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APPLICATION NUMBER: NDA 20-934

MEDICAL REVIEW(S)

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MEDICAL OFFICER'S REVIEW OF AMENDMENT TO NDA 20-934

February 17, 1999

SPONSOR: Connectics Corporation
Palo Alto, CA

DRUG: Luxiq (Betamethasone valerate foam 0.1%)

CLINICAL INDICATION: Corticosteroid-responsive dermatoses

DATE OF AMENDMENT: January 19, 1999

REASON FOR AMENDMENT: Response to teleconference of 12/16/98

This amendment is in response to the Agency's request that the sponsor provide information to enable a risk assessment of 1,3-butadiene in the propellant used in Luxiq, particularly in regard to potential carcinogenicity. In this submission the sponsor has provided a report on risk assessment, information on the test method for 1,3-butadiene, the raw data for lots of propellant tested to date, and comments on labeling changes in this regard.

The sponsor states that no 1,3-butadiene has been detected in the Luxiq propellant. Their discussions with various suppliers of propellants to the cosmetic and pharmaceutical industry indicate that the typical limit of detection for 1,3-butadiene is 100 ppm (equivalent to 0.01 mol %).

The sponsor contracted with _____ to perform the risk analysis. Because 1,3-butadiene rapidly vaporizes to gaseous form at room temperature, the risk with inhalation as well as with dermal exposure was evaluated. The assumptions used for modeling the risk were 1) 1,3-butadiene is present in the propellant at the limit of detection of the analytical method (mol %), 2) a female patient with a steroid-responsive dermatosis applied Luxiq to 20% of the body surface area, and 3) 12.5 gm of Luxiq is applied twice daily, 365 days per year, for 25 years.

The sponsor states that the results of this risk assessment 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.

The sponsor feels that no labeling changes are necessary, 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'.

FDA Chemistry assessment

Mr. Ernest Pappas has reviewed the data provided by the sponsor, and has found that the information that was submitted in support of the analytical methodology is acceptable to test for 1,3-butadiene and other components of the hydrocarbon mixture, and that the test method is capable of detecting 1,3-butadiene at levels as low as mol % (100 ppm).

FDA Toxicology assessment

Dr. Paul Brown has reviewed the information submitted by the sponsor and feels that essentially, the risk is negligible. He states the following conclusion: "Based on current information about the cancer risk of butadiene and the sponsor's risk assessment, the specification of mole % for dienes in the propellant appears to ensure a level of butadiene in Luxiq that does not exceed a cancer risk of 1×10^{-6} except in extreme exposure scenarios."

Reviewer's evaluation: Based on Dr. Brown's extensive review of this issue dated 2/19/99, this reviewer concurs that the risk potentially posed by the presence of 1,3-butadiene in the propellant is insignificant.

cc: Orig NDA 20-934

HFD-540

HFD-540/Wilkin

HFD-540/TL/Walker SW 2/23/99

HFD-540/MO/Huene

HFD-540/PHARM/Brown

HFD-540/CHEM/Pappas

HFD-54-/PM/Cintrop

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JW 2/24/99

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Phyllis A. Huene, M.D.

2/22/99

ADDENDUM TO MEDICAL OFFICER'S REVIEW OF NDA 20-934

November 16, 1998

SPONSOR: Connectics Corporation
Palo Alto, CA

NOV 17 1998

DRUG: Luxiq (betamethasone valerate) Foam 0.1%

CLINICAL INDICATION: Corticosteroid-responsive dermatoses

REASON FOR ADDENDUM: Safety issues concerning the formulation
propellant

There have recently been safety issues raised concerning the propellants in Luxiq foam. These propellants are an industrial grade hydrocarbon mixture of propane, butane, and isobutane. There is a concern in regard to the human toxicity of possible impurities and contaminants in the mixture, particularly sulfites, hydrogen sulfide, organic mercaptans, and other hydrocarbons such as 1,3-butadiene and other dienes.

The sponsor has been advised to provide all relevant information on the levels of impurities found in the propellant mixture, and existing toxicological data on each compound.

