CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-934

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

SEP 8 1998

Betamethasone Valerate Foam 0.1%
NDA 20-934
Luxiq™ ViaFoam
Reviewer: E.D. Bashaw, Pharm.D.
APW

Connectics Corp.
Palo Alto, CA 94303

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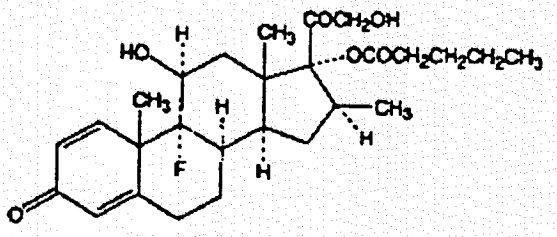
Review of an NDA

I. Background

Betamethasone Valerate (BMV) is a derivative of the naturally occurring corticosteroid prednisolone. Chemically it is 9α-Fluoro-11β,17,21-trihydroxy-16βmethylpregna-1,4-diene-3, 20-dione 17-valerate. It has a molecular weight of 476.58, an empirical structure of $C_{27}H_{37}FO_6$ and the following chemical structure:



betamethasone 17-valerate

It differs from prednisolone in that it is fluorinated at the 9 position, has a methyl group at the 16th position, and a valerate ester at the 17th position. The net result of these modifications is a corticosteroid that is 6x as potent as prednisolone (25x as potent as hydrocortisone) as an anti-inflammatory with no mineralocorticoid (sodium retaining) activity.

BMV has a long history of topical use in corticosteroid responsive dermatoses as cream, lotion, and ointment. This application is for a novel route of delivery for BMV, namely a foam product. It is being developed for use as a topical corticosteroid for scalp use.

II. Recommendation

In this NDA the sponsor has included the results of two in vivo studies of corticosteroid effects. These studies were an assessment of topical vasoconstriction and the potential of the product to suppress the HPA axis (Hypothalamic-Pituitary-Adrenal axis). These studies were carried out in accordance to both the FDA guidance on topical drug products and with FDA input on protocol and trial design during the IND phase. While the results of the topical vasoconstriction study were somewhat equivocal, there was no evidence of HPA suppression following topical application. From a biopharmaceutic standpoint the sponsor has established the in vivo bioavailability of their product relative to marketed reference products and its potential for HPA suppression. On the basis of these studies the product is acceptable from a biopharmaceutic standpoint.

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III. Overview

As noted in the background section this NDA is for a novel delivery system for betamethasone valerate, namely a foam delivery system. This system was chosen as being appropriate for application to the hair/scalp to treat localized corticosteroid responsive dermatoses. In this setting a foam vehicle provides a convenient way to deliver drug to the scalp without the application of either thick coating vehicles (such as creams and ointments) or thin runny vehicles (lotions) to the hair/scalp area. The formulation used in the pivotal clinical studies and the ultimate to-be-marketed formulation is reproduced below:

Active Ingredient	Amount (%w/w)
Betamethasone Valerate, USP	0.12
Inactive Ingredients	
Dehydrated Alcohol, USP	
Cetyl Alcohol, NF	
Stearyl Alcohol, NF	
Polysorbate 60, NF	
Propylene Glycol, USP	
Purified Water, USP	
Citric Acid Anhydrous, USP	
Potassium Citrate, USP	
Propellant	
Propane/Butane (Butane 70)	

*amount of propellant per 100.5g of product

An alternative formulation (referred to as the "Evans Formulation") using British Pharmacopoeia (not USP) grade materials was used in two supportive trials conducted in England. These

differences are minor and as both the in vivo biopharmaceutic trials and the clinical trials were done with the to-be-marketed formulation, this "alternative" formulation is of no regulatory concern from a biopharmaceutic standpoint.

As noted on page 1, this NDA consists of two in vivo biopharmaceutic studies. Unlike most in vivo biopharmaceutic studies there are no plasma levels of BMV contained in this NDA. This is due to the low and undetectable nature of circulating levels of BMV. Instead of direct measurement of corticosteroid levels the FDA has accepted the demonstration of in vivo effects (i.e., pharmacodynamics) as assessed by topical vasoconstriction and assessment of HPA axis suppression as being acceptable for a regulatory decision. Inherent in this assessment is the need to have appropriate reference products with which to compare the effects of the new formulation.

