

ANSWER TO QUESTION #1, PART II:

Approved drug products containing the same active moiety:

Topical creams, 0.1%:

ANDA 18-642	BETA-VAL	Lemmon
ANDA 18-839	BETADERM	Roaco
ANDA 70-053	Betamethasone Valerate	Clay Park
ANDA 18-861	Betamethasone Valerate	Fougera
ANDA 70-062	Betamethasone Valerate	Thames
ANDA 18-962	Betatrex	Savage Labs.
ANDA 72-041	Dermabet	Taro
NDA 16-322	Valisone	Schering
ANDA 70-050	Valnac Cream, 0.1%	NMC

Topical lotions, 0.1%:

ANDA 70-072	BETA-VAL	Lemmon
ANDA 70-052	Betamethasone Valerate	Alpharma
ANDA 71-883	Betamethasone Valerate	Copley Pharm.
ANDA 18-866	Betamethasone Valerate	Fougera
ANDA 18-867	Betatrex	Savage
NDA 16-932	Valisone	Schering

Topical ointments, 0.1%:

ANDA 70-069	BETA-VAL	Lemmon
ANDA 18-865	Betamethasone Valerate	Fougera
ANDA 70-051	Betamethasone Valerate	NMC
ANDA 18-863	Betatrex	Savage
NDA 16-740	Valisone	Schering

Topical aerosol:

NDA 16-957	Valisone	Shering
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PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

TE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 20-934

Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 540 Trade and generic names/dosage form: Luxiq (betamethasone valerate) Foam, 0.1% Action: AP AE NA

Applicant Cosmetics Therapeutic Class 35

Indication(s) previously approved _____
Pediatric information in labeling of approved indication(s) is adequate _____ inadequate _____

Proposed indication in this application Relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? Yes (Continue with questions) No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

Neonates (Birth-1month) Infants (1month-2yrs) Children (2-12yrs) Adolescents(12-16yrs)

- 1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. 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 age groups. Further information is not required.
- 2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
- 3. 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. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
 - c. 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, attach memo describing status of discussions.
 - d. 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.

4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed. Diagnosis is rare in pediatric patients

5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? Yes No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Medical Officer (e.g., medical review, medical officer, team leader)

IS/
nature of Preparer and Title

11/2/98
Date

cc: Orig NDA/BLA # 20934
HFD 540 Div File
NDA/BLA Action Package
HFD-006/ KRoberts

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

(revised 10/20/97)

MEMORANDUM OF TELEPHONE CONVERSATION

DATE: February 22, 1999.

DRUG: Luxiq (betamethasone valerate) Foam, 0.12%

FEB 23 1999

NDA: 20-934

SPONSOR: Connetics Corporation
Claire Lockey, Vice President, Regulatory Affairs

FDA: Olga Cintron, R.Ph., Project Manager, HFD-540

IS/
2/23/99

The Sponsor contacted the Agency with respect to the revised draft labeling that was faxed to the Sponsor on February 19, 1999. The Sponsor indicated that they were in agreement with the revised labeling that was faxed to them on February 19, 1999.

The Agency requested the Sponsor to submit a letter to the NDA indicating the above, and to submit revised draft carton and container labeling in accordance to the revised labeling that was faxed to the Sponsor on 2/19/99. The Sponsor agreed.

The Sponsor indicated that the routine testing method to detect 1,3 butadiene validation data, requested by the Agency, may not be submitted in the near future, as expected. They expressed concern as to whether this delay may have an impact on the approvability of the application. The Agency indicated that this issue could be discussed by the review team which was meeting the same day and that adequate feedback would be provided.