Until this information has been supplied, the application is not approvable.

/S/

Phyllis A. Huene, M.D.

cc: Orig IND

HFD-540/Division file

HFD-540/Wilkin

HFD-540/Walker

HFD-540/Huene

HFD-540/DeCamp

HFD-540/Jacobs

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MEDICAL OFFICER'S REVIEW OF NDA 20-934
ORIGINAL SUBMISSION

OCT 19 1998

February 27, 1998

SPONSOR: Connectics Corporation
Palo Alto, CA

DRUG: Betamethasone Valerate Foam 0.1%

CLINICAL INDICATION: Corticosteroid-responsive dermatoses

Proposed labeling indication statement: 'For relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.'

FORMULATION:

✓ Betamethasone valerate	0.1%
✓ Cetyl alcohol	%
✓ Stearyl alcohol	%
✓ Polysorbate 60	%
✓ Propylene glycol	%
✓ Citric acid anhydrous	%
✓ Potassium citrate	%
✓ Purified water	%

DOSAGE AND ADMINISTRATION: Applications BID

DATE OF SUBMISSION: December 16, 1997

RELATED SUBMISSIONS: NDA 16-322 for Valisone cream 0.1% and 0.01% (Schering); NDA 16-740 for Valisone ointment 0.1%, and NDA 16-932 for Valisone lotion 0.1%.
IND

PHARMACOLOGY AND CONTROLS REVIEWS: These are currently pending.

Marketing history - Betamethasone valerate

Valisone (betamethasone valerate) cream, ointment, and lotion (Schering) were marketed from 1969 to 1996, at which time they were discontinued in the US for business reasons. Generic equivalents of each dosage form, containing 0.1% betamethasone base, continue to be marketed in the US; these include E. Fougera and Co's Betamethasone Valerate Cream 0.1%, Lotion 0.1%, and Ointment 0.1%.

FDA - Sponsor meetings

At a pre-IND meeting on November 4, 1996 between Connectics and the Division of Dental and Dermatologic Drug Products, it was agreed that data which demonstrates comparable bioavailability of Betamethasone Valerate Foam 0.1% (BMV foam) and currently marketed dosage forms of BMV would be sufficient for approval. These data would include the following three studies:

1. A comparative vasoconstrictor assay.
2. A multicenter, double blind study to compare the safety and effectiveness of BMV foam, the foam vehicle, a marketed BMV lotion, and the lotion vehicle.
3. A comparative HPA axis suppression study.

Preliminary results of these studies were presented by the sponsor to DDDDP at a pre-NDA meeting on October 20, 1997. For the comparator products the sponsor used BMV lotion and BMV ointment purchased from _____ At this meeting the Division agreed that Phase II studies, namely dermal irritation, sensitization, phototoxicity, and photosensitization studies, will not be required for BMV foam, on the basis of the extensive clinical experience with betamethasone valerate and with the excipients of the foam formulation.

Foreign marketing history

Connectics has not submitted any marketing applications for BMV foam in any country other than the US.

The Connectics BMV foam is very similar to a BMV foam marketed by Evans Medical Ltd. in the U.K., differing only in the nature of the _____ excipient. The Evans foam product has been marketed since 1996 for the treatment of steroid-responsive dermatoses of the scalp.

Rationale for the foam formulation

The Connectics BMV foam is a solution contained in a pressurized aluminum can, which forms a foam when the solution is dispensed from the can. The foam is thermolabile, so that on contact the temperature of the skin causes the foam to break down to a vehicle most closely resembling a lotion.

As described by the sponsor, the foam formulation is felt to have particular advantages over other topical formulations, particularly for application to certain areas of the body such as the scalp. Cream and ointments have cosmetic disadvantages such as greasiness, inconvenient application, and difficult removal. Lotions often run off the desired site of application. In contrast, the foam is not greasy, stays at the site of application, and is a low residue vehicle.

Overview of the clinical program

As was agreed at the meeting of November 4, 1996, between the sponsor and the Division, the following studies have been provided.

