# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 19958/S008

## PHARMACOLOGY REVIEW(S)

## REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

**KEY WORDS:** Topical Corticosteroid, Labeling supplement, Pediatric supplement

**Reviewer Name:** Barbara Hill
**Division Name:** Dermatologic and Dental Drug Products
**HFD#:** HFD-540
**Review Completion Date:** 6-8-99

JUN 10 1999

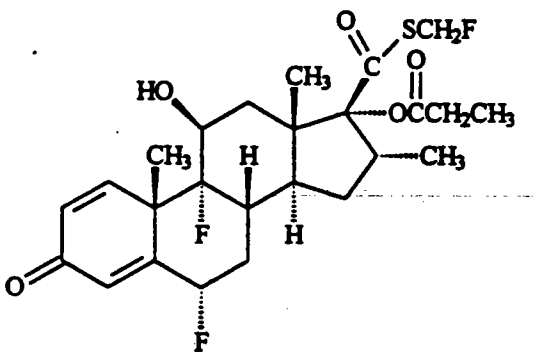
**NDA number:** 19-958
**Serial number/date/type of submission:** SLR-011 & SE5-008 / 7-10-98 & 12-17-98 / Labeling Supplement & Pediatric Supplement with updated labeling information
**Information to sponsor:** Yes () No (X)

**Sponsor:** Glaxo Wellcome Inc.
Glaxo Dermatology
Five Moore Drive
PO Box 13398
Research Triangle Park, NC 27709-3398
(919) 483-2100

**Drug:**

**Code Name:** N/A
**Generic Name:** Cutivate Cream, 0.05%
**Trade Name:** Fluticasone Propionate, CCI 18781
**Chemical Name:** Androsta-1,4-diene-17-carbothioic acid, 6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1- oxopropoxy)-, S-(fluoromethyl) ester, (6-alpha, 11-beta,16-alpha,17-alpha)-
**CAS Registry Number:** 80474-14-2
**Molecular Formula/ Molecular Weight:** 500.62 / $C_{25}H_{31}F_3O_5S$

**Structure:**



**Relevant INDs/NDAs/DMFs:**

1) IND

2) IND

3) IND

4) IND

5) IND
6) IND

7) IND

1) NDA 19-957 (Cutivate ointment for the topical treatment of corticosteroid responsive dermatoses, HFD-540, approved 12-14-90)
2) NDA 20-121 (Flonase nasal spray for the relief of the symptoms of seasonal or perennial rhinitis, HFD-570, approved 10-19-94)
3) NDA 20-548 (Flovent aerosol for maintenance treatment of bronchial asthma, HFD-570, approved 3-27-96)
4) NDA 20-549 (Flovent/Rotadisk inhalation powder for maintenance treatment of bronchial asthma, HFD-570, approved 11-7-97)

**Drug Class:** Anti-inflammatory agent

**Indication:** Eczema and Corticosteroid Responsive Dermatoses

**Clinical formulation:**

Each gram of Cutivate Cream contains fluticasone propionate 0.5 mg in a base of propylene glycol, mineral oil, cetostearyl alcohol, Ceteth-20, isopropyl myristate, dibasic sodium phosphate, citric acid, purified water, and imidurea as preservative.

**Dose:**

The following information is contained in the label in the dose and administration section.

Eczema: Apply a thin film of Cutivate Cream to the affected skin areas once or twice daily. Rub in gently.

Other Corticosteroid-Responsive Dermatoses: Apply a thin film of Cutivate Cream to the affected skin areas twice daily. Rub in gently.

As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary. Cutivate Cream should not be used with occlusive dressings.