The conversation ended cordially.

cc:

NDA 20-934

HFD-540/Div File



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: November 23, 1998
To: NDA 20-934 file
From: Wilson H. DeCamp, Ph.D.
Chemistry Team Leader, HFD-540
Subject: Team Leader's Addendum to Chemistry Review #2

NOV 23 1998

The fax submission of 11/9/98 (followed up by a hard copy on 11/20/98) responded to our request for specifications for the components of the hydrocarbon propellant mixture. This submission included limits for total

The methods are standard methods [either BS (British Standard) or ASTM]; a description is only included for the hydrogen sulfide test, which relies upon discoloration of lead acetate paper. In addition, the specifications included a limit on "dienes" at 0.5 mole%. These were not identified individually, but are presumed to be propene and 1,3-butadiene. The latter is a known carcinogen.

This now raises additional concerns about the appropriate specifications for the hydrocarbon propellant. Specifically, the product is an industrial grade of butane/propane, and may not be appropriate for pharmaceutical use. The pharmacology amendment to their review #1 (dated 11/18/98) requested additional safety information. Pending their review of such safety data, a chemistry conclusion concerning the specifications must be reserved.

JS/

cc: Orig: NDA 20-934
Division file: NDA 20-934
HFD-540/Wilkin
HFD-540/Cintron
HFD-540/Huene
HFD-540/Walker
HFD-540/Brown
HFD-540/Jacobs
HFD-540/Pappas
HFD-540/DeCamp
HFD-540/Bashaw
HFD-540/Srinivasan

92) 11/24/98

11/23/98



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: November 3, 1998

To: NDA 20-934 file [Luxiq (betamethasone valerate) Foam, 0.1%]

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

Subject: Team Leader's addendum to Chemist's Review #2: Proposed trade name

Concur: Ernest G. Pappas
Chemistry Reviewer, HFD-540

NOV - 3 1998

Chemistry Review #2, dated 10/30/98, included a recommendation from the Labeling and Nomenclature Committee that found the proposed trade name of "Luxiq ViaFoam" to be acceptable. This recommendation was accepted by the review chemist.

The accompanying memorandum dated November 2, 1998, identifies clinical concerns about the potential for confusion of this trade name with Vioform, a recently withdrawn trade name for a topical clioquinol product (formerly marketed OTC by Sandoz as an antifungal and antibacterial agent). On the basis of this concern, I am reversing the recommendation of the review chemist, and recommending that the applicant for NDA 20-934 be advised that the term "ViaFoam" may not be shown on the label or labeling.

It should be noted for the records that clioquinol at a concentration of 3 percent may be marketed OTC under the provisions of 21 CFR 333.210. There is, therefore, no assurance that the Vioform product will not return to the market.

cc: HFD-540 Division file (NDA 20-934)
HFD-540/Wilkin
HFD-540/Walker
HFD-540/Huene
HFD-540/Cintron
HFD-540/Jacobs
HFD-540/Pappas
HFD-540/DeCamp
HFD-590/Boring

EGP 11/3/98

92) 11/17/98

/S/

1

11/3/98

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 2, 1998

FROM: Phyllis Huene, M.D.
Medical Officer, Dermatology

THROUGH: Susan Walker, M.D. *SW 11/2/98*
Team Leader, Dermatology

THROUGH: Jonathan Wilkin, M.D. *JW 11/2/98*
Division Director
Division of Dermatologic and Dental Drug Products

TO: Tony DeCamp, Ph.D.
Team Leader, Chemistry

SUBJECT: NDA 20-934
Betamethasone valerate foam (Luxiq)
Proposed name change

We understand that Connectics Corp., the sponsor of NDA 20-934 for Betamethasone valerate foam, has proposed the name ViaFoam as the trade name for the product. We feel that this may be confused with the product Vioform. While Vioform is no longer marketed, at one time it was marketed extensively in the US, and was a major component of the dermatological armamentarium. The potential for renewed marketing of Vioform exists.

Vioform was marketed for a number of clinical indications, but was used primarily as an antifungal agent. We feel that if ViaFoam were mistakenly used for the indications for which Vioform was used, adverse effects for the patient might result. This would include effects such as striae, telangiectasia, and skin atrophy, and possibly exacerbation of skin infections.

For this reason, we feel that ViaFoam is not an appropriate name for Betamethasone valerate foam.

/S/

H.D.