1. A comparative vasoconstrictor assay.
2. A multicenter, double blind study to compare the safety and effectiveness of BMV foam, the foam vehicle, a marketed BMV lotion, and the lotion vehicle.
3. A comparative HPA axis suppression study.

The sponsor has also provided as supportive data the results of two clinical studies performed by Evans Medical on their BMV foam, which, as stated previously, differs slightly from the Connecticut BMV foam in the excipient. These two studies were a Phase I safety study in normal volunteers and a Phase II placebo-controlled study in psoriasis patients.

Vasoconstrictor study (Study BMSP.C.005)

This was a randomized, double blind study in 35 normal subjects, conducted by [redacted]. The comparator products were the Connecticut BMV foam 0.1%, and the E. Fougera BMV ointment 0.1% and BMV lotion 0.1%.

Eight sites on the ventral forearms of each subject were randomly assigned different periods of drug exposure, which were 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 4.0, and 6.0 hours. Within each site, three 1.2 cm diameter circular areas were randomly assigned to receive a 5 μ L application of BMV ointment, lotion, or foam. Additional circular areas on the upper arms served as untreated control sites. Skin blanching assessments were performed at one hour before drug application, immediately after drug removal, and at 2, 4, 6, 19, and 24 hours after drug removal.

Blanching response was measured by two methods: a validated chromameter, and a visual evaluation. The scale used for the visual assessment of blanching was as follows.

Visual assessment of blanching	
Score	Description
0	no pallor, no change from surrounding area
1	mild pallor, slight or indistinct outline of application site
2	moderate pallor, discernible outline of application site
3	moderate pallor, clean, distinct outline of application site
4	intense pallor, clean, distinct outline of application site

For each method the E_{max} (maximal skin blanching) and the ED_{50} (the dose at which blanching is half maximal) were determined for the three test products.

Results were that all three products showed a dose response relationship in that higher dose-durations were associated with greater skin blanching than lower dose-durations. The E_{max} and the ED_{50} values were as follows.

Vasoconstrictor study results		
Assessment method	E_{max}	ED_{50}
Chromameter		
Ointment	- 49.9	4.48
Foam	- 42.2	2.67
Lotion	- 37.0	0.36
Visual		
Ointment	69.3	4.52
Foam	39.0	0.26
Lotion	46.9	0.18

The E_{max} value for the foam was between that of the ointment and lotion by chromameter assessment, but was lower than those of both the ointment and the lotion by visual assessment. The ED_{50} values showed an order of potency of BMV ointment > BMV foam > BMV lotion. The values obtained from the chromameter were judged to be the more reliable, as the chromameter has greater sensitivity to skin blanching than does visual assessment.

The sponsor's conclusions are that the results of the vasoconstrictor study support an intermediate potency for the Connecticut BMV foam formulation between those of the E. Fougera BMV ointment and the E. Fougera BMV lotion formulations.

Reviewer's comments: This reviewer is in agreement with the sponsor that the results of the vasoconstrictor study support the conclusion that BMV foam has a potency intermediate between that of the marketed BMV lotion and BMV ointment.

HPA axis suppression (Study BMSP.C.009)

This study was conducted by Alan Heller, M.D., San Jose Clinical Research, San Jose, CA. and Bruce Miller, M.D., Dermatology Associates Clinical Research Center, Portland, OR. The subjects studied were 18 adult male and female patients with psoriasis or atopic dermatitis affecting at least 30% of the body surface area. Of these, 12 subjects had psoriasis and 6 subjects had atopic dermatitis.

The study objective was to evaluate the effect of BMV foam on the HPA axis in comparison to that of BMV ointment, using the cosyntropin-stimulated change in the plasma cortisol response.

Randomization to treatment with ointment or foam was done separately for subjects with eczema or psoriasis in order to maintain a balance for each disease condition. Each treatment group was comprised of 9 subjects, 6 of which had psoriasis and 3 with eczema. Eleven of the subjects were enrolled at one site and 7 were enrolled at the other.

