

FEB 12 1999

**Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products, HFD-540**

Draft Completed: February 11, 1999

Revised:

NDA 20-934

Submission number

BC

Submission Date

11/20/98

Center Receipt Date

11/23/98

SPONSOR: Connetics Corporation

DRUG: Luxiq™, Betamethasone valerate foam 0.1%

SUMMARY: The sponsor has submitted the British standard specifications for butane and propane in response to a request from the chemistry reviewer for more information about the impurities in the butane:isobutane:propane propellant used in Luxiq. The specifications include a limit for dienes content of 0.5 mole%. The British standard states:

"LPG containing more than 0.1 % (m/m) of any substance classified as carcinogenic is also required to be classified as carcinogenic. Users of this standard should be aware of this requirement when making contractual arrangements, since commercial propane and commercial butane may contain the substance 1,3-butadiene which is classified as a Class II carcinogen."

CONCLUSIONS: The toxicity of dienes has not been previously considered in the evaluation of this product. The presence of 1,3-butadiene may be a safety concern since it is classified as a probable human carcinogen. The potential risk from the presence of 1,3-butadiene in Luxiq should be further evaluated.

Note: A more thorough review of the possible exposure to 1,3-butadiene from Luxiq foam was completed and submitted as an amendment to the original review of NDA 20-934. This amendment is dated 11/17/98. Additional information about the toxicity of the impurities was requested from the sponsor.

ISI

2/11/99

Paul C. Brown, Ph.D.
Reviewing Pharmacologist

cc:

NDA 20-934

HFD-340

HFD-540

HFD-540/PHARM/BROWN

HFD-540/TL/AJACOBS

HFD-540/MO/HUENE

HFD-540/CHEM/PAPPAS

HFD-540/PM/CINTRON

Concurrence Only:

HFD-540/DD/WILKIN *g w* 2/19/99

HFD-540/TL/AJACOBS *g j* 2/12/99

Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products, HFD-540

NOV 18 1998

Draft Completed: November 17, 1998

NDA 20-934

Amendment to original review

SPONSOR: Connetics Corporation

DRUG: Luxiq™, Betamethasone valerate foam 0.1%

INTRODUCTION: The sponsor has recently provided information about the propellant used in their foam products in response to questions asked by the chemistry reviewer. From this new information, it became apparent that the propellant may contain dienes at a total concentration of 0.5%. The toxicity of dienes has not been previously considered in the evaluation of this product. The presence of 1,3-butadiene may be a safety concern since it is classified as a probable human carcinogen. Other impurities may also be found in the propellant such as sulfur-containing compounds.

Possible exposure to 1,3-butadiene from the propellant of the betamethasone foam formulation produced by Connetics.

The propellant is a combination of 55% propane, 15% isobutane and 30% *n*-butane. The propellant may contain as much as 0.5 mole % dienes. If these are all molar percentages then the following calculations can be made, assuming the dienes were all 1,3-butadiene.

Component	MW	mole %	moles/1 mole mix	grams/1 mole mix
Propane	44.09	55	0.55 mole	24.25 g
Isobutane	58.12	15	45 (merged) 0.45 mole	26.15 g
<i>n</i> -butane	58.12	30		
1,3-butadiene	54.09	0.5	0.005 mole	0.27 g

Approximate grams per 1 mole of mix = 50.67 g

The entire can of propellant contains 4.5 g of propellant. How many moles of propellant is this?

$$\frac{4.5 \text{ g}}{50.67 \text{ g/mole}} = 0.089 \text{ mole}$$

How much 1,3-butadiene could be in the entire can?

$$\frac{0.27 \text{ g}}{\text{mole}} \times 0.089 \text{ mole} = 0.024 \text{ g} = 24 \text{ mg}$$

How does this compare to limits on 1,3-butadiene exposure in occupational settings?

The American Conference of Governmental Industrial Hygienists 1994-1995 recommendation for a threshold limit value for 1,3-butadiene is 2 ppm as an 8-hour time weighted average (TWA). This is equivalent to approximately 4 mg/m³.

