FORWARD PLANNING MEETING MINUTES

NDA 20-934	**Betamethasone Valerate Foam. 0. 1%**
Date:	February 2, 1998.
Sponsor:	Connectics Corporation
Pharmacologic class:	Topical corticosteroid
Type:	3S
Indication:	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses
Active ingredient:	betamethasone valerate
Filing Date:	February 14, 1998.
Regulatory Due Date:	June 15, 1998.
User Fee Due Date:	December 17, 1998.

Attendees:

Jonathan Wilkin, M.D., Division Director, HFD-540
Phyllis Huene, M.D., Medical Officer, HFD-540
Dennis Bashaw, Pharm. D., Team Leader Biopharmaceutics, HFD-880
Paul Brown, Ph.D., Pharmacologist, HFD-540
Ernest Pappas, Chemist, HFD-830
Wilson DeCamp, Ph.D., Team Leader/Chemistry, HFD-830
R. Srinivasan, Ph.D., Team Leader/Biostatistics, HFD-725
Shahla Farr, M.S., Biostatistics< HFD-725
Don Hare, Special Assistant Director, OGD, HFD-604

Purpose: To determine fileability of NDA 20-934.

The meeting was convened to determine the adequacy of NDA 20-934 for filing. All sections of the New Drug Application (NDA) were evaluated in terms of general content and format requirements.

From a preliminary evaluation of the general content and format as well as the non clinical pharmacology and toxicology, human pharmacokinetics, clinical data, chemistry, microbiology, and statistical sections of the application, it was recommended that NDA 20-934 be filed.

All disciplines stated that no additional information from the sponsor is needed at this time.

Expected date of draft review:

Chemistry	June 15, 1998.
Pharmacology	Completed.
Biopharmaceutics	May 1, 1998.
Biostatistics	June 30, 1998.
Clinical	March 15, 1998.
Microbiology	April 15, 1998.

It was agreed that an action on this application should be issued by October 17, 1998.

/S/ 2/4/98.

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

cc:
Original NDA 20-934
HFD-540/DIV FILE
HFD-540/CHEM/Pappas
HFD-540/SR CHEM/DeCamp
HFD-540/PHARM/Brown
HFD-540/SR PHARM/Jacobs
HFD-725/BIOSTAT/Farr
HFD-725/SR BIOSTAT/Srinivasan
HFD-540/MO/Huene
HFD-880/SR BIOPHARM/Bashaw
HFD-540/ACTING SUPV PROJ MGR/Kozma-Fornaro
HFD-540/PROJ MGR/Cintron

MEMORANDUM OF TELEPHONE CONFERENCE

DATE: February 1, 1999.

FEB 2 1999

NDA: 20-934

DRUG: Luxiq (betamethasone valerate) Foam, 0.12%

SPONSOR: Connetics Incorporated
Claire Lockey, Vice President, Regulatory Affairs
Dawn Parcell, Regulatory Affairs
Max Nygaard, Regulatory Affairs
Joe Henney, Director, Quality Assurance

FDA: Ernest Pappas, B.S., Chemistry Reviewer, HFD-830
Olga Cintron, R.Ph., Project Manager, HFD-540

/S/ 2/2/99
2/2/99

The Agency contacted the Sponsor to request the following information:

1. On page 141 of the January 19, 1999, amendment, the Sponsor provides a calibration mixture chromatograph followed by a data table on page 142. Please identify the additional peaks that are shown in this chromatograph and in the data table, as well.

The Sponsor indicated that this chromatograph refers to a mixture of a variety of gases and not of the propellant mixture. This will be used as a reference standard.

The Agency indicated that according to the chromatograph, it appears that one level of magnitude lower could be achieved. Since the peak at 19.029 minutes revealed a peak height of one tenth of the peak of that of the 1, 3-butadiene (20 minutes), it appeared that half of the amount of the 19.029 minutes peak could be achieved. This would reveal 0.001 mol% (10 ppm).

The Sponsor responded that they have contacted many suppliers and they have not been able to find a supplier that could guarantee that amount.

The Sponsor clarified that the validation plan included in the January 19, 1999, submission is to validate the method as a limit test for detection of 1, 3-butadiene at a level of 0.01 mol%. The validation is not intended to demonstrate linearity.

The Sponsor agreed to fax the requested information.

The conversation ended amicably.

cc:

NDA 20-934
HFD-540/Div File
HFD-540/DeCamp
HFD-540/Pappas
HFD-540/Cintron

Filename: c:\telecons\bmvf.tl

MEMORANDUM OF TELEPHONE CONVERSATION

DATE: December 16, 1998.