The subjects were pre-screened at least three days prior to baseline to establish that they had a normal response to a cosyntropin-stimulation test. In this test the serum cortisol levels were measured immediately before and at 30 minutes after IM injection of 0.25 mg Cortrosyn. A normal response was defined as:

1. A pre-injection plasma cortisol level >5 $\mu\text{g/dL}$.
2. A post-injection cortisol level >18 $\mu\text{g/dL}$.
3. A difference between the post- and pre-injection levels ≥ 7 $\mu\text{g/dL}$.

Applications of 15 gm of the test products were made twice daily for 7 days to areas of dermatitic skin involving 30% of the body surface area. At baseline, day 5, and day 9 the subjects were given a cosyntropin-stimulation test. The primary response variable was the change from baseline at day 5 and at day 9 in the difference between the pre-injection and post-injection cortisol levels (the cortisol increment).

Results were that the differences between BMV foam and BMV ointment in the mean values for the cortisol increment at day 5 and at day 9 were not significant. Twelve of the 18 subjects had normal pre-stimulation cortisol levels and a normal cosyntropin response at all assessments. In 4 subjects on the foam and 2 on the ointment, at least one abnormal cortisol value occurred which could possibly have been related to treatment. In none of these subjects was there clear evidence of HPA axis suppression as defined by low pre-stimulation cortisol levels plus an abnormal response in both elements of cosyntropin stimulation (see the above criteria for a normal response). The abnormalities in these four subjects treated with BMV foam are described further as follows.

1. Subject **1**: The pre-stimulation cortisol level was low (4.4 $\mu\text{g/dL}$) at day 9, but the response to cosyntropin testing was normal at day 9, and all values were normal on re-testing at day 13.

2. Subject [REDACTED] The cortisol increment at day 5 was below normal at 5.7 ug/DL, but was also below normal at baseline at 6.1 ug/DL. The values at day 9 and at day 13 were normal.
3. Subject [REDACTED] The cortisol increment was below normal at day 9 (5.6 ug/DL) and Day 13 (5.5 ug/DL), but was also below normal at baseline (6.0 ug/DL).
4. Subject [REDACTED] The cortisol increment was low at day 5 (5.7 ug/DL) while the baseline increment was normal. This subject's post-injection cortisol level on day 5 was not low, but was similar to the post-injection levels at screening, baseline, and day 9. The below normal cortisol increment at day 5 appeared to be due to a high pre-injection cortisol level at day 5, which was higher than the pre-injection levels at the other three visits. The day 9 cortisol increment was normal.

The sponsor's conclusion was that the results of this study show that BMV foam had no effect on the HPA axis, as measured by the cosyntropin-stimulated change in plasma cortisol levels, following the application of 15 gm twice daily for 7 days to the dermatitic skin of patients with $\geq 30\%$ involvement of the body surface area.

Reviewer's comments: The HPA axis suppression study is felt to have been adequately designed and conducted. This reviewer is in agreement with the sponsor's conclusion that no HPA axis suppression was shown after the application of 15 gm of BMV foam twice daily for 7 days to the dermatitic skin of patients with psoriasis or atopic eczema.

Pivotal clinical effectiveness study (Study BMSP.C.006)

This study is entitled 'A Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Betamethasone Valerate Foam in Treating Scalp Psoriasis'. The investigators for the study were as follows.

Ed Bronsky, M.D. Salt Lake City, UT	David Miller, M.D. North Dartmouth, MA
Frank Dunlap, M.D. Tuscon, AZ	Jennie Muglia, M.D. Providence, RI
Holly Faust, M.D. Indianapols, IN	Lawrence Parish, M.D. Philadelphia, PA
David Fivenson, M.D. Detroit, MI	Tolvo Rist, M.D. Knoxville, TN
Cynthia Guzzo, M.D. Philadelphia, PA	Ronald Savin, M.D. New Haven, CT
Mark Lebwohl, M.D. New York, NY	Ken Washenik, M.D. New York, NY
Dale Martin, M.D. San diego, CA	Gerald Weinstein, M.D. Irvine, CA
Bruce Miller, M.D. Portland, OR	

The conduct of the study was as follows.