Given that normal minute volume = 7.5 L/min

and 1 L = 10^{-3} m^3

Therefore: Normal minute volume = $\frac{10^{-3} \text{ m}^3}{1 \text{ L}} \times 7.5 \text{ L/min} = 7.5 \times 10^{-3} \text{ m}^3 / \text{min}$

Volume of air breathed in 8 hours = minutes in 8 hours \times minute volume
 $= 8 \text{ hours} \times \frac{60 \text{ min}}{1 \text{ hour}} \times 7.5 \times 10^{-3} \text{ m}^3 / \text{min} = 3.6 \text{ m}^3$

Amount of 1,3-butadiene breathed in 8 hours at TWA = minute volume \times concentration
 $= 3.6 \text{ m}^3 \times 4 \text{ mg/m}^3 = 14.4 \text{ mg}$

Therefore, the entire can could contain more than a recommended maximum exposure of 1,3-butadiene based on the occupational threshold limit value. However, a patient may not be exposed to this much 1,3-butadiene for several reasons.

1. The patient may be unlikely to use the entire contents of a can on one day. Use of one gram of foam would reduce the maximum possible exposure to approximately 0.24 mg dienes.
2. The diene content may be less than 0.5% of the propellant.
3. 1,3-butadiene may be only one component of the total dienes and therefore there may be less than 0.5% 1,3-butadiene even if the total concentration of dienes is 0.5%.
4. The patient may not breathe or absorb all of the 1,3-butadiene that is released from the can at each use.

Carcinogenicity Information on 1,3-butadiene:

Preclinical studies show that 1,3-butadiene is mutagenic with metabolic activation. The mutagenic species appear to be epoxide metabolites. Studies *in vitro* suggest that metabolism of 1,3-butadiene is qualitatively similar in humans and experimental animals.

Preclinical studies also show that 1,3-butadiene is carcinogenic. All doses tested have produced tumors in experimental animals (6.5 to 8000 ppm). These studies have not identified a no-effect level. ✓

Epidemiologic studies of workers exposed occupationally to 1,3-butadiene have provided some evidence of carcinogenicity in humans.

The International Agency for Research on Cancer has determined that 1,3-butadiene is *probably carcinogenic to humans* (Group 2A) (IARC Monograph 54:237-285, 1992).

DISCUSSION: The sponsor should submit information to support the safety of the propellant. The presence of 1,3-butadiene in the propellant is probably most concerning since this compound is genotoxic and is characterized as a probable human carcinogen. Additional impurities may also be of concern.

Although, in theory, no safe threshold may exist for genotoxic carcinogens, in reality exposures may be so low as to produce undetectable effects. Unfortunately, animal studies have not identified a NOAEL for the carcinogenicity of 1,3-butadiene; therefore, a dose that does not produce detectable effects can not be easily calculated from the animal data.

Considering the various factors that influence final exposure of the patient to any 1,3-butadiene in the product, it may be possible that the exposure would be low as compared to that permitted in industrial settings. However, these levels may still be considered inappropriate for a pharmaceutical agent.

The sponsor stated in a submission dated 9 November 1998 that additional purification of the blended hydrocarbons is conducted to remove sulfur-containing compounds. The propellant is tested after blending to verify the absence of the characteristic odor of sulfur compounds. This is probably sufficient to assure that hydrogen sulfide and organic mercaptans have been reduced to safe levels.

CONCLUSIONS: Since 1,3-butadiene is a probable human carcinogen, the only way that the propellant can be considered safe is by showing that exposure to 1,3-butadiene is nonexistent or significantly below an animal NOAEL. For other impurities, both toxicity and exposure data may help demonstrate whether the impurities are a safety concern. In the absence of such information, it is recommended that NDA 20-934 not be approved.

RECOMMENDATIONS:

The sponsor should provide information on the long-term, as well as short-term, safety (animal and human) of the impurities found in the propellant, including butadiene, other dienes, or any other hydrocarbon compounds present. This information should include No Observed Adverse Effect Levels (NOAELs). The sponsor should provide an integrated assessment of the safety of the propellant based on this information and on estimated human exposure to the impurities in the propellant under conditions of use. This information will be reviewed to determine whether use of the propellant is safe.

/S/

11/18/98

Paul C. Brown, Ph.D.
Reviewing Pharmacologist

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NDA 20-934
HFD-340
HFD-540
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HFD-540/TL/AJACOBS
HFD-540/MO/HUENE
HFD-540/CHEM/PAPPAS
HFD-540/PM/CINTRON

Concurrence Only:
HFD-540/DD/WILKIN 11/18/98
HFD-540/TL/AJACOBS u.j. 11/18/98

OCT 8 1998

**Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products, HFD-540**

Draft Completed: October 7, 1998

Revised:

NDA 20-934

Submission number

BL

Submission Date

7/27/98

Center Receipt Date

7/28/98

SPONSOR: Connetics Corporation

DRUG: Luxiq™, Betamethasone valerate foam 0.1%

INTRODUCTION: This submission contains the sponsor's draft labeling. The labeling will be reviewed and changes suggested.