A. Reference Product Selection

The selection of a reference product in this situation was somewhat complicated by the fact that during the development of this product the innovator (Schering) opted to discontinue production of Valisone® cream for marketing reasons (appendix, page 1). Without a marketed (Orange Book listed) comparator the sponsor was effectively unable to proceed in their drug development. Upon consultation with the Division of Dermatological and Dental Drugs Products and the Office of Generic Drugs it was decided that the sponsor would be allowed to use betamethasone valerate cream from E. Fougera as the reference product. Since this meeting the Orange Book staff has gone through the procedure for deleting Schering's product as the reference product and identifying Fougera's product as the FDA approved reference (appendix, page 2).

IV. In Vivo Studies

A. Topical Vasoconstrictor Assay

Study Title: *Bioavailability of topical 0.1% betamethasone valerate in human skin from lotion, ointment, and foam vehicle formulation.*

Investigator:

Study Site:

Treatments:

0.1% betamethasone valerate lotion-marketed (Fougera)	Lot#	9027
0.1% betamethasone valerate ointment-marketed (Fougera)	Lot#	8391
0.1% betamethasone valerate foam-test (Connectics)	Lot#	6M710

Study Design: Single period, drug activity assessment in vivo using the skin blanching response in human skin.

Objective: The objective of this study was to determine the Emax dose-duration response of betamethasone valerate 0.1% from three vehicle formulations using skin blanching response over time for the purpose of comparing the potency of these dosage forms.

Study Methods

As noted previously this study was conducted under the general guidance given in the *"Guidance For Topical Dermatological Corticosteroids: In Vivo Bioequivalence"* that was issued by the FDA on June 2, 1995. The vasoconstrictor study design called for in this guidance calls for a screening study in which subjects which meet the study entrance criteria (generally good health, within normal body weight limits, etc.) are tested for a positive vasoconstrictor (skin blanching response). This was done by applying 5mg of 0.1% betamethasone valerate cream (reference product) to a 1.13cm^2 skin site on the ventral part of the forearm for 4 hrs. The skin blanching response was assessed at 2hrs. by both visual assessment and with a chromameter.

A total of 49 subjects were screened for the study and 45 met the criteria for study inclusion. Of these a total of 37 subjects entered the trial and 35 subjects (13M, 22F) completed all phases of the trial. Two subjects were removed from the trial due to their arriving at the study unit after the appointed time. Attached in the appendix as Table I (page 3) is a demographic breakdown of the enrolled subjects by gender, age, race, skin type, and handedness.

Upon entry into the study each subject had twelve 1.2cm diameter circular skin sites marked on the ventral portion of each forearm. Skin sites were placed 2.5cm from each other (center-to-center), and were arranged in groups of three, with each group defining an anatomical region. Thus, eight anatomical regions were defined I-IV on the right forearm and V-VIII on the left forearm (see Figure 1, appendix page 4). Dose duration assignments (0.25, 0.5, 0.75, 1, 1.5, 2, 4, and 6hrs) were made to each anatomical region according to a pre-determined randomization schedule. In addition three skin sites were demarcated 3cm above the antecubital fossa on each upper arm to serve as a untreated control.

Once the skin sites were prepared, approximately 5mg of each formulation was applied to one of each study sites in each anatomical region in staggered fashion (see appendix, page 5). Following dosing each study site was surrounded by a rubber O-ring that was covered with non-occlusive tapeguard to protect the area. This covering remained inplace until the drug was removed from the skin at six hours post dose.

The effect of skin blanching was assessed by two methods: examination using the chromameter[1] and visual assessment. The chromameter is a camera like instrument which measures the reflectance of light from the skin. In the presence of a vasoconstrictor skin reflectance drops due to the lightening of skin color. The changes in skin reflectance for an individual subjects are corrected against a standard baseline color and against the untreated control sites. In this way between subjects the chromameter is corrected for baseline and individual variance in skin color. For both visual and chromameter methods assessments of activity will be made 1 hr. before application, at the time of dose removal (time 0), and at 2, 4, 6, 19, and 24hrs. after dose removal.

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[1] Minolta® CR200 Colorimeter

For visual examination an assessment of the degree of skin blanching was obtained from a blinded observer using the following scale:

Value	Description
0	no pallor; nor change from surrounding area
1	mild pallor; slight or indistinct outline of application site
2	moderate pallor; discernible (1/2) outline of application site
3	moderate pallor; clean distinct outline of application site
4	intense pallor; clean distinct outline of application site

This same observer was used for all visual assessments and was not the observer used for the chromameter observations.