Phyllis A. Huene, M.D.

cc: Orig NDA
HFD-540
HFD-540/Huene
HFD-540/Cintron
HFD-540/Jacobs



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NFD 540/cinton

Food and Drug Administration
Rockville MD 20857

NDA 20-934

Connetics Corporation
Attention: Claire J. Lockey, Vice-President, Regulatory Affairs
3400 West Bayshore
Palo Alto, CA 94303

JUN 24 1998

Dear Ms. Lockey:

Please refer to your pending December 16, 1997 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for betamethasone valerate foam, 0.1%.

We have completed our review of the Chemistry, Manufacturing and Controls section of your submission and have identified the following deficiencies:

1. The NDA does not include a certificate of analysis for a typical batch of betamethasone valerate as received from their supplier.
2. The specifications for the Propane/Butane (Butane 70) Propellant system do not provide limits for the individual hydrocarbon blend and residual sulfur.
3. The in-process tests failed to include a flammability test for the finished product. We recommend that you perform appropriate tests to provide assurance that the product is not flammable, both under conditions simulating normal use and extreme use (*e.g.*, exposure to an open flame). Should the product be found to be flammable, a warning statement may need to be considered for the labeling.
4. Under Betamethasone Valerate Foam Specifications, the Appearance test is performed by visual examination. This method is too subjective; we recommend that it be performed by a microscopic examination in addition to the visual observation.
5. The Certificate of Analysis as submitted in pg. 4-0465 does not report the results of testing for Spray Rate or Microbial Limits.
6. Since this is a multiple dose product, the preservative properties of the formulation should be demonstrated. Antimicrobial effectiveness testing should be completed as described in USP <51>. The formulation should meet or exceed compliance requirements for antimicrobial preservative effectiveness.
7. Please explain the reason why the sample preparation on pg. 4-0290 refers to a placebo sample that is used in the calculations. How is this placebo made?
8. Please explain the statement on pg. 4-0291 "Any peaks obtained that correspond to peaks in the placebo are ignored".
9. Since a tradename was not submitted for the finished product, we recommend that you submit one at your earliest opportunity.

NDA 20-934
Page 2

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Olga Cintron, Project Manager, at (301) 827-2020.

Sincerely yours,

WHD 6/24/98

Wilson H. DeCamp, Ph.D.
Chemistry Team Leader for
Division of Dermatologic and Dental Drug
Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc: Original NDA 20-934
HFD-540/Div. Files
HFD-540/PM/Cintron
HFD-540/Pappas *egl 6/17/98*
HFD-540/DeCamp
HFD-830/Chen

Drafted by: whd/6/16/98/n20934.ir

INFORMATION REQUEST (IR)

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Mr Dan Boring, Chair, (HFD-530)

From: Division of Dermatologic and Dental Drug Products W 7/28/98
HFD-540
Attention: Ernest G. PAPPAS Phone: 827-2066

Date: 7/28/98

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Luxiq NDA # 20-934

Company Name: Connectics Corporation

Established name, including dosage form: Betametasone Valerate Foam, 0.1%

Other trademarks by the same firm for companion products: N.A.

Indications for Use (may be a summary if proposed statement is lengthy): treatment of relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

Initial comments from the submitter (concerns, observations, etc.): This reviewer has a concern on the flammability of the product since it contains _____ and propellant in the formulation. Therefore, the applicant addressed this concern by including a the following warning statement: Flammable. Avoid Fire, Flame or Smoking During Use.

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev July 98

Antum
540
Kozma-Fornaro

MEETING MINUTES

Date : November 4, 1996

Time: 2:30PM

Location: N-225

Sponsor: Connective Therapeutics, Inc.