DRUG: Luxiq (betamethasone valerate) Foam, 0.1%

NDA: 20-934

FEB 2 8 1999

SPONSOR: Connetics Corporation
Claire Lockey, Vice President, Regulatory Affairs
Dawn Parcell, Regulatory Affairs
Scott Harkonen, M.D., Vice President Research

FDA: Jonathan Wilkin, M.D., Division Director, HFD-540
Wilson DeCamp, Ph.D., Chemistry Team Leader, HFD-540
Ernest Pappas, B.S., Chemist, HFD-540
Olga Cintron, R.Ph., Project Manager, HFD-540

Subject: Information request - Status of review of major amendment dated November 23, 1998.

The Agency informed the Sponsor that the November 23, 1998, amendment is currently under review and that the review team is working together to find an answer regarding 1, 3-butadiene concern. The team is researching for additional background information with the intent to determine what would be the risk of exposure with the Luxiq Foam.

The Agency indicated that it was in the best interest to the Sponsor to try to determine how much 1, 3-butadine is present in the propellant. This may be achieved by utilizing an assay methodology sensitive enough to detect quantitative levels of 1, 3-butadiene. This would provide useful information to the Sponsor by which they could compare the amount of this impurity present in the propellant with other propellant bulk suppliers.

The chemistry team requested the following information:

1. In reference to the submission dated December 15, 1998, that has been transmitted to the Agency, it is noted that the submission does not contain the validation study of the method used to test the presence of 1,3 butadiene. The validation study needs to be submitted for review in order to be able to evaluate the analytical capabilities of the test method.

2. The submission dated November 23, 1998, does not contain the raw data on limits of detection for the 1,3 butadiene. The Sponsor needs to submit the raw data along with the test method validation study results.

The Agency delineated the process that could provide the necessary information to support the

regulatory decision and labeling as follows:

- determine how much 1, 3-butadiene is in the propellant currently used for the product,
- determine if the assay methodology used is capable to detect the low levels of the impurity,
- consider other bulk suppliers that may contain lower levels of 1, 3-butadiene,
- provide an assessment of the risk of exposure based on the quatitative level of 1, 3- butadiene. This information should be reflected in the carcinogenicity section of the labeling.

The conversation ended cordially.

Signature, minutes preparer: /S/ 2/17/98
Concurrence, Chair: 2/28/99

cc:
NDA 20-934
HFD-540/Div File
HFD-540/Wilkin
HFD-540/Walker
HFD-540/Huene
HFD-540/Jacobs
HFD-540/Brown
HFD-540/DeCamp 2/2/99.
HFD-540/Pappas 2/2/99.
HFD-540/Cintron

MEMORANDUM OF TELEPHONE CONFERENCE

DATE: December 3, 1998.

DEC 9 1998

NDA: 20-934

DRUG: Luxiq (betamethasone valerate) Foam, 0.1%

SPONSOR: Connetics Incorporated
Scott Harkonen, M.D., Vice President, Product Development

FDA: Robert DeLap, M.D., Director, ODE V, HFD-105
Olga Cintron, R.Ph., Project Manager, HFD-540

SUBJECT: Luxiq (betamethasone valerate) Foam - Sponsor's labeling and major amendment concerns

The Agency contacted Dr. Harkonen in response to the labeling and major amendment concerns outlined in the facsimile from Connetics, Inc., dated December 1, 1998. The following are the highlights of the discussion:

Major amendment issue:

- The Agency acknowledged the receipt of the facsimile dated December 1, 1998, and indicated that, while we understand that this type of propellant is used in a variety of products, the possible presence of a carcinogenic impurity is still a concern that needs to be further examined. Because of the complexity of this issue, and the need to consult Agency staff outside the Office to resolve this issue, it was determined that the review of the additional information regarding the propellant would extend the review clock for 3 more months. However, the Agency intends to work with the Sponsor to complete the review of the amendment in a timely fashion.

- The Sponsor indicated that they are working in developing a specification for the 1,3 butadiene impurity. It may be that the impurity is actually not present at detectable levels in the propellant supply that is used to manufacture this product. The Sponsor was encouraged to submit any available information regarding the assay for the 1,3 butadiene along with proposed specifications for this impurity.