REVIEW OF PROPOSED LABELING: Suggested changes to sections of the label associated with pharm/tox issues are discussed in the following paragraphs.

The Carcinogenesis section of the label should be changed from:

to

This change is recommended since the carcinogenicity of some topical corticosteroids has been studied, thus making the original wording incorrect.

Recent submissions from Schering to their betamethasone NDA's indicate that betamethasone is genotoxic in two genotoxicity assays: an *in vitro* human peripheral blood lymphocyte chromosome aberration assay and in an *in vivo* mouse bone marrow micronucleus assay. In addition, hydrocortisone is clastogenic in micronuclei and sister chromatid exchange assays. Therefore, the following sentence should be removed from the proposed label.

The sentence may be replaced with a statement about the mutagenicity of betamethasone.

The relevant sections of the sponsor's proposed label are reproduced below with suggested deletions marked with strikethrough and additions marked by underline.

The following paragraphs comment on other sections of the label and discuss additional possible changes to the label.

The table in the Clinical Studies section is difficult to interpret without knowing the total number of subjects in each treatment group. The total number in each group can be calculated using the number of subjects and the corresponding percentage. For the Luxiq group the total number of subjects can be calculated to be 64, in the BMV lotion group the total number of subjects is 63 and in the vehicle group the total number of subjects is 32. Adding these numbers together provides a total for the entire trial of 159, instead of 190 as stated in the label. The difference may be that 190 patients began the trial but only 159 were evaluable. I would suggest that the total number of subjects per group be included in the table to facilitate interpretation of the data. ✓

The patient information leaflet includes the instruction to wash hands after applying the foam. Perhaps this instruction should be included in the dosage and administration section of the package insert. ✓

Note: The preceding two paragraphs were conveyed to Phyllis Huene, the medical reviewer for the NDA.

The How Supplied section of the package insert states that the product should be stored at controlled room temperature 59-86°F (15-30°C). The warning section states that the product should not be exposed to heat or stored at temperatures above 120°F (49°C). These statements are not consistent. Even though the objectives of these two label sections are different, the two statements should probably agree. One possible change would be to have the warning section say that the product should not be exposed to heat and that it should be stored at controlled room temperature.

Note: The preceding paragraph was conveyed to Ernie Pappas, the chemistry reviewer for the NDA.

CONCLUSIONS: The proposed labeling is acceptable from a pharm/tox perspective with the suggested changes.

/S/

10-7-98

Paul C. Brown, Ph.D.
Reviewing Pharmacologist

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NDA 20-934

HFD-340

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HFD-540/PHARM/BROWN

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HFD-540/MO/HUENE

HFD-540/CHEM/PAPPAS

HFD-540/PM/CINTRON

Concurrence Only:

See below,

HFD-540/DD/WILKIN

FW 10/30/98

HFD-540/TL/AJACOBS

a.g. 10/16/98

190 patients were in the ITT population,
but one arm (placebo lotion), $n=31$, was
not presented in the table.

FW 10/30/98

Review and Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products (HFD-540)
NDA 20-934 (Original Submission, dated 12/16/97)

Drug Name: Betamethasone Valerate Foam, 0.1%

JAN 21 1998

Category: Corticosteroid

Indication: steroid-responsive dermatoses

Sponsor: Connetics, Inc., Palo Alto, CA

Number of Vols.: 40

Date CDER Received: 12/17/97

Date Assigned: 12/22/97

Date Review Started: 1/16/98

Date 1st Draft Completed: 1/20/98

Date Review Accepted by Supervisor:

Related Submissions: IND

Review Objective: To determine approvability of this application from review of preclinical safety studies.

Composition: See Attachment 1

Preclinical Studies

Only the following three preclinical safety studies have been performed with this new 0.1% foam formulation of betamethasone valerate:

1. Acute Dermal Irritation Study in Rabbits (Study No. A/S/40571)
2. Acute Eye Irritation Study in Rabbits (Study No. A/E/40591)
3. Skin Sensitization Study in the Guinea Pig (Study No. A/K/40675)

All these studies had been submitted in IND and have been reviewed. (See Attachment 1).

Rest of the toxicology and pharmacology information have been taken from the published literature and/or from the available information in the public domain (e.g. under FOI acts from various NDAs for Valisone^R).

