CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-934

CHEMISTRY REVIEW(S)

FEB 2 3 1999

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-934 CHEM.REVIEW #: 4 REVIEW DATE: 2/23/99

SUBMISSION/TYPE	DOC. DATE	CDER DATE	ASSIGNED DATE	
ORIGINAL	12/16/97	12/17/97	2/22/97	Review #1
Amendment/BL	07/21/98	07/22/98	Unknown	Review #2
Amendment/BL	07/27/98	07/28/98	08/13/98	" " "
Amendment/BC	08/07/98	08/10/98	08/13/98	" " "
Amendment/BC	08/07/98	08/10/98	08/13/98	Review #3
Amendment/BC	08/07/98	08/10/98	08/13/98	" " "
Amendment/BL	11/03/98	11/05/98	02/04/99	" " "
Amendment/BC	11/20/98	11/23/98	12/04/98	Review #4
Amendment/AZ	11/23/98	11/24/98	11/30/98	Review #3
Amendment/BC	12/15/98	12/16/98	12/30/98	" " "
Amendment/BZ	01/19/99	01/20/99	01/28/99	" " "
Facsimile	02/01/99			" " "
Facsimile (1&2)	02/22/99			Review #4

NAME & ADDRESS OF APPLICANT: Connetics Corporation
3400 West Bayshore
Palo Alto, CA 94303

DRUG PRODUCT NAME
Proprietary: None
Nonproprietary/USAN: (USAN) Betamethasone Valerate, USP
Code Names/#'s: None
Chem.Type/Ther.Class: 3 S

ANDA Suitability Petition/DESI/Patent Status:
N/A

PHARMACOL.CATEGORY/INDICATION: Glucocorticoid

DOSAGE FORM: Foam
STRENGTHS: 0.1%
ROUTE OF ADMINISTRATION: Topical
DISPENSED: x Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
See Chemist's Review #1

SUPPORTING DOCUMENTS:

See Chemist's Review # 1

RELATED DOCUMENTS (if applicable):
See Chemist's Review # 1

CONSULTS:

See Chemist's Review # 1

REMARKS/COMMENTS:

This chemist's review will address the Agency's concerns regarding 1,3-butadiene as a potential impurity in the propane/butane propellant and the pending validation data on the routine testing of this impurity in the finished product.

In this regard, Chemist's Review #2 found the NDA acceptable for Chemistry, Manufacturing and Controls. However, an addendum to Chemist Review #2 requested specifications for the components of the hydrocarbon propellant mixture . These specifications led to the discovery in the British Standard 4250:1997 of a specification for 1,3-butadiene as a potential impurity of the hydrocarbon mixture.

Analytical methodology was requested to determine quantitatively 1,3-butadiene in the propellant. This methodology was found capable to test for 1,3-butadiene as low as 0.01 mol% (100 ppm); see Chemist's Review #3. Validation of this analytical methodology was requested per telecon on 12/16/98. To date, this validation data are not available as promised for mid-February, 1999 (see telecon dated 2/22/99).

Therefore, this chemist review will not address the validation data for reasons as stated above. The validation data are not available at the time of this review. A post-approval commitment (Phase 4) is recommended for the submission of this data. Validation of a limit test for an impurity in an excipient is not essential to the quality of the drug product.

This chemist's review will also address the draft labeling that was submitted in amendment dated 11/3/98 and facsimiles dated 2/22/99. In this regard, the labeling was found acceptable from a technical standpoint

CONCLUSIONS & RECOMMENDATIONS:

The NDA remains acceptable from Chemistry, Manufacturing and Controls standpoint. An approval letter should be drafted with the phase 4 commitment noted above.

This phase 4 commitment should request the Applicant to submit to the NDA the complete validation data for the routine testing method for 1,3-butadiene impurity in the propellant within 60 days of approval.

Labeling: The labeling is acceptable from a technical standpoint; FPL should be submitted.

Establishment Inspection: The NDA was acceptable for CGMPs (see EES memo dated 5/1/98).

Methods Validation: Methods validation has not been requested to date; to be requested.