**Route of administration:** Topical dermal

**Disclaimer:** Note some material may be taken directly from sponsor's submission.

**Introduction and drug history:**

Cutivate cream, 0.05%, was approved in December 1990 for the treatment of corticosteroid-responsive dermatoses. In the SRL-011 submission (7-10-98), the sponsor submitted a labeling supplement. The purpose of this supplement was:

1) to standardize wording between the Cutivate Cream and Cutivate Ointment package inserts where appropriate
2) to update information contained in both package inserts
3) to address product information issues raised during the review and approval of S-009 (once daily dosing for eczema) for the Cutivate Cream package insert only

This supplement also provides for inclusion of additional information in the **Clinical Pharmacology, Pharmacokinetics** and **Information for Patients** sections, inclusion of class labeling in the **Information for Patients** and **Dosage and Administration** sections, clarification of data already presented under **Precautions** and changes to the **Adverse Reactions** and **Clinical Studies** sections in relation to the once daily dosing regimen. No changes have been made to the **Carcinogenesis, Mutagenesis, and Impairment of Fertility, Pregnancy** or **Nursing Mothers** sections of the label.

In the SE5-008 submission (12-17-98), the sponsor submitted the final report for the clinical study "Study FPC40001: An Open Label Adrenal Suppression Study of Fluticasone Propionate Cream, 0.05% used Twice Daily in Pediatric Subjects Aged 3 Months to 5 Years with Moderate to Severe Eczema or Psoriasis". This report was submitted to support approval of a pediatric indication for Cutivate Cream, 0.05%.

The sponsor submitted additional revision information to the updated label submitted in the SRL-011 submission. This included the new product information presented in the SE5-008 supplement. A complete copy of the revised Cutivate Cream package insert submitted under SLR-011 was included in the supplement and revisions of sections of the label that relate to the clinical data submitted in SE5-008. Therefore, a review of the pharmacological/toxicological portions of the label in SE5-008 is performed in this review since this is the most recent version of the label for Cutivate Cream, 0.05%.

The previous updated label for Cutivate Cream was submitted in SE5-009 on 4-25-96. The sponsor requested a change in the package insert that would have added a once daily dosing for patients with eczema. The pharmacological/toxicological review of this change conducted by

Javier Avalos, stated that since the extent of exposure to the drug product will be reduced, no pharmacology toxicology concerns exist. In this labeling supplement, the sponsor also incorporated changes in the **Clinical Pharmacology** section of the label. The pharmacological/toxicological review of the references submitted to support these claims was conducted by Javier. Javier's recommendations are provided below as background information. Strike out lines indicate information to be removed from the label. No strike out lines indicate that the change proposed by the sponsor was acceptable.

*Reviewer's Comments:* The sentence "Fluticasone propionate binding to glucocorticoid receptor is rapid." contained in bullet 2 above may be misleading. This same sentence appears in the Sponsor's proposed label in the current supplement. A more detailed discussion concerning this statement will be provided below during the discussion of the **Clinical Pharmacology** section of the label.

**Review of Pharmacological/Toxicological Portions of the submitted Label:**

*Reviewer's Comments:* No changes were made to this section. The information is correct based on nonclinical toxicology studies conducted for fluticasone propionate. The wording follows the guidelines established for topical corticosteroid labeling. This section of the label is acceptable.

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*Reviewer's Comments:* The wording follows the guidelines established for topical corticosteroid labeling. This section of the label is acceptable.

The entire sponsor proposed **Clinical Pharmacology** and **Pharmacokinetics** sections of the label are reproduced below. ~~Strikeout~~ text indicates proposed sections to be removed from the label. Underlined text indicates proposed sections to be added to the label. I will evaluate the information in this portion of the label that pertains to a nonclinical animal study (contained in the **Pharmacokinetics: Absorption** section). This information pertains to a nonclinical study report completed in 1989 (reference #4). The information that pertains to human studies will be evaluated by the Clinical Pharmacology reviewer, Veneeta Tandon. Veneeta has informed me that the human pharmacokinetic data has already been reviewed and approved for the nasal spray formulation of fluticasone propionate.