Evaluation and Comments:

Corticosteroids, particularly various formulations of Valisone, have been in use for dermatologic indications for many years. Its pharmacologic effects and toxicities in animals and humans are well known. The application appears to satisfy the criteria for a 505(b)(2) application. In a pre-IND/End-of-Phase II meeting held at FDA on 11/4/96, it was decided that the Sponsor would have to demonstrate a comparable bioavailability from the new foam formulation to that of Valisone or another comparable formulation of betamethasone valerate.

Since Valisone is longer manufactured by its maker, FDA suggested to use Fougera product. The Sponsor claims that in the vasoconstriction study, the potency of the foam product was found to be between that of BMV ointment and BMV lotion. Also, in the clinical trial, BMV foam showed a safety profile similar to that of BMV lotion (see the clinical review). Therefore, no additional preclinical studies are needed.

The three studies already performed with the foam showed that it was not a skin sensitizer or skin irritant, but was a moderate eye irritant. The labeling should have a warning about eye irritation. The Sponsor has also addressed the inhalation toxicity of the propellant (propane/butane). The Sponsor stated: There should be no toxicity (narcosis) from inhalation of propane/butane aerosol with normal use of the product, as most of the propellant expelled from the can is trapped in the

foam structure. The propellant gas will diffuse rapidly in air as the foam breaks down." Also the labeling instructs to avoid direct application to the face or scalp.

Recommendation:

The application is found approvable with minor labeling changes.

/S/

Syed N. Alam, Ph.D.
Pharmacologist

HFD-540/DD/Concur/Wilkin *[Signature]* 2/18/98
HFD-540/TL/Concur/Jacobs a.g. 1/21/98

cc:
NDA 20-934

HFD-540/

HFD-540/Pharm/Alam

HFD-540/TLPharm/Jacobs

HFD-540/MO/Huene

HFD-540/Chem/DeCamp

HFD-540/CSO/Cintron

Review and Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products (HFD-540)

IND (Original Submission, dated 12/6/96)

Drug Name: Betamethasone Valerate Foam 0.1%

Category: Corticosteroid

Indication: Steroid-responsive dermatoses

Sponsor: Connective Therapeutics Inc., Palo Alto, CA

Number of Vols.: One

Date CDER Received: 12/9/96

Date Assigned: 12/12/96

Date Review Started: 12/29/96

Date 1st Draft Completed: 12/30/96

Date Review Accepted by Supervisor:

Related Submissions: NDAs: 16-322 (Valisone Cream), 16-740 (Valisone Ointment 0.1%), 16-932 (Valisone Lotion 0.1%)

Review Objective: To determine, based on available preclinical safety data, whether the proposed initial clinical studies are reasonably safe to initiate.

Index of Studies:

<u>Study</u>	<u>Page</u>
Acute dermal irritation study in rabbits	179
Acute eye irritation study in rabbits	189
Skin sensitization study in guinea pigs	204

Composition:

<u>Component</u>	<u>Amount (% W/W)</u>
✓ Betamethasone Valerate	
✓ Cetyl Alcohol	
✓ Stearyl Alcohol	
✓ Polysorbate 60	
✓ Ethanol	
✓ Purified Water	
✓ Propylene Glycol	
✓ Citric Acid Anhydrous	
✓ Potassium Citrate	

Proposed Clinical Trials: Proposals for the following three studies have been submitted:

- a comparative vasoconstrictor study
- a comparative safety and efficacy study in scalp psoriasis
- an HPA axis function study

Only for the comparative vasoconstrictor assay a complete clinical protocol has been submitted.

This is titled:

“Bioavailability of topical 0.1% betamethasone valerate in human skin from a lotion, ointment and foam vehicle formulation.”

The study will determine the E_{max} dose-duration response of 0.1% betamethasone valerate in three different formulations (ointment, lotion and foam) in 36 to 50 normal healthy volunteers of either sex (aged 18- 65 years). A 5 μ l (approx. 5 mg) of each formulation will be applied to the appropriate designated skin site with a surface area of 1.13 cm^2 . Each subject will receive all three formulations. Skin blanching response will be measured 1 hour before drug application (baseline), immediately after drug removal (0 hour) and again 2, 4, 6, 19 and 24 hours after drug removal.

Preclinical Studies. All 3 studies were performed at

1. Acute Dermal Irritation Study (Toxicol Study # A/S/40571)

The back and flanks of three New Zealand White female rabbits were clipped, and three parallel abrasions were made on the right flank of each rabbit with a needle. A 0.5 g aliquot of betamethasone valerate foam was massaged onto both flanks, and the application sites were bandaged for 4 hours. The skin reaction at each site was determined after removing the patches, at various time intervals.