Labeling issue:

- The Agency intends to work with the Sponsor to address the Sponsor's labeling concerns, specifically, whether the indication will be for whole body or restricted to the scalp. However, labeling is affected by the propellant issue. If there is a question regarding presence of a carcinogenic impurity in the propellant, that might require a restricted indication to limit exposure.

The Sponsor emphasized that they would like to discuss the rationale as to why the labeling was restricted to the scalp. The Sponsor will accept restricted labeling if the Agency's scientific rationale supports scalp labeling only. If such case, the Sponsor will follow with a proposal for a Phase 4 study to support class labeling.

The Agency reiterated that they intend to work with the Sponsor to resolve these issues in a timely fashion and that discussions on labeling can proceed, and can be concluded once the propellant issue is resolved.

The conversation ended amicably.

Signature, minutes preparer: /S/ 12/8/98
Concurrence, Chair: 12/9/98

cc:
NDA 20-934
HFD-540/Div File
HFD-105/DeLap
HFD-540/Wilkin
HFD-540/Walker
HFD-540/Jacobs
HFD-540/Brown
HFD-540/DeCamp
HFD-540/Pappas
HFD-540/Cintron

MEMORANDUM OF TELEPHONE CONFERENCE

DATE: November 30, 1998.

DEC 1 1998

NDA: 20-934

DRUG: Luxiq (betamethasone valerate) Foam, 0.1%

SPONSOR: Connetics Corporation
Scott Harkonen, M.D., Vice President of Drug Development

FDA: Susan Walker, M.D., Acting Division Director, HFD-540
Olga Cintron, R.Ph., Project Manager, HFD-540 Olga Cintron 12/1/98.
Mary Jean Kozma-Fornaro, Supv. Project Manager, HFD-540

SUBJECT: Luxiq (betamethasone valerate) Foam- Sponsor's Labeling and Major Amendment Concerns

The Agency called Dr. Harkonen in response to the labeling and major amendment concerns that were relayed to Ms. Cintron on November 30. During the conversation, Dr. Harkonen indicated that Connetics would like to have the opportunity to discuss labeling for the drug product and that Connetics did not agree that the additional information requested by the Agency be a major amendment, thus extending the review clock.

The Agency indicated that the amendment will receive immediate attention, and that it is not appropriate to engage in labeling discussions until the reviews are completed. The additional information that the Agency requested warrants a multidisciplinary review and that this is considered a major amendment.

Dr. Harkonen stated that he will discuss this with his group, but that he may wish to contact the office as Connetics feel that this should not be considered a major amendment that would extend the PDUFA clock.

The conversation ended amicably.

cc:
NDA 20-934
HFD-540/Div File
HFD-540/Walker (Concurrence: 12/1/98.)
HFD-540/Cintron
HFD-540/Kozma-Fornaro

MEMORANDUM OF TELECONFERENCE

FEB 2 8 1999

Date: November 10, 1998.

NDA: 20-934

Drug: Luxiq (betamethasone valerate) Foam, 0.12%

External participants: Max Nygaard, Regulatory Affairs, Connetics

Dawn Parcell, Regulatory Affairs, Connetics
Claire Lockey, Vice President, regulatory Affairs, Connetics

FDA participants: Jonathan Wilkin, M.D., Division Director, HFD-540
Olga Cintron, R.Ph., Project Manager, HFD-540

The purpose of this teleconference was to request the Sponsor to provide additional information to assess the safety of the Luxiq Foam and to indicate the impact of this amendment on the review timeline of this NDA. The following was conveyed to the Sponsor:

1. The Agency indicated that a new safety concern has been raised as a result of the new information (specifically, the British Standard 4250: 1997, containing specifications for commercial butane and commercial propane) that the Sponsor provided to the Agency via facsimile on November 9, 1998. To further assess this safety concern the following information was requested to be submitted to the NDA:

   a. Please provide information on the long-term, as well as short-term, safety (animal and human) of various impurities found in the propellant, including hydrogen sulfide, organic mercaptans, butadiene, other dienes, or any other hydrocarbon compounds present. An estimate of human exposure to the various components under conditions of use would also be very useful.

   b. Please provide the labeling for the betamethasone valerate foam marketed by Evans Medical, Ltd., in the U.K.

   c. Please obtain from and submit to the NDA the full tests results for the lots of propellant used in the clinical studies.

2. The Agency indicated that this information will constitute a major amendment to the NDA, thus extending the review clock for 3 additional months. However, the Agency's goal is to review this information once submitted and not wait to the end of the review cycle.