Results

The skin blanching observations from this trial were analyzed via an Area Under the Effect Curve approach, where the timed observations post-dosing were related to individual treatment sites and a corresponding AUC for each duration of application time was calculated. In the following data it should be noted that when one refers to the 6hr timepoint it is referring to the fact that it was the site to which drug was applied to 6 hours prior to drug removal. By the same token the 0.25hr. timepoint refers to the data collected from the application site where drug was applied 0.25hr. prior to drug removal. This "convention" in naming the samples is a bit at odds with the normal way one considers trials, however, it is consistent with the staggered drug removal protocol used by the sponsor. Reproduced below are the results of the AUEC calculations for both the chromameter and visual assessment observations. (appendix pg. 6-11)

Mean (SD) Dose Response $AUEC_{0\text{-}24hr}$ Profiles (n=35)

Duration of Application	Chromameter			Visual Assessment		
	Ointment	Lotion	Foam	Ointment	Lotion	Foam
0.25	-8.29 (19.95)	-22.73 (24.49)	-23.67 (25.79)	13.3 (14.7)	39.9 (20.1)	32.7 (22.7)
0.5	-8.54 (19.39)	-21.62 (26.68)	-20.28 (26.65)	18.6 (17.2)	38 (16.2)	33.3 (22.6)
0.75	-22.33 (29.77)	-28.1 (20.94)	-25.44 (23.33)	20.2 (17.8)	35.7 (19.4)	29.5 (18.5)
1	-21.57 (25.44)	-28.18 (28.23)	-20.81 (22.78)	21.5 (18.4)	39.7 (21.8)	35.2 (17.4)
1.5	-21.76 (23.40)	-28.76 (23.28)	-22.84 (24.76)	24 (18.1)	49.2 (18.9)	32.6 (23.6)
2	-27.14 (29.05)	-30.79 (32.14)	-27.31 (27.54)	34.3 (23.1)	42.9 (19.1)	36.2 (20.5)
4	-30.27 (25.82)	-34.21 (26.79)	-26.97 (29.96)	31 (18.5)	42.8 (22.1)	38.9 (20)
6	-33.63 (24.03)	-31.96 (22.55)	-29.37 (29.12)	40.9 (17.5)	46.2 (22.2)	35 (18.5)

In this form the data is not especially useful, nor is it directly comparable between the methods as the scales and methods of observations are not directly equivalent. The true use of this data is to estimate an Emax dose response (i.e., maximal skin blanching) and ED_{50} (dose duration at 50% maximal response) for each formulation. This was done by taking the observed data and modeling it with the population based pk/pd program PPharm (ver. 1.3). Details on the model used and the methods used were not provided by the sponsor (see Comment #1). The results of this analysis are summarized below:

Mean (SD) values for PD (n=35)

	Emax	ED_{50} (hrs)
Chromameter		
Ointment	-49.98 (39.31)	4.48 (7.41)
Lotion	-37.01 (19.97)	0.36 (0.51)
Foam	-42.25 (42.48)	2.67 (5.24)
Visual		
Ointment	69.33 (53.66)	4.52 (7.07)
Lotion	46.97 (16.43)	0.18 (0.35)
Foam	39.03 (15.11)	0.26 (0.63)

The evaluation of this data is somewhat problematical due to the lack of agreement between the chromameter and visual assessment methods. Looking at the Emax data, based on the chromameter method, the potency ranking of these formulations are ointment>foam>lotion. If one uses the visual method it is clear that the ointment>lotion>foam for Emax. This suggests that the foam and lotion are very similar in terms of potency and are both inferior to the ointment.

As for the ED_{50} data, analysis of is somewhat consistent in that they both give "potency" rankings of ointment>foam>lotion, but the values for the foam between the methods differ by a factor of 10. The authors explain this by noting that the chromameter can be influenced by any local erythema present at the application site (a factor that a trained observer can ignore). This explanation, while plausible, is difficult to prove with only 5 of 35 subjects reporting significant erythema (3 with foam alone, 2 with both foam and ointment). Given the large standard deviations noted for the data it is apparent that this methodology is not very reproducible.

However, in this setting the purpose of this study is to assign a potency class to the formulation in question. Clearly the foam is less potent that the ointment and is probably equipotent to the lotion. The sponsor erred in choosing as a reference treatment a lotion that was roughly as potent as the test product (see Comment #2). The objective of this trial is to "bracket" the new formulation with a higher and lower strength product to make the proper comparisons with both high and low side sensitivity. In the trial as performed, there was no low side sensitivity (i.e., discrimination potential) in terms of skin blanching.