During the 72-hour observation period, no skin reaction was noted at any site (intact or abraded) in any animal. The primary irritation index was 0.0 for both the abraded and intact skin sites.

2. Acute Eye Irritation Study (Toxicol Study # A/E/40591)

0.1 ml of betamethasone valerate foam (collapsed to form liquid) was instilled into the right eyes of 3 New Zealand White rabbits with the contralateral eyes serving as the controls. The eyes were not washed. The ocular irritation was scored at 1, 24, 48 and 72 hours and 7 days after treatment.

The foam produced conjunctival irritation (hyperemia and chemosis) in all three rabbits within 1 hour of instillation. Only at 7-day examination, all the eyes were found clear of irritation. Corneal

opacity was observed in one rabbit.

The maximum mean irritation score was 8.7 occurring at 24 hours after dosing.

3. Skin Sensitization (DTH) Study in Guinea Pigs (Toxicol Study # A/K/40675)

The delayed dermal hypersensitivity (Type) reaction was assessed in guinea pigs by the method of Magnusson Kligman Maximization Test.

Groups of 10 control and 20 test animals (female albino guinea pigs) were injected in the shoulder region on Day zero with 1:1 mixture of Freund's Complete Adjuvant (FCA) and betamethasone valerate foam (diluted in water 1:100 v/v), followed on Day 6 with topical application to clipped skin of 10% sodium lauryl sulfate in paraffin. On Day 7, a topical patch containing the steroid was applied to boost the response.

On Day 14, the animals were challenged by topical application of patches containing BMV foam or the vehicle.

No positive responses to challenge with BMV or the vehicle was reported in any of the test or control animals at 24 and 48 hours post dosing.

Evaluation

Betamethasone valerate, a glucocorticosteroid, has been marketed in the USA by the Schering Corporation since 1967, and was available in the dosage forms of a cream, an ointment and a lotion for topical uses at a strength of 0.1% betamethasone base. The 0.1% foam dosage form to be investigated under the present IND, has recently received marketing approval in the UK for the treatment of steroid-responsive scalp dermatoses.

The pharmacology and toxicology of betamethasone valerate have been studied by Schering during their NDA approval process, as well as by other outside research organizations. The

Schering data includes acute and subacute toxicity studies in mice, rats and dogs with oral, intraperitoneal or subcutaneous administration. Schering performed 90-day dermal toxicity studies in rabbits and guinea pigs. Over many years of topical use, the safety of 0.1% betamethasone valerate (BMV) in humans is well-established. Toxicities are usually seen at high doses or during prolonged use. The potential for systemic toxicity from topical dosing is usually low and includes anorexia and weight loss, HPA axis suppression, adrenal and thymic atrophy, thinning of skin, gastric erosion, cataracts, and increased blood glucose and cholesterol. The present foam formulation differs from these other commercial products in some inactive ingredients. A mixture of propane and butane, used in cosmetic industries, is present in the formulation as a propellant. The concentration and the amount that would be used per application should not pose any threat of serious adverse effects. However, there has to be a warning about flammability of the preparation in the labeling.

At this time, the most important issue for toxicologic safety evaluation is whether the submission could be considered a 505 (b)(2) application so all preclinical data generated by Schering could be used for this application. Ms. Elizabeth Dickinson of the General Counsel's Office has assured me that it would be proper to examine other Sponsor's data on BMV for the safety evaluation of this foam product without any authorization letters from them.

In such situation, the Sponsor only has to show that the proposed product is bioequivalent to the innovator product. The Sponsor has proposed such a study, i.e. a vasoconstriction study in humans. In the past, such assays have routinely been allowed to proceed under screening INDs. The Sponsor has performed three acute studies with the foam formulation, one of which is a guinea pig sensitization study. The foam product was not a skin sensitizer in this study.

It was not a skin irritant, but it was a moderate eye irritant.

Recommendation for the Project Manager:

It would be helpful if we could get a more clear assessment about applicability of Section 505 (b)(2) for this drug product from the General Counsel's Office.

Regulatory Recommendation:

1. The labeling should have warning about flammability of the product.
2. The proposed vasoconstriction assay may be allowed to be initiated.
3. The other two proposed clinical trials should not be initiated until we have reviewed the bioavailability study to be performed by the Sponsor.

/S/

Syed N. Alam, Ph.D.
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HFD-540/DD/Concur/Wilkin

HFD-540/TL/Concur/Jacobs 0.9. 12/31/90

cc:
IND

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HFD-540/Chem/DeCamp

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