CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-934

CORRESPONDENCE

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July 27, 1998

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 20-934 Betamethasone Valerate Foam 0.1%
Corticosteroid-Responsive Dermatoses

Submission of Draft Labeling

Dear Dr. Wilkin:

Pursuant to a telephone conversation with the Division, we are submitting four hard copies and an electronic copy of the draft package insert / patient information leaflet for Betamethasone Valerate Foam 0.1%.

As we stated in the cover letter to the amendment we submitted on July 21, 1998 (which included duplicate copies of the draft package insert / patient information leaflet), the draft package insert has been modified from that submitted in our original NDA (December 17, 1997) in the following ways:

- A title (Clinical Studies) has been added immediately prior to the last paragraph on page 3-0003.
- On page 3-0007, the NDC number has been moved from the middle to the end of the sentence, following the heading "How Supplied."
- The storage conditions on page 3-0007 have been changed to) to reflect controlled room temperature as defined in the U.S. Pharmacopeia.
- A warning regarding the flammability of the product has been added to page 3-0007, following the heading "Warning" that reads: **FLAMMABLE. AVOID FIRE, FLAME OR SMOKING DURING USE.**

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

If you have any questions of comments regarding this submission, please contact Max Nygaard at (650) 843-2818 or me at (650) 843-2889.

Sincerely,

Claire J. Lockey
Vice President
Regulatory Affairs

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DRUG AMENDMENT
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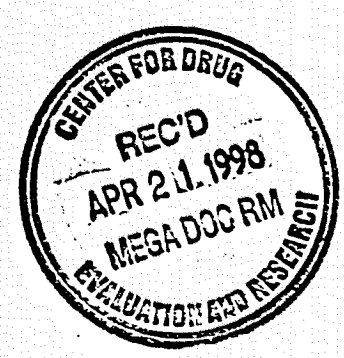

April 17, 1998

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

RE: NDA #20-934 Betamethasone Valerate Foam 0.1%
Corticosteroid-Responsive Dermatoses

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 Betamethasone Valerate Foam 0.1% (NDA #20-934) is enclosed. There has been no new safety information.

If you need any additional information, please do not hesitate to contact Max Nygaard at (650) 843-2818 or me at (650) 843-2889.

Sincerely,

Claire J. Lockey
Vice President
Regulatory Affairs

SAFETY UPDATE REPORT

The Integrated Summary of Safety (ISS) submitted in the clinical data section of NDA #20-934 for Betamethasone Valerate Foam 0.1% (BMV foam) included safety information derived from nonclinical and clinical studies, spontaneous reports from foreign marketing experience, and a literature review. This four-month report will provide an update of any new safety information since the NDA was submitted to FDA on December 16, 1997.

Nonclinical and clinical studies

The cut-off date for information in the ISS for all nonclinical and clinical studies conducted with BMV foam was December 1997. All of the nonclinical and clinical studies reported in the NDA had been completed by the time of the submission, and final study reports were included in the NDA. Connetics is not aware of any other nonclinical or clinical studies conducted with BMV foam or any new safety information from such studies.

Spontaneous reports from foreign marketing experience

The cut-off date for information concerning the foreign marketing experience of BMV foam was April 1997. A third periodic safety report for the period May 1 - October 31, 1997, has been filed with the U.K. authorities by Evans Medical Ltd. (Evans), a subsidiary of Medeva plc (Leatherhead, Surrey, U.K.). A non-serious event was included in this report to the U.K. authorities, but it does not raise any new safety issues.

Literature review

The cut-off date for publications included in the literature review in the ISS was May 1997. Connetics is not aware of any publications reporting on studies conducted with BMV foam. Since May 1997, there have been no reports in the literature that raise any new safety issues concerning the drug substance betamethasone valerate.

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February 22, 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 #20-934 Luxiq™
(betamethasone valerate) Foam 0.12%

Revised container and carton labeling

Dear Dr. Wilkin:

This submission contains revised draft container and carton labels with paragraph breaks inserted as per the Agency's February 22, 1999 request.

This submission also serves to confirm that, on both the container and the carton label, the size of the trade name will not be more than twice the size of the generic name (e.g., the height of the letter "L" in Luxiq is 6 mm and the height of the "b" in "betamethasone" is 3.5 mm).

We also accept the change in the package insert relayed to us by Olga Cintron via telephone on February 22, 1999 which states that on lines 1 and 2 of the patient information leaflet the end of the first sentence will read "...for the relief of corticosteroid-responsive skin conditions of the scalp."