S

Review Chemist 2/23/99

CC: Orig. NDA 20-934
HFD-540/Division File
HFD-540/Pappas
HFD-540/Huene
HFD-540/Brown
HFD-850/Stinavage
HFD-540/Cintron
R/D Init by: Team Leader WD 2/23/99

JZ 2/24/99

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

FEB 10 1999

NDA #: 20-934 **CHEM.REVIEW #:** 3 **REVIEW DATE:** 2/9/99

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12/16/97	12/17/97	2/22/97
Amendment/BL	07/21/98	07/22/98	Unknown
Amendment/BL	07/27/98	07/28/98	08/13/98
Amendment/BC	08/07/98	08/10/98	08/13/98
Amendment/BC	08/07/98	08/10/98	08/13/98
Amendment/BC	08/07/98	08/10/98	08/13/98
Amendment/BC	11/20/98	11/23/98	12/4/98
Amendment/AZ	11/23/98	11/24/98	11/30/98
Amendment/BC	12/15/98	12/16/98	12/30/98
Amendment/BZ	01/19/99	01/20/99	01/28/99
Facsimile	02/01/99		

NAME & ADDRESS OF APPLICANT: Connetics Corporation
3400 West Bayshore
Palo Alto, CA 94303

DRUG PRODUCT NAME

Proprietary: None

Nonproprietary/USAN: Betamethasone Valerate, USP (USAN)

Code Names/#'s: None

Chem.Type/Ther.Class: 3 S

ANDA Suitability Petition/DESI/Patent Status:
N/A

PHARMACOL.CATEGORY/INDICATION: Glucocorticoid

DOSAGE FORM: Foam
STRENGTHS: 0.1%
ROUTE OF ADMINISTRATION: Topical
DISPENSED: x Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
See Chemist's Review #1

SUPPORTING DOCUMENTS:

See Chemist's Review # 1

RELATED DOCUMENTS (if applicable):
See Chemist's Review # 1

CONSULTS:
See Chemist's Review # 1

REMARKS/COMMENTS:

This chemistry review addresses the Agency's concerns regarding the impurity profile of the Butane 70, a propellant in Luxiq Foam. A specification limit for residual sulfur in the Butane 70 propellant was noted
Chemist Review #2 dated 10/30/98).
The concern prompted a request by the chemist on 11/6/98 for details of the specification limits of the hydrocarbon mixture
Specification limits were submitted by the applicant, which also indicated that the hydrocarbon mixture could contain 1,3-butadiene (see Addendum to Chemist Review #2 dated 11/23/98). This impurity profile was conveyed to the pharm/tox reviewer (HFD-540) for assessment.

The information, which addresses the Agency's concerns regarding 1,3-butadiene, is summarized under the Chemist's Review

CONCLUSIONS & RECOMMENDATIONS:

The information that was submitted in support of the **analytical methodology was found acceptable to test for 1,3-butadiene and other components of the hydrocarbon mixture.**

The test method is capable of detecting 1,3-butadiene as low as 0.01 mol% (100 ppm) from the review of the

It should be noted that the test method is able to quantitate 1,3-butadiene at one order of magnitude lower than 0.01 mol%. [i.e., 0.001 mol%, (10 ppm)] based on the review of the The applicant indicated that this might be true; however, they unable to find a supplier that could guarantee an amount lower than 0.01 mol% (see Memo dated 2/1/99).

The review of the forthcoming validation data will be performed in another chemistry review.

LABELING: The review of the technical portions (11/3/98 Amendment) will be deferred pending the outcome of the Chemist's concerns regarding the potency declaration on the PI, carton labels, etc. An addendum to chemistry review (#3) will be drafted after this concern has been addressed. This will be addressed on labeling day.