*Reviewer's Comments:* It was recommended to the Clinical Pharmacology reviewer, Veneeta Tandon, to remove the sentence

from the **Clinical Pharmacology** section of the label. Veneeta agreed to discuss this proposal with upper management within the Clinical Pharmacology division. The reference to rapid binding of fluticasone propionate to the glucocorticoid receptor has no true scientific meaning. It may have been placed in the label as a marketing statement. The reference included in support of this statement discussed receptor binding studies performed with lung tissue. These studies demonstrated that fluticasone propionate had a high affinity binding constant for the glucocorticoid receptor but this does not necessary equate with the statement rapid binding. In addition, these results may not be relevant to skin where penetration through the skin to the

glucocorticoid receptor plays as important a role in therapeutic benefit as does the binding affinity for the glucocorticoid receptor.

*Reviewer's Comments:* The reference for the single nonclinical pharmacokinetic study that was mentioned in the **Pharmacokinetics:** ***Absorption*** section of the label was reviewed in the original submission of NDA 19-958 (Cutivate Cream). The title of the study report is "Radioactive balance study and plasma level time profile of radioactivity in rats after topical administration of fluticasone ointment or cream." The analysis of this study by the pharmacology/toxicology reviewer, Harold Carlin, supports the claim proposed in the label. I have recommended a few minor modifications for clarification purposes. Deletions are marked with ~~strikeout~~ text and additions are highlighted in shadowed text.

**RECOMMENDATIONS:**

Internal comments:

The information contained in the pharmacological/toxicological portions of the label is acceptable. No changes are recommended for the **Carcinogenesis, Mutagenesis, and Impairment of Fertility, Pregnancy** or **Nursing Mothers** sections of the label.

The following changes are recommended for the nonclinical animal study reference in the **Pharmacokinetics:** ***Absorption*** section of the label. Deletions are marked with ~~strikeout~~ text and additions are highlighted in shadowed text.

/S/

Barbara Ann Hill, Ph.D.
Reviewing Pharmacologist

cc:
NDA: 19-958 (SE5-008)
HFD-340
HFD-540/DIV FILES
HFD-540/TOX/JACOBS
HFD-540/PHARM/HILL
HFD-540/MO/COOK
HFD-540/CHEM/PAPPAS
HFD-540/PM/WRIGHT
C:/MY DOCUMENTS/WORD/NDAS/NDA19958/19958SE5008.DOC

Concurrence Only: Discussed at labeling day.
HFD-540/DD/JWILKIN /S/ 6/17/99
HFD-540/Team Leader/ASJACOBS /S/ 6/10/99

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER:NDA 19958/S008

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# Clinical Pharmacology/Biopharmaceutics Review

NDA: 19-958 (SE5-008) SUBMISSION DATE: 12/17/98

PRODUCT: CUTIVATE® Cream 0.05%
(fluticasone propionate cream)

JUN 11 1999

SPONSOR: Glaxo Wellcome
North Carolina 227709 REVIEWER: Veneeta Tandon, Ph.D.

## Review of NDA Supplement

### I. Background

Eczema and psoriasis are dermatological conditions occurring in children as well and are frequently treated with topical corticosteroids. Cream and ointment dosage forms of fluticasone propionate have been marketed since 1991 under the tradename CUTIVATE®. Fluticasone cream has been shown be effective in children (3-14 years) in three clinical studies with twice daily and once daily regimen for up to four months in these condition.

Topical corticosteroids are generally safe drugs, since the amount entering the general circulation is less than that required for oral dosing. However, both local adverse effects (skin thinning) and systemic adverse effects (suppression of adrenal function) can occur with long term use. Factors increasing the risk of local and systemic effects from topical use include potency of the drug, amount applied, percent of body surface area (BSA) treated. Because of the higher ratio of skin surface to body mass, children treated with topical corticosteroids may be at greater risk of hypothalamic-pituitary-adrenal (HPA) axis suppression than adults.