Type of meeting: Pre IND/End of Phase II meeting

Meeting recorder: Mary Jean Kozma-Fornaro, Acting Supv. Project Management
Olga Cintron, Project Manager

FDA attendees:

Linda Katz, M.D., Deputy Director, DODDDP, HFD-540
Phyllis Huene, M.D., Medical Officer, HFD-540
R. Srinivasan, Ph.D., Team Leader Biostatistics, HFD-725
Shahla Farr, M.S. Biostatistics, HFD-725
Syed Alam, Ph.D., Pharmacologist, HFD-540
Wilson De Camp, Team Leader/Chemistry, HFD-540
Dennis Bashaw, Pharm. D., Team Leader Biopharmaceutics, HFD-880
Sue Chin Lee, Ph.D., Biopharmaceutics, HFD-880
Elizabeth Dickinson, General Attorney, General Council, GCF-1
Bonnie Dunn, Deputy Director, DNDC3, HFD-830
Don Hare, Special Assistant Director, OGD, HFD-604
Mary Jean Kozma-Fornaro, R.N., M.S.A., Acting Supv. Project Management, HFD-540
Olga Cintron, R.Ph., Project Manager, HFD-540
Robin Anderson, R.N., M.B.A., Project Manager, HFD-540

Sponsor attendees:

Scott Harkonen, M.D., Sr. Vice President Product Development, Connective Therapeutics, Inc.
Ronald Marks, M.B.B.S., Professor of Dermatology, University of Wales, Cardiff, Wales, U.K.
Martin Rose, M.D., J.D., Clinical Consultant, BRI International, Inc.
Steve Tickle, Research and Development Director, CCL Pharmaceuticals
Gary Novack, Ph.D., Consultant, Connective Therapeutics, Inc.
Robert Hill, Toxicology Consultant, Connective Therapeutics, Inc.
John Hannigan, Biostatistics Consultant, Connective Therapeutics, Inc.
Caroline Whately-Smith, Consultant Biostatistician, Harris Labs.
Margaret Dillon, Ph.D., Associate Director-Regulatory Affairs, Connective Therapeutics, Inc.

Objective:

To discuss the proposed application described in the package and to answer the questions outlined in the meeting agenda.

Discussion:

After a brief introduction by each of the meeting participants, the Agency responded to the following questions:

1. Does FDA agree with Connective that its overall approach to this project is sound, i.e., that a Sec. 505 (b)(2) application for a betamethasone valerate mousse product with limited clinical data can be approved?

The Agency stated that they were willing to discuss the requirements for a 505(b)(2) application, but that the decision as to whether this form of application would be the best approach should be decided upon by the sponsor.

The Agency also stated that if a 505(b)(2) application is submitted that relies in part upon the Agency's finding of safety and effectiveness for a previously approved drug, the sponsor must provide all the data necessary to support the finding that a dosage form different than that originally approved is safe and effective. In order to rely upon the finding of safety and effectiveness for the previously approved drug, the sponsor must provide a link to that product by providing comparative bioavailability data. A comparative pharmacodynamic study and a comparative clinical trial may be necessary. In addition, a 505(b)(2) applicant must provide certification to patents listed for the reference drug, and the timing for approval is governed by patents and exclusivity protecting the reference drug.

2. Does FDA agree with Connective that the proposed clinical plan is sufficient to support the application? If not, what additional studies will be necessary for approval?

As noted above, should the sponsor choose to submit a 505(b)(2) application, the sponsor needs to conduct a comparative bioavailability study to the reference drug. The reference drug must be an approved drug in which efficacy and safety has been established. In this regard, the establishment of a "bridge" to the referenced product is essential for approval of an application submitted under a 505(b)(2). This "bridge" may be established by conducting a comparative efficacy study and a comparative vasoconstrictor study. The studies that are required will depend on the type of indication being claimed in the labeling.

3. Does FDA agree with Connective that the proposed studies could support an indication similar to the indication in topical corticosteroid class labeling, which is the relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses?

If the sponsor is planning to claim unrestricted class labeling for the foam, then the following studies need to be conducted to support this kind of labeling:

- A) a comparative efficacy study designed as a four arm comparison, using the reference product as a comparator and including a placebo arm. (active foam,

placebo foam, active comparator, placebo comparator) The comparator should be the closest that matches the foam. The study should show 80% power with an alpha equal to .05 in order to detect one grade difference.