/S/ 2/9/99

Review Chemist

CC: Orig. NDA 20-934
HFD-540/Division File
HFD-540/Pappas
HFD-540/Huene
HFD-540/Brown
HFD-850/Stinavage
HFD-540/Cintron
R/D Init by: Team Leader WS 2/10/99

QJ 2/18/99

OCT 30 1998

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-934 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 10/30/98

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12/16/97	12/17/97	2/22/97
Amendment/BL	07/21/98	07/22/98	Unknown
Amendment/BL	07/27/98	07/28/98	08/13/98
Amendment/BC	08/07/98	08/10/98	08/13/98

NAME & ADDRESS OF APPLICANT: Connetics Corporation
3400 West Bayshore
Palo Alto, CA 94303

DRUG PRODUCT NAME

Proprietary:	None
Nonproprietary/USAN: (USAN)	Betamethasone Valerate, USP
Code Names/#'s:	None
Chem.Type/Ther.Class:	3 S

ANDA Suitability Petition/DESI/Patent Status:
N/A

PHARMACOL.CATEGORY/INDICATION: Glucocorticoid

DOSAGE FORM:	Foam
STRENGTHS:	0.1%
ROUTE OF ADMINISTRATION:	Topical
DISPENSED:	x Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

SUPPORTING DOCUMENTS:

Document Type & Number	Subject	Holder	Status	Review Date	Letter Date
DMF	Betamethasone Valerate		Under Review		
DMF	Betamethasone Valerate Foam Manufacturer		Under Review		

RELATED DOCUMENTS (if applicable):

IND

NDA 16-322 - Schering Corporation [Valisone (betamethasone valerate) Cream, 0.1% and 0.01%]
NDA 16-740 - Schering Corporation [Valisone (betamethasone valerate) Ointment, 0.1%]
NDA 16-932 - Schering Corporation [Valisone (betamethasone valerate) Lotion, 0.1%]
NDA 16-932 - Schering Corporation [Valisone (betamethasone valerate) Lotion, 0.1%]

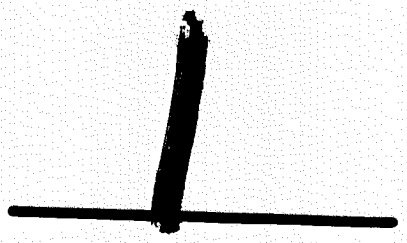
CONSULTS:

Microbiology review dated 4/20/98 contained Micro concerns which was conveyed to the applicant on 6/24/98. The Micro concerns were addressed by applicant on 7/15/98. The microbiologist found the applicant's response acceptable and recommends approval of the NDA from a Micro perspective (see Micro review dated 8/27/98).

Labeling consult was requested on 7/28/98 from the Labeling and Nomenclature Committee for tradename "Luxiq". The tradename " Luxiq" was found acceptable by the Committee on 9/3/98. However, the applicant submitted new labeling on 7/27/98 which identified the Betamethasone Valerate Foam, 0.1% as Luxiq "ViaFoam". The use of "ViaFoam" with the product tradename "Luxiq" tantamount to another tradename which was reviewed by the Labeling and Nomenclature Committee and found acceptable.

REMARKS/COMMENTS:

Chemist review #1 dated 5/6/98 found the NDA in an APPROVABLE state from a chemistry, manufacturing and controls standpoint, pending corrections to the minor deficiencies found with the CMCs. These deficiencies were conveyed to the applicant by an IR letter on 6/24/98. In this regard, the applicant amended their NDA on 8/7/98, responding to the following CMC deficiencies:

Redacted 

pages of trade secret and/or confidential commercial information

CONCLUSIONS & RECOMMENDATIONS:

The CMC deficiencies were corrected by the applicant with their amendment to the NDA on 8/7/98. This amendment was reviewed and found acceptable in several CMC areas, including microbiology concerns.

EER found acceptable by the Office of Compliance (see EES memo dated 5/1/98).

Methods Validation is remains pending.

The labeling is an approvable state from a technical standpoint. The Labeling and Nomenclature Committee has found trademarks, "Luxiq" and"ViaFoam", acceptable for use in labeling the finished product (see Memo from LN&C dated 10/29/98).