B. HPA Suppression Study

As part of the safety analysis of a topical corticosteroid one of the primary concerns is the potential for suppression of adrenal function due to feedback inhibition of ACTH. The consequence of ACTH suppression is (following long term inhibition) atrophy of the adrenal glands atop the kidney. As the adrenal glands are responsible for secretion of a number of important hormones and the "fight or flight" response, atrophy of the adrenals can be associated with major metabolic and physiologic abnormalities (Addison's Disease) including death.

In order to assess the impact of a corticosteroid on adrenal function current FDA guidelines call for an assessment of HPA (hypothalamic-pituitary-adrenal) function via a ACTH stimulation test (a/k/a cosyntropin stimulation). In short subjects with the disease state for which the product is being developed (psoriasis, atopic dermatosis, etc.) are given a standardized dose of synthetic ACTH (~250 μg) and a timed cortisol level is obtained at either 0.5 or 1 hr after dosing. This value is compared to baseline and an increase in cortisol levels of >7μg/dL is defined as a normal response. Subjects then begin treatment with the test product using maximal topical doses, over maximal diseased skin surface area, and using the maximal dosing regimens proposed for the label. At the end of the treatment period the subject undergo a repeat cortisol stimulation test with pre- and post-stimulation cortisol levels being obtained. In general a negative test (i.e. no suppression) is defined as a doubling in plasma cortisol levels post stimulation.

Study Title: *An open label study to evaluate the effect of betamethasone valerate foam 0.1% on the Hypothalamic-Pituitary-Adrenal Axis.*

Investigator:

Study Site: Multi-Site (see under Investigator)

Treatments: 0.1% betamethasone valerate ointment-marketed (Fougera) Lot# A015
0.1% betamethasone valerate foam-test (Connectics) Lot# 6M710

Study Design: This was a multi-center (2 sites), randomized, parallel-design, open-label study in 18 subjects with psoriasis or atopic dermatitis.

Objective: The objective of this study was to comparing the effect of BMV foam with BMV ointment on the HPA axis via ACTH stimulation.

Study Methods

As noted above this study is designed to measure the degree of systemic absorption of corticosteroid via assessment of HPA function pre- and post- exposure. For this study a total of 18 subjects with either psoriasis (12) or atopic dermatitis (6) covering at least 30% of body surface area were enrolled in the study. Except for their topical conditions the subjects were in good health and all subjects completed all phases of the trial. (A detailed demographic and treatment breakdown is provided in the appendix as pg. 12). Because of the potential for confounding the results of this trial, all subjects had to be off of systemic corticosteroids for at least 8 weeks and topical corticosteroids for 2 weeks.

All subjects in the trial were randomized to receive either the BMV foam or ointment treatment in a random manner such that there were equal numbers of psoriatic and atopic dermatitis patients in each treatment group. Due to unequal numbers of subjects this meant that each treatment group consisted of 6 psoriatic and 3 atopic dermatitis patients.

Upon entry into the study the subjects underwent an ACTH stimulation test with administration of 250 μg of ACTH (as Cortrosyn®). Prior to and at 30min post-dose a single blood sample was collected for the determination of cortisol levels. Following the 30min sample each subject applied 15gm of either treatment to their affected areas. They returned to the study site twice daily (10hrs apart) for drug application. On the 5th day a repeat ACTH stimulation test was done. Dosing continued for two additional days. On day 9 another repeat ACTH stimulation test was done. A negative test was defined (in this setting) as both a >7μg/dL change in cortisol levels and a post injection cortisol level of >18μg/dL. As a safety measure, those subjects displaying an abnormal response were followed up with an additional ACTH stimulation test at either 12 or 13 weeks to demonstrate return to baseline levels.

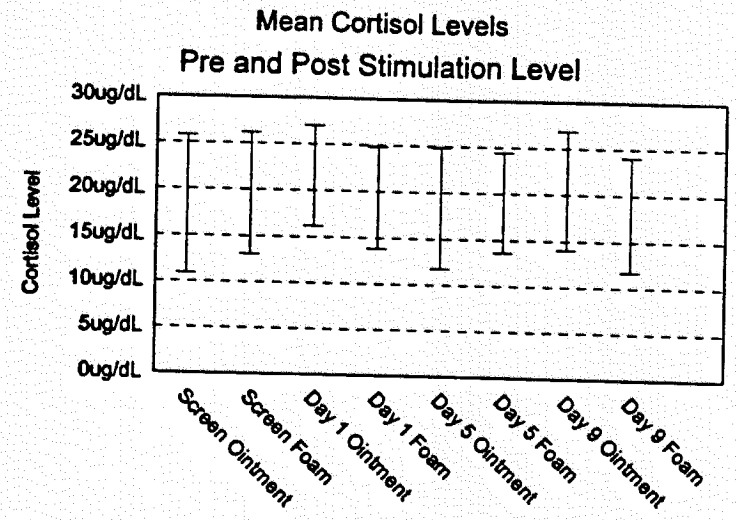
Results

The individual subject and formulation results are attached in the appendix as pages 13 and 14. A within day and within formulation descriptive statistical analysis was conducted by the reviewer and a summary of the data is attached as page 15. A tabular summary of these results is presented below:

Cortisol Levels μg/dL Pre- and Post-Stimulation Mean(SD)

Ointment	Screening	Day 1	Day 5	Day 9
Pre-	10.92(3.63)	16.17(7.72)	11.76(3.36)	14.01(5.04)
Post-	25.82(5.42)	27.02(5.62)	24.87(4.28)	26.87(4.71)
Foam				
Pre-	13.01(2.54)	13.8(4.40)	13.6(2.75)	11.74(4.31)
Post-	26.18(3.35)	24.81(3.08)	24.46(3.46)	24.07(3.79)

A graphical representation of the mean data from each treatment is presented below:



The results of these analysis is that there is no evidence of HPA suppression following treatment with either betamethasone formulation. There were, however, more individuals in the foam group that required an additional evaluation of HPA function at 13 weeks (3 of 9) due to abnormal levels. These levels in two cases (subs. were related not to low levels of cortisol but due to a less than expected increase in cortisol levels following stimulation (see table below):

Abnormal Cortisol Levels in µg/dL

	Day 9 Pre	Day 9 Post	Day 13 Pre	Day 13 Post
Subj.	18.7	24.3	20.7	26.2
Difference	5.6*		5.5*	
Subj	17	22.7	9.5	20
Difference	5.7*		10.5	

*less than the required 7 µg/dL increase

The fact is that after looking at the data it is clear that neither of these subjects has any degree of HPA suppression as both their pre and post dose levels are adequate and there is obvious evidence that the adrenal gland is secreting cortisol. What has happened here is that the subjects were caught by the first criteria calling for a 7µg/dL increase in cortisol levels. While their cortisol levels did not increase by this limit, they clearly are not suppressed.

As for their third subject he did have an abnormal pre-stimulation cortisol level at 9 days of 4.4µg/dL, however, with stimulation this subjects post-stimulation level rose to 28.1µg/dL. A similar pattern was seen day 13 where there was a 22.5µg/dL increase in cortisol levels post stimulation, indicating a functioning adrenal gland.

V Summary

Summary

The results of these two studies have demonstrated that the proposed betamethasone valerate foam is of intermediate potency and with 1 weeks dosing has no evidence of HPA suppression. One criticism of the studies, noted earlier, was that the topical vasoconstriction study lacked downside sensitivity. While this is true, the ointment was clearly more potent than the foam by both the chromameter and visual inspection. The lack of a clear separation between the foam and lotion is problematic but not a fatal flaw to the study. Had the result of the study indicated a similar result relative to the ointment then there would be a problem in data interpretation, with repercussions for the selection of control products for the clinical and HPA axis trials.

In regards to the HPA axis trial, while there is a controversy in the scientific community relating to the use of low dose ACTH stimulation (doses of <5μg) tests of adrenal function. The "high-dose" ACTH stimulation test has been validated as clinically relevant in numerous studies in adults. The ability of the low dose test to pickup subtle changes in adrenal function may be more important in certain areas (such as pediatrics and growth related changes), but this has not yet been demonstrated. At the present time the "high-dose" test is the regulatory standard and the study conducted by the sponsor here meets the current regulatory standard in this area.

Comments (to be sent to the sponsor)

1. The objective of the topical vasoconstriction study is to incorporate appropriate reference products such that the potency of the test product is bracketed. In the study performed by the sponsor the potency of the foam was roughly equal to that of the lotion (depending on analysis method). This resulted in an analysis that lacked adequate down or low side sensitivity. Had these equivocal results been seen with the high side reference product it would have been a fatal flaw in the study. In the future the sponsor should take this caution into consideration in their trial design.

2. In the analysis of the topical vasoconstriction study the sponsor presented the results of pk/pd modeling. Their report contained only a raw data listing from the program and the final output table. For an analysis that is central to interpretation of the trial results such lack of detail is difficult from a review perspective. In the future the sponsor should provide sufficient detail to support their analysis and conclusions.

/S/

9/21/98

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/S/

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Sept. 8, 98

HFD-540/DIV File
HFD-540/CSO/Cintron
HFD-880(Bashaw)
HFD-880(Drug)
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HFD-344(Viswanathan)