Topically applied fluticasone has shown minimal potential for HPA axis suppression in adults as measured by morning serum cortisol levels. A study conducted in children with atopic dermatitis treated with once daily fluticasone cream up to 4 weeks demonstrated that urinary excretion was not changed from baseline[1]. However, no previous study in children assessed adrenal response to stimulation with cosyntropin (synthetic adrenocorticotropic hormone [ACTH]).

This supplement provides safety information in pediatric patients in support of the approval of a pediatric indication for CUTIVATE® cream, 0.05%. In a meeting on November, 7, 1997, it was agreed that adequate efficacy data has been provided. The protocol for the safety study design was approved by the agency. The study results are

[1] Woolkerstorfer et. Al. J. Am. Acad. Dermatol; 39: 226-31, 1998.

discussed in this review. Serum cortisol level in response to intravenous cosyntropin was the primary assessment criteria for adrenal responsiveness as representative of systemic corticosteroid effect.

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## II. Study Title

**Study FPC40001: An open label adrenal suppression study of fluticasone propionate cream 0.05% used twice daily in pediatric subjects aged 3 months to 5 years with moderate to severe eczema or psoriasis.**

*II.1 Objective*

This was an open label, safety study of a 3- or 4-week course of treatment covering more than 35% of BSA conducted in 10 centers in US. Safety was assessed by monitoring the following:

1. Effect on the HPA axis as determined by response to 30- minute cosyntropin stimulation tests (pre and post-stimulation serum cortisol levels)
2. Plasma levels of fluticasone following twice daily treatment for 3- or 4-weeks
3. Hematology and blood chemistry
4. Signs of skin atropy and pigmentation changes at application site
5. Other adverse events

## III. Study design

Study medication was applied twice daily to skin covering ≥35% of body surface area without occlusive dressing, at a dose up to 17.1 g/day (120 g/week) for subjects aged 3 months to 2 years, and up to 25 g/day (175 g/week) for subjects aged 3-5 years. The length of treatment was determined according to the following plan;

At the end of 2 weeks of treatment

- Subjects who are 100% cleared were treated for 1 more week
- Subjects who are <100% cleared were treated 2 more weeks

At the end of 3 weeks of treatment

- Subjects who are <100% cleared will be treated 1 more week
- Subjects who are not cleared at 2 weeks, but cleared at 3 weeks, were treated 1 more week

51 subjects with eczema were enrolled with an average BSA of 68% (range 35-94%), almost twice the protocol defined minimum treated BSA. 46 subjects completed the study, 32 in the younger group (Group A: 3m-2yrs) and 14 in the older group (Group B: 3-5 yrs). The demographics are attached in the Appendix on page 14. Two subjects were discontinued at baseline due to inability to collect blood samples. One subject lost to follow-up. One subject was discontinued (B242) due to abnormal baseline cosyntropin stimulation test (CST). This subject had received the test medication. One subject discontinued due to inadequate disease severity at baseline. The number of subjects completing each evaluation is attached in the Appendix on page 13. The mean amount of drug used was 5.1 grams/day.

*III.1 Cosyntropin stimulation test (CST)*

An acute cosyntropin stimulation test (CST) was administered at baseline visit and at end-treatment visit. It was also repeated at follow-up visits if the results from end-treatment visit were abnormal. The CST test began after the topical application of an anesthetic cream (EMLA) and after obtaining pre-stimulation blood sample for the analysis of serum cortisol and serum chemistry. Cortrosyn® (0.125 mg for Group A and 0.25 mg for Group B children) was administered intravenously. The batch number of the formulations used is also attached in the Appendix on page 13. The children were fed after the pre-stimulation CST sample was taken. A post stimulation sample was obtained at 30- minutes after injection.

Serum Cortisol was assayed using two methods:

1. the primary determinant (LOQ 1 µg/dL)
2. the secondary determinant (LOQ 0.5 µg/dL)

*Evaluation criteria*

- A normal adrenal response to cosyntropin by was defined as a post stimulation cortisol value of >18 µ/dL.