1. Study objective: This was to evaluate the safety and efficacy of betamethasone valerate foam in the treatment of psoriasis of the scalp, as compared to vehicle and to a lotion form of betamethasone valerate and a placebo lotion.
2. Study design: This was a multicenter, randomized, double-blind, double-dummy, placebo and active controlled, parallel group comparison of BMV foam, BMV foam vehicle, BMV lotion, and placebo lotion in patients with moderate to severe scalp psoriasis. Patients were randomly assigned in a 2:1:2:1 ratio to the four treatment groups as listed above.
3. Test materials: The four test products were as follows:
 - a. BMV foam 0.1% (Connectics)
 - b. BMV foam vehicle
 - c. BMV lotion (E. Fougera), containing 0.1% betamethasone valerate in isopropanol, carbomer 934P and water.
 - d. Placebo for BMV lotion, containing isopropanol, carbomer 934P and water.

4. Patient selection: The patient inclusion criteria were as follows.
 - a. Male or female patients aged 18 years or older.
 - b. A history of stable or worsening scalp psoriasis involving at least 10% of the scalp.
 - c. Moderate to severe scalp psoriasis, defined by the presence of a target lesion measuring at least 2 cm², which had a minimum score of 2 for each of the signs erythema, scaling, and plaque thickness, on a scale of from 0 to 4.
5. Patient exclusions: Patients were excluded from enrollment into the study for the following reasons.
 - a. Known allergy to betamethasone or other topical corticosteroids or to any component of the test formulations.
 - b. Known sensitivity to DHS shampoo.
 - c. Presence of a scalp condition other than psoriasis.
 - d. Severe, uncontrolled manifestations of any disease, including psoriasis.
 - e. Known failure to respond to topical corticosteroids at any time.
 - f. Use of systemic anti-psoriatic therapy (e.g., corticosteroids or retinoids) within the past four weeks.
 - g. Use of any topical drug to the scalp (e.g., corticosteroids or retinoids) within the past two weeks.
 - h. Use of oral antipruritic medications within the past two weeks.
 - I. Use of PUVA or UVB therapy within the past two weeks.
 - j. Expectation of exposure to atypically strong sunlight during the course of the study (e.g., planned holiday in a high sunlight location).
 - k. Pregnant or nursing females.
 - l. Women or men of reproductive potential unless they are using effective contraception during the full course of the study.
6. Treatment regimen: Applications were made BID to the entire scalp for 28 days. All patients were required to use DHS shampoo throughout the study.
7. Blinding procedures: Medication kits which were identical in appearance and sequentially numbered were supplied to the study centers. After assignment of a number to a patient at the baseline visit, the medication kit was opened by a coordinator who instructed the patient on product application. The coordinator and the patient were unblinded as to the nature of the formulation (foam or lotion) but were blinded as to whether the product were active or placebo. The investigator was blinded throughout the study to both the nature of the formulation and to whether it was active or placebo.

8. Effectiveness parameters. The patients returned for evaluation on days 15 and 29, at which time the following assessments were made.

- a. Clinical signs and symptoms: A target psoriatic lesion on the scalp was selected at baseline and evaluated at return visits for the severity of erythema, scaling, and plaque thickness; these were graded on the following scale.

Grading scale for clinical signs			
Score	Plaque thickness	Scaling	Erythema
0	No plaque elevation	No scaling	No erythema
1	Slight, barely perceptible elevation	Sparse fine scale, lesions only partially covered	Faint erythema, pink to very light red
2	Definite elevation, but not thick	Coarser scales, most of lesions covered	Definite light red erythema
3	Definite elevation, thick plaque with sharp edge	Entire lesion covered with coarse scales	Dark red erythema
4	Very thick plaque with sharp edge	Very thick, coarse scales, possibly fissured	Very dark red, 'beefy' erythema

Scalp pruritus was evaluated at baseline and at each return visit on the following scale.

Grading scale for scalp pruritus	
Score	Description
0	No pruritus
1	Occasional pruritus; barely noticeable
2	More frequent pruritus; not troublesome
3	Frequent and sometimes troublesome pruritus; sleeps OK
4	Frequent, troublesome pruritus; interferes with sleep and/or other activities

- b. Extent of scalp involvement. At baseline and each return visit, the investigator evaluated the extent of scalp involvement, using the following scale.