/S/ 10/30/98

Review Chemist

cc: Orig. NDA 20-934
HFD-540/Division File
HFD-540/Pappas
HFD-540/Huene HFD-540/Brown HFD-850/Stinavage
HFD-540/Cintron R/D Init by: Team Leader

10/30/98

11/12/98

MAY 27 1998

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-934 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 5/6/98

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12/16/97	12/17/97	2/22/97

NAME & ADDRESS OF APPLICANT: Connetics Corporation
3400 West Bayshore
Palo Alto, CA 94303

DRUG PRODUCT NAME

Proprietary:	None
Nonproprietary/USAN: (USAN)	Betamethasone Valerate, USP
Code Names/#'s:	None
Chem.Type/Ther.Class:	3 S

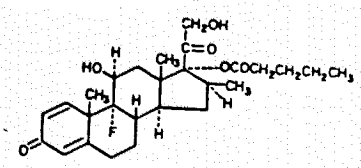
ANDA Suitability Petition/DESI/Patent Status:
N/A

PHARMACOL.CATEGORY/INDICATION: Glucocorticoid

DOSAGE FORM: Foam
STRENGTHS: 0.1%
ROUTE OF ADMINISTRATION: Topical
DISPENSED: _x_ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Betamethasone Valerate [*1969*]. USP. $C_{27}H_{37}FO_6$. 476.59. (1) Pregna-1,4-diene-3,20-dione, 9-fluoro-11,21-dihydroxy-16-methyl-17-[(1-oxopentyl)oxy]-, (11β,16β)-; (2) 9-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-valerate. *CAS-2152-44-5*. BAN



SUPPORTING DOCUMENTS:

Document Type & Number	Subject	Holder	Status	Review Date	Letter Date
DMF	Betamethasone Valerate		Under Review		
DMF	Betamethasone Valerate Foam Manufacturer		Under Review		

RELATED DOCUMENTS (if applicable):

IND

NDA 16-322 - Schering Corporation [Valisone (betamethasone valerate) Cream, 0.1% and 0.01%]
NDA 16-740 - Schering Corporation [Valisone (betamethasone valerate) Ointment, 0.1%]
NDA 16-932 - Schering Corporation [Valisone (betamethasone valerate) Lotion, 0.1%]
NDA 16-932 - Schering Corporation [Valisone (betamethasone valerate) Lotion, 0.1%]

CONSULTS:

Microbiology consult was requested January, 1998; see Micro Review dated 4/20/98.

Labeling consult was not requested since no tradename was proposed by applicant.

REMARKS/COMMENTS:

The applicant has provided a New Drug Application for Betamethasone Valerate Foam 0.1%. Betamethasone valerate is the subject of many topical commercial products, which have been marketed for years in the USA. It was originally approved for Schering's Valisone products and later for the Generic equivalents of each dosage form as listed above. In 1996, Schering discontinued marketing the Valisone products for business reasons. In this regard, the applicant has picked-up the product line and has proposed a new dosage form of betamathasone valerate for ease of application as a topical product.

This foam, when heated to body temperature, breaks down and delivers the active ingredient in a vehicle closely resembling that of a lotion. The drug product is a hydroalcoholic formulation which is packaged in an epoxy lined aluminum can, pressurized with a propellant

[propane/butane (Butane 70)]. Please note that the propellant was not calculated in the composition of the formulation since it evaporates immediately upon use. By not listing it as part of the composition reflects the actual strength delivered of the drug substance. However, it is listed as a footnote to the composition in order to declared it as an inactive ingredient of the formulation [see Drug Product (Item 3) below].

In support of this NDA, a comprehensive description of the CMCs was submitted. This information was reviewed and found deficient under the specifications and tests for the drug substance and finished drug product. Refer to chemist's review notes for details regarding these CMCs.

Draft labeling was also submitted. This information was found acceptable from a technical standpoint with the exception that it failed to include a warning statement regarding the flammability of the product. Should the applicant find that the product to be flammable, a warning statement should be added the labeling. In addition, the product's tradename should be requested.

EER found acceptable by the Office of Compliance (see EES memo dated 5/1/98).

Microbiology Review dated 4/20/98 found the NDA approvable pending resolution of microbiology concerns.

CONCLUSIONS & RECOMMENDATIONS:

The NDA was reviewed and found deficient in several CMC areas, including microbiology concerns. The draft labeling was found acceptable from a technical standpoint with the exception of the flammability issue. In addition, the product's tradename should be requested. Before this NDA can be approved these deficiencies should be corrected.

/S/ 5/13/98
Review Chemist

cc: Orig. NDA 20-934
HFD-540/Division File
HFD-540/Pappas
HFD-540/Huene HFD-540/Brown HFD-850/Stinavage
HFD-540/Cintron R/D Init by: Team Leader 5/27/98

6/24/98