If you have any questions about this submission, please call me at (650) 843-2889.

Sincerely,

Claire J. Lockey
Vice President
Regulatory Affairs

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February 25, 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 #20-934 Luxiq™
(betamethasone valerate) Foam 0.12%

Phase IV commitment

Dear Dr. Wilkin:

Connetics commits to submit to the NDA the complete validation data for the routine testing method for 1,3-butadiene impurity in the propellant used in the manufacture of Luxiq within 60 days of approval of the NDA.

If you have any questions, please call me at (650) 843-2889.

Sincerely,

Dawn Parsell for

Claire J. Lockey
Vice President
Regulatory Affairs

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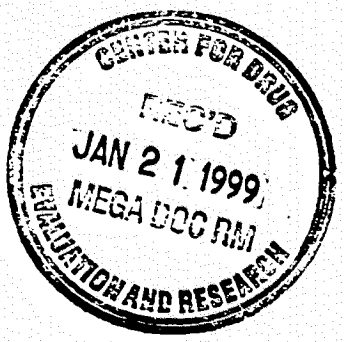

January 20, 1999

Robert J. DeLap, M.D., Ph.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V
9201 Corporate Boulevard
HFD-105
Rockville, MD 20850

RE: NDA #20-934 Luxiq™ (Betamethasone Valerate Foam 0.1%)
Corticosteroid-Responsive Dermatoses

Dear Dr. DeLap:

At the request of Dr. Scott Harkonen, enclosed is a desk copy of Connetic's response to the Agency's request for additional information regarding the propellant used in the manufacture of Luxiq. This is being sent to you in follow up to previous discussions that he had with you regarding the status of our NDA.

Dr. Harkonen can be reached at (650) 843-2800 if you have any questions.

Sincerely,

Max Nygaard

Max Nygaard
Regulatory Affairs Associate

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

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NDA ORIG AMENDMENT
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January 19, 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 #20-934 Luxiq™ (Betamethasone Valerate Foam 0.12%)
Corticosteroid-Responsive Dermatoses

Response to teleconference (December 16, 1998)

Dear Dr. Wilkin:

This submission is in response to our teleconference of December 16, 1998, in which the Agency asked us to address the theoretical risk of 1,3-butadiene in the propellant used in the manufacture of Luxiq.

We would like to begin by reiterating that, to date, no 1,3-butadiene has been detected in our propellant. We understand the concern about the potential for exposure to trace levels of 1,3-butadiene in the propane/butane propellant and the potential carcinogenicity risk of this compound. To this end, we have contracted for an assessment of the theoretical risk associated with the use of Luxiq, if 1,3-butadiene were present in the propellant raw material. Our discussions with various suppliers of propellants to the cosmetic and pharmaceutical industry indicate that, when they test for the presence of the 1,3-butadiene, its typical limit of detection is 100 ppm (equivalent to 0.01 mol%). The results of the risk assessment using this upper limit of 1,3-butadiene concentration clearly demonstrate that the carcinogenic risk from using Luxiq (2×10^{-7}), is well below the 1×10^{-6} value considered to be an "insignificant level" by the FDA when evaluating carcinogenic risks from drug contaminants (see Gaylor et al., 1997, Attachment 1).

This submission also contains the other information the Agency requested: proposed labeling changes, the test method for 1,3-butadiene, and the raw data for the lots of propellant tested to date.

Risk assessment of 1,3-butadiene in Luxiq

We have consulted with several independent risk assessment experts regarding the mathematical modeling of risk associated with the use of Luxiq. We contracted with the to perform the risk analysis. This analysis is appended in To provide information for the risk analysis, Connetics had an independent analysis performed to describe the physico-chemical behavior of 1,3-butadiene (if present in our propellant),

when a dose of Luxiq is dispensed from the can. This was conducted by chemists at . Their report is provided in . These reports were independently reviewed by consultant experts in 1,3-butadiene and risk assessments, . Their evaluation is appended in . Relevant background for these contract organizations and curricula vitae for the responsible individuals are appended in . The contract organizations employed have internationally recognized expertise on 1,3-butadiene and/or its risk assessment.

1,3-Butadiene is highly volatile and rapidly vaporizes to gaseous form at room temperature and atmospheric pressure. Therefore, we have evaluated the risk associated with inhalation in addition to dermal exposure. 1,3-Butadiene is currently classified as a "probable human carcinogen" (Group 2A: IARC 1998; B2: USEPA, 1985). Substantial human epidemiological data exist regarding its carcinogenicity, and potency risk factor values derived from this data can be used with a high level of confidence to model the risk associated with exposure to 1,3-butadiene (USEPA, 1998).