B) a comparative vasoconstrictor study using the most similar dosage form. The comparators should be chosen to "bracket" the foam on one potency by one grade spread above and below.

C) an HPA-axis suppression study, which is required as a safety assessment, using cosyntropin stimulation test. For this study, the patient would have to apply the foam to 30% of their body surface area. This area must be dermatotic skin. This study should be performed in children if the sponsor plans to claim use in children.

The requirement for HPA-axis suppression study for restricted labeling will need further discussion.

4. Does FDA agree with Connective that a vasoconstrictor study should serve simply to characterize the potency of the product, and that a finding of strict bioequivalence to the reference product is not required.

The Agency clarified that the requirement of bioequivalency studies will depend on the type of application that will be submitted. If the application is submitted as a new drug with no reliance on the Agency's finding for a reference product no bioequivalency studies are required, but bioavailability data may be necessary. Only the required clinical studies will need to be conducted. Should the application be submitted as an ANDA through the petition procedure, bioequivalency studies will be required.

5. Does FDA agree with Connective that no additional information regarding HPA axis suppression is required for approval of the proposed Sec. 505 (b)(2) application?

The Agency reemphasized that an HPA-axis suppression study is required for approval of a 505(b)(2) application if the sponsor is planning to eventually claim unrestricted class labeling for their product.

6. Does FDA agree with Connective that its proposed Sec 505 (b)(2) application would not be subject to a User Fee?

The Agency suggested that the sponsor should consult Tom Hassell for specific information regarding User Fees.

7. Does FDA agree with Connective that the proposed application, if it is approved, will entitle Connective to marketing exclusivity pursuant to 21 CFR Part 314.108? If not, what additional clinical studies should be performed in order for exclusivity to apply?

A 505(b)(2) application is eligible for exclusivity. However that determination is not made until after the NDA has been approved.

8. It is Connective's understanding that Valisone, the reference betamethasone valerate product, is no longer marketed by Schering Plough in any form. What product should Connective use as a control in its vasoconstrictor study?

The Agency suggested that if it was too difficult to obtain Valisone to conduct the comparative efficacy study and the vasoconstrictor study then the Fougera product could be used as the reference product since it has been approved through the Division of Anti-Infective Drugs. However, the Office of Generic Drugs is in the process of selecting a new reference product for this entity. The Agency suggested that the sponsor should await for the new reference drug prior to conducting the studies.

The following points were presented by FDA team members:

Pharmacology and Toxicology

- * Complete studies and safety summaries will need to be submitted if the sponsor submits a 505(b)(1) application that does not rely on approval of a reference drug.
- * Submit preclinical studies information from the United Kingdom to the IND.
- * Preclinical studies may not be needed if full bioequivalence and bioavailability clinical studies are performed.
- * Address possible systemic inhalation due to the propellant affect in this particular dosage form.

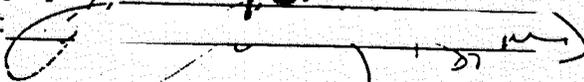
Chemistry

- * Concern that upon the propellant removal (part of sample preparation) the concentration of the active is slightly raised. The percent in the approved product may be different from the percent stated in the label, and both may be different from the concentration in the "liquid foam" as applied to the skin.

The meeting ended cordially.

Signature, minutes preparer:

Concurrence Chair:

IS/


cc:

HFD-560/Katz 2/26/97

HFD-540/Huene 2/21/97

HFD-725/Srinivasan

HFD-725/Farr 2/24/97

HFD-540/Alam 1/29/97

HFD-540/DeCamp 2/24/97

HFD-880/Bashaw 2/12/97

HFD-880/Lee

GCF-1/Dickinson 2/21/97

HFD-830/Dunn

HFD-604/Hare 2/10/97

HFD-540/Kozma-Fornaro

HFD-540/Anderson

HFD-005/Axelrad

HFD-540/Wilkin

HFD-540/Jacobs

File in original IND

HFD-540/DIU FILE