Extent of scalp involvement	
Score	Percent scalp involvement
1	0
2	1 - 9%
3	10 - 24%
4	25 - 49%
5	50 - 74%
6	75 - 100%

- c. Investigator's global assessment of response. At day 29 the investigator graded the global response on the following scale.

Investigator's global assessment	
Score	Description of response
1	Completely clear: except for possible residual discoloration
2	Almost clear: very significant clearance (about 90%); however, slight degree of scaling and elevation as well as some erythema may be present
3	Marked improvement: significant improvement (about 75%); however, some disease remaining
4	Moderate improvement: intermediate between slight and marked; representing about 50% improvement
5	Slight improvement: some improvement (about 25%); however, significant disease remaining
6	No change
7	Worse

- d. Patient's global assessment of response. At day 29 the patient graded the global response on the same scale as that used by the investigator.

The primary efficacy variables were considered by the sponsor to be the changes in the scores for erythema, scaling, and plaque thickness, and the investigator's global assessment of response.

8. Safety parameters. At each return visit the patients were queried as to adverse events and application experiences. The latter included a description of the nature and severity of any immediate symptoms at the application site within 30 minutes of application, or delayed symptoms after 30 minutes of application.

Laboratory evaluations were performed at screening and at day 29; this included the following parameters: CBC, chemistry profile, and urinalysis.

Results were as follows.

- 1) Baseline and demographic characteristics: 190 patients were enrolled into the study, of which 172 patients were evaluable for efficacy. The characteristics of all patients enrolled were as follows.

Demographic and baseline characteristics All patients enrolled				
	BMV foam	Vehicle foam	BMV lotion	Placebo lotion
<u>Age (years)</u>				
Mean	46.7	50.2	48.4	48.1
Range	(19-77)	(24-84)	(24-80)	(20-81)
<u>Sex</u>				
Male	28 (44%)	15 (47%)	34 (54%)	16 (52%)
Female	36 (56%)	17 (53%)	29 (46%)	15 (48%)
<u>Race</u>				
Caucasian	60 (94%)	32 (100%)	58 (92%)	31 (100%)
Other	4 (6%)	0	5 (8%)	0

2) Patient disposition: The patient disposition and discontinuations were as follows.

Patient disposition				
	BMV foam	Vehicle foam	BMV lotion	Placebo lotion
<u># pts randomized</u> (ITT population)	64	32	63	31
<u># pts randomized who applied medication</u> (Safety population)	63	32	63	30
<u># pts at each visit</u>				
Baseline	64 (100%)	32 (100%)	63 (100%)	31 (100%)
Day 15	58 (91%)	30 (94%)	62 (98%)	29 (94%)
Day 29	58 (91%)	30 (94%)	62 (98%)	29 (94%)
<u>Protocol violations</u>				
Prohibited medication	0	1	3	0
<10% scalp involvement at baseline	1	1	1	0
Did not complete study	6	2	1	2
<u># pts that completed study</u> (Per protocol population)	57 (89%)	28 (86%)	58 (92%)	29 (94%)

The number of premature patient discontinuations and the reasons were as follows.

Premature patient discontinuations				
	BMV foam	Vehicle foam	BMV lotion	Placebo lotion
Adverse event	1	1	0	1
Protocol violation	1	0	0	0
Patient request	2	0	0	0
Disease worse	1	1	0	0
Non-compliance	0	0	1	1
Lost to followup	1	0	0	0
Total # pts	6	2	1	2

3) Effectiveness parameters.

a. Clinical signs.

For each of the signs scaling, erythema, and plaque thickness are provided a) the mean values, b) the change in mean values from baseline, c) the percentage of patients with a score of 0 at endpoint, and d) the percentage of patients with a score of 0 or 1 at endpoint. In addition, a composite psoriasis score is provided, which is the sum of the individual scores for the signs scaling, erythema, and plaque thickness.

Results for the Per Protocol population were as follows.