLUX Foam and LUXIQ Foam). The labeling instructions call for the drug product to be applied once daily to the affected areas after the skin is washed with mild soap and allowed to fully dry, and to use enough to cover the entire affected area. The package insert also contains the following specific use instructions:

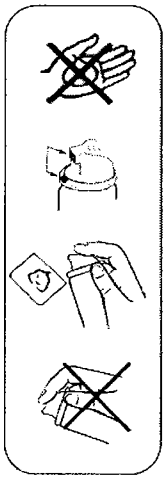
1. Do not dispense "Trademark" directly onto your hands, because the foam will begin to melt on contact with warm skin.
2. Remove the clear cap. Align the black mark with the nozzle of the actuator.
3. Hold the can at an upright angle and then press firmly to dispense. Dispense an amount directly into the cap or onto a cool surface. Dispense an amount of "Trademark" Foam that will cover the affected area(s). If the can seems warm or the foam seems runny, run the can under cold water.

4. Pick up small amounts of "Trademark" Foam with your fingertips and gently massage into the affected areas until the foam disappears.

Throw away any of the unused medicine that you dispensed out of the can.

Avoid contact of Evoclin with eyes. If contact occurs, rinse eyes thoroughly with water.

The following cartoon is provided in the package insert alongside the specific use instructions quoted above.



Connetics proposes an expiration dating period of 24 months, which is supported by 12 months of long-term stability data (25°C/60% RH) and six months of stability data at 40°C/75% RH. The recommended storage and handling conditions on the labeling are:

Store at controlled room temperature 20°-25°C (68° - 77°F).

FLAMMABLE. AVOID FIRE, FLAME OR SMOKING DURING AND IMMEDIATELY FOLLOWING APPLICATION.

Contents under pressure. Do not puncture or incinerate. Do not expose to heat or store at temperature above 120°F (49°C).
Keep out of reach of children.

C. Basis for Approvability or Not-Approval Recommendation

After evaluation for GMP compliance, all manufacturing and testing facilities were found to be acceptable. Clindamycin phosphate, is a well-established chemical whose structure has been fully elucidated. It is characterized through the USP monograph, and listed in USAN and in the Merck Index. The DMF of the main drug substance supplier has been previously reviewed (September 8, 2003) and found to be adequate. The foam

formulation has been successfully used by the applicant in two previously approved drug products (LUXIQ Foam and OLUX Foam. The NDA submission and its amendments (responses to information requests) provide adequate information on the chemistry, manufacturing and controls for the production of Evoclin (clindamycin phosphate) Foam, 1%.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Saleh A. Turujman, Ph.D./18 October 2004
Acting Deputy Division Director/Date: Norman R. Schmuff, Ph.D./
Project Manager: Melinda Harris, MS

C. CC Block

Cc: NDA 21-709
HFD-540/Division File
HFD-540/Chem/SATurujman
HFD-830/ActgDepDivDir/NRSchmuff
HFD-540/ProjMgr/MHarris
HFD-540/MedOff/JLindstrom
HFD-540/Pharm/JMerrill
HFD-540/BioPharm/EBashaw
HFD-540/Biometrics/SThomson

C:\Data\My Documents\turujman\reviews\NDA\NDAs 2004\21-709 Evoclin (clindamycin PO4) Foam 1%\21-709 Evoclin (clindamycin PO4) Foam, 1%\21-709 CMC rev #1.ctd.doc

55 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry Review 1

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

/s/

Saleh Turujman
10/20/04 11:26:09 AM
CHEMIST

For your concurrence

Norman Schmuff
10/20/04 03:11:46 PM
CHEMIST

NDA FILEABILITY CHECKLIST

NDA Number: 21-709 **Drug Name:** —— (clindamycin phosphate) Foam, 1%

Applicant: Connetics Corporation

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

Table 1 Fileability Checklist

The following parameters are necessary for initiating a full review, e.g. complete enough for review but may have deficiencies.