3. The Agency indicated that discussions on the indication (unrestricted class labeling versus corticosteroid-responsive dermatoses of the scalp) will be deferred until the

requested information is reviewed.

Action items:

1. The Agency will fax the information requests to the Sponsor.

2. The Sponsor will submit the amendment to the NDA as quickly as possible.

Signature, minutes preparer: /S/ 11/17/98
Concurrence, Chair: 11/28/99

cc:
NDA 20-934
HFD-540/Wilkin
HFD-540/DeCamp
HFD-540/Pappas
HFD-540/Brown
HFD-540/Jacobs
HFD-540/Huene
HFD-540/Walker
HFD-540/Cintron

MEMORANDUM OF TELECONFERENCE

FEB 2 1999

Date: November 6, 1998.

NDA: 20-934

Drug: Luxiq (betamethasone valerate) Foam, 0.12%

External participants: Max Nygaard, Regulatory Affairs, Connetics
Dawn Parcell, Regulatory Affairs, Connetics
Joel Henner, Sr. Director of Q.A. and Q.C., Connetics

FDA participants: Jonathan Wilkin, M.D., Division Director, HFD-540
Wilson DeCamp, Ph.D., Chemistry Team Leader, HFD-540 (2/2/99)
Phyllis Huene, M.D. Clinical Reviewer, HFD-540
Paul Brown, Ph.D., Pharmacologist/Toxicologist, HFD-540
Abby Jacobs, Ph.D., Pharm/Tox Team Leader. HFD-540
Olga Cintron, R.Ph., Project Manager, HFD-540 11/2/98.

The purpose of this teleconference was to request the Sponsor to provide additional information regarding the content of the mixed hydrocarbon propellant in the foam. The highlights of the teleconference are presented below:

- The Agency indicated that the Sponsor's response to the informational request letter provided information with respect to the supplier as to how the supplier controls the levels. However, the Sponsor's response did not provide the specification for limits of each of the hydrocarbon mixture components. The Agency indicated that additional information is needed, specifically, the quatitative measurements of content of the hydrocarbon blend to assess any safety risks.

- The Sponsor indicated that, to their knowledge, the hydrocarbon blend was not tested for content. However, they will contact the supplier and request them to provide any information regarding sulfur measurements.

  The Sponsor clarified that all three components of the hydrocarbon blend need to pass the odor test in conformance to the British Standards 4250 (1997 edition).

- The Agency requested to provide this information along with any additional information that the supplier be able to provide. The Sponsor agreed.

The conversation ended cordially.

cc:
NDA 20-934
HFD-540/Wilkin
HFD-540/DeCamp
HFD-540/Pappas
HFD-540/Brown
HFD-540/Jacobs
HFD-540/Huene
HFD-540/Walker
HFD-540/Cintron

MEMORANDUM OF TELEPHONE CONVERSATION

OCT 13 1998

Date: October 5, 1998.

Sponsor Participant: Ms. Claire Lockey, Vice President, Regulatory Affairs, Connetics

FDA Participants: Ernie Pappas, Chemistry Reviewer, HFD-540
Wilson DeCamp, Ph.D., Chemistry Team Leader, HFD-540
Olga Cintron, R.Ph., Project Manager, HFD-540 Olga Cintron 10/5/98

Subject: NDA 20-934, Betamethasone Valerate Foam, 0.1%

The purpose of this telephone conversation was to answer the sponsor's question regarding the status of pre approval inspection and tradename for this application.

The Sponsor was advised of the following:

Status of Pre Approval Inspection:

- The Agency does not always schedule a pre approval inspection for every application. An Establishment Evaluation is performed for every application, however the evaluation may be based on inspectional history rather than a new inspection. For this application, the Establishment Evaluation for , facilities were based on previous inspections with a recommendation to not to withhold approval. The Office of Compliance do not plan to schedule a pre approval inspection for any of these firms at this time. This is mostly due to limited resources. However, this does not mean that the Office of Compliance might decide to re inspect the facilities for other reasons.

Status on the Tradename:

- Review of the tradename is still pending from the Labeling and Nomenclature Committee. However, the sponsor is advised that the use of a second tradename to identify the vehicle foam is new to the Agency. The response from the L&N Committee will be provided as soon it becomes available.

The conversation ended cordially.

cc:
Original NDA 20-934
HFD-540/DIV FILE
HFD-540/DeCamp Concurrence: 10/13/98.
HFD-540/Cintron
HFD-540/Pappas Concurrence: 10/6/98.

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