To provide a "worst case" scenario of the potential exposure, the assumptions used for modeling the risk associated with the use of Luxiq were the following: (1) 1,3-butadiene is present in the propellant at the limit of detection of the analytical method (0.01 mol%), although none has been detected to date; (2) a female patient with psoriasis or other steroid-responsive dermatoses applies Luxiq to 20% of her total body surface area; (3) the patient applies 12.5 g of Luxiq twice daily, 365 days per year, for 25 years. A more detailed explanation of the assumptions employed in the modeling and why we believe they represent a reasonable "worst case" scenario is presented in the risk assessment report.

The results of the risk assessment demonstrate that even at an unrealistically high lifetime level of clinical use, insignificant risk (2×10^{-7}) is realized. This value is well below the accepted FDA safety standard of "reasonable certainty of no harm" ($<1 \times 10^{-6}$) (Gaylor et al., 1997). Therefore, we believe that the results of the risk assessment demonstrate that an assay specification of <0.01 mol% (or 100 ppm) 1,3-butadiene in the propellant raw material will provide a product that is safe for patients being treated with Luxiq.

Proposed labeling statement for Luxiq

Given that the risk associated with the use of Luxiq has been shown to be well below the accepted FDA safety standard of "reasonable certainty of no harm," no labeling changes are necessary.

1,3-butadiene test method

Since the results of the risk assessment demonstrate a safety standard of "reasonable certainty of no harm" to patients being treated with Luxiq, we stand by our previous proposal of a specification for 1,3-butadiene in the propellant raw material of "none detected" in an assay with a limit of detection of 0.01 mol% (or 100 ppm) (submitted December 15, 1998).

Our proposed specification is consistent with what is typical for cosmetic and pharmaceutical propellant suppliers. We have contacted a number of propellant manufacturers to inquire about their specifications for 1,3-butadiene. In the U.S.,

are two major propellant manufacturers that provide propellants to the cosmetic and pharmaceutical industry. Although neither company routinely specifies limits for 1,3-butadiene in their propellant blends, both companies monitor their feed stocks for the presence of 1,3-butadiene as part of their ongoing quality assurance of the gasses. Neither company has ever seen evidence of 1,3-butadiene contamination in their propellant using methodology that is sensitive to 100 ppm.

, a partner company of
and a major propellant manufacturer and supplier in Europe, routinely employs a specification of <100 ppm for 1,3-butadiene in their propellant blends. We plan to use as an alternate supplier of propellant for Luxiq. Their address is:

We have previously provided the Agency with summary results for the routine monitoring of propellant blends from our propellant supplier for the period 1997-1998 (submitted November 23, 1998). As a follow-up, four recent lots of propellant purchased from have been tested utilizing assay at , a contract gas testing laboratory. The results show that no 1,3-butadiene was detected in these samples. These results are consistent with those previously submitted. The analytical method employed is a

A description of the method and the chromatographic data are provided as Attachment 6 of this submission. Also provided in is a work plan for validating the 0.01 mol% (100 ppm) limit of detection of this test method.

The currently available methodology for detecting 1,3-butadiene in air samples at part-per-billion levels utilizes adsorbents or condensation methods to concentrate the molecule prior to analysis. These methods are not applicable in our situation, as the butane in the propellant will also be concentrated. In collaboration with , we have initiated a research project to attempt to determine the level of 1,3-butadiene present in representative propellant samples.

We trust that this submission adequately addresses the Agency's concern regarding the theoretical presence of 1,3-butadiene in the propellant used in the manufacture of Luxiq. We believe that the risk assessment report and our suggested specification of "none detected" using the currently available assay with a detection limit of 0.01 mol% are sufficient for the Agency to come to the same conclusion we have: that 1,3-butadiene, even if present at a limit of <0.01 mol% in the propellant used in Luxiq, does not constitute a safety concern.

We anticipate a timely response to this submission, continuation of our labeling discussions, and approval of our NDA. We will provide both the validation of the routine testing method for 1,3-butadiene and results from the research study as soon as they become available (anticipated by mid-February). I will call Olga Cintron to schedule a teleconference, if the Agency feels one is necessary.

Sincerely,

Claire J. Lockey
Vice President
Regulatory Affairs

cc: Robert DeLap, M.D., Ph.D.