	PARAMETER	YES	NO	COMMENT
1	Is the NDA organized adequately for its CMC content?	X		
2	Are the CMC sections adequately indexed & paginated?	X		
3	Is the CMC sections legible?	X		
4	Are all facilities identified with full street addresses, contact names & CFN#s?	X		
5	Is there a statement that all facilities are prepared for GMP inspections?	X		
6	Has an environmental assessment or categorical exclusion been provided?	X		
7	Does the drug substance section contain controls?	X		
8	Does the drug product section contain controls?	X		
9	Has stability data been submitted to justify the requested expiry date?		X	**12 month long term/ 6 month accelerated**
10	Has the applicant provided all requested data by the division during the IND & pre-NDA phases?	X		
11	Have draft container labels been provided?	X		**Label unacceptable to DMETS**
12	Has a draft package insert been provided?	X		
13	Has an Investigational Formulations section been included?	X		
14	Are there three Methods Validation documents?	X		
15	Is a statistical consult required?		X	
16	Is there a separate microbiological section? Is a micro consult required?		X	

EER REPORT ATTACHED

Table 2 STABILITY DATA REQUIRED FOR FILEABILITY

	STABILITY DATA REQUESTED	YES	NO
1	Does the NDA include 12 or more months of stability data?	X	
2	Does the stability data cover the expiry date?		X
3	Does the stability data include only the largest & smallest container sizes?	N/A*	
4	Does the stability data include all packages sizes?	X*	
5	Are there tabular data for each size and batch?	X*	
6	Are there graphical data for each size and batch?		X
7	Is a statistical consult required?		X
8	Is a stability protocol included?	X	
9	Are the stability-indicating assays described?	X	
10	Is there the three-point stability commitment?	X	

*** Only one size**

Table 3 DMF INFORMATION

DMF #	DMF HOLDER	TYPE	LOA DATE	DATE OF LAST REVIEW
[redacted]		II	December 9, 2003	September 8, 2003
		III	January 31, 2002	November 7, 2002

Mid-cycle review completion date: May 27, 2004
Estimated Review Completion Date: September 1, 2004

Saleh A. Turujman, Ph.D.
Review Chemist

Wilson H. DeCamp, Ph.D.
Chemistry Team Leader

Attachment

Cc: Original NDA 21-709
HFD-540/Division File
HFD-540/Chm/SATurujman
HFD-540/ChmTL/WHDeCamp
HFD-540/ProjMgr/MHarris
HFD-830/DepDivDir/DLin

C:\Data\My Documents\turujman\reviews\NDA\NDAs 2004\21-709 —— (clindamycin PO4) Foam, 1%\21-709 FILEABILITY CHECKLIST.doc

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ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21709/000 Sponsor: CONNETICS
Org Code : 540 3290 WEST BAYSHORE RD
Priority : 3S PALO ALTO, CA 94303

Stamp Date : 24-DEC-2003 Brand Name : [redacted] 'CLINDAMYCIN PHOSPHATE
PDUFA Date : 24-OCT-2004 FOAM) 1%
Action Goal : Estab. Name:
District Goal: 25-AUG-2004 Generic Name: CLINDAMYCIN PHOSPHATE FOAM
Dosage Form: (AEROSOL)
Strength : 1%

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

--Overall Recommendation:

Establishment : CFN [redacted] FEI [redacted]

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CSN OAI Status: NONE
Last Milestone: SUBMITTED TO DO
Milestone Date: 21-JAN-04
:
:

Establishment : CFN [redacted] FEI [redacted]

[redacted]

DMF No: [redacted] AADA:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 21-JAN-04
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : [redacted] FEI : [redacted]

[redacted]

DMF No: AADA:

Appears This Way
On Original

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Responsibilities:

Profile : ADM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 27-JAN-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN FEI :

DMF No: AADA:

Responsibilities:

Profile : ADM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 27-JAN-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN FEI :

DMF No: AADA:

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: ASSIGNED INSPECTION TO IB
Milestone Date: 21-JAN-04

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

/s/

Saleh Turujman
3/25/04 05:38:12 PM
CHEMIST
No CMC issues identified for incluson in the 74-day letter
For your concurrence

Wilson H. DeCamp
3/26/04 03:36:00 PM
CHEMIST
concur with fileability recommendation; PM please note that there are no CMC filing review (74-day) issues