The Cortrosyn® package insert provided two other criteria for evaluation: post stimulation cortisol at least 7 µg/dL greater than pre-stimulation cortisol and post stimulation cortisol approximately double pre-stimulation cortisol value, provided the pre-stimulation cortisol does not exceed the normal range. However, these two criteria were not used to assess adrenal suppression and were only used to assess the consistency

of the results and to help in the interpretation of marginal responses based on changes in peak cortisol values.

Reason being: The response of the adrenal gland to exogenous stimulation, e.g. cosyntropin testing, is dependent not only on the dose and potency of the exogenous agent, but also on the existing level of endogenous stimulation, e.g. plasma ACTH level at the time of testing. The normal physiologic diurnal pattern of endogenous control of adrenal secretion peaks in the morning and wanes in the evening. Because of this, the expected increase in plasma cortisol values in response to cosyntropin stimulation will vary with the time of the day of the test, reflecting variations in underlying endogenous ACTH stimulation. In this study, all sampling was to begin at 8.00 a.m., the time the endogenous stimulation of the adrenal gland is normally maximum. Therefore, given the high pre-stimulation cortisol levels expected from the morning values, the post-stimulation cortisol levels would not necessarily be expected to double or increase by at least 7 µg/dL.

- A post-stimulation cortisol value of 14.5 µg/dL based on assay.

Post-stimulation cortisol values based on assay is generally lower than that based on A good correlation (r=0.992) between has been observed; the values being substantially lower[2]. In addition the Pulmicort® Turbuhaler 200 µg package insert uses a post-stimulation cortisol level of 14.5 µg/dL based on assay. The most likely explanation for the assay yielding lower cortisol values is that is specific for cortisol, where as measures synthetic as well as endogenous steroids other than cortisol[3].

Serum cortisol values by were mostly measured in Group B children due to ethical reasons. However, some younger subjects have both results when investigators inadvertently requested test for younger subjects.

*III.2 Plasma levels of fluticasone*

Plasma fluticasone values were measured to assess the degree of systemic absorption of drug and to determine whether or not there was any relationship between end-treatment post-stimulation cortisol values and systemic absorption, particularly in any subject with adrenal suppression. These levels were measured at baseline and final visit in Group B children only due to ethical reasons.

Fluticasone propionate was quantified by automated solid phase extraction. The extracts were analyzed by detection. The LOQ was 50 pg/mL. The calibration range was pg/mL from mL plasma (Precision <5.3%, accuracy <+7.7%, recovery 71.9%).

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[2] Vargas R, J Allergy Clin Immunol; 102(2): 129-7, 1998

[3] Cortisol [package assay] Abbott park, IL, Abbott Laboratories; 1996

*Reviewer's Comment*

*The sponsor had not submitted the assay validation report. The information was requested. It was noticed that the calibration range in the report was 20-1520 pg/ml. However, the detection of fluticasone levels at 20 pg/ml will not effect the results of this study as no correlation was obtained between the levels of fluticasone and the adrenal suppression. Some subjects with very high fluticasone levels did not show any evidence of suppression.*

## IV. Study Results

The total mean dose for the entire treatment was 134.2 grams for all subjects, with 96.7 grams for the younger group (maximum 355.7 grams) and 209.1 grams for the older group (maximum 561 grams). 90% subjects were treated 20 or more days with a maximum period of 35 days.

The results of were compared at each time point. The results confirmed that the post-stimulation cortisol values have a mean ratio of about 80.9% with the corresponding post-stimulation value. This is consistent with the 18:14.5 for the package insert cortisol interpretation standards.

The Spearman correlation coefficients between the two assays were calculated for baseline pre-stimulation and post-stimulation cortisol values, and end-treatment pre-stimulation and post-stimulation cortisol values. If the two methods had a correlation coefficient for each time point of at least 0.8, then it was concluded that the two methods are supportive of each other. At baseline, pre-stimulation cortisol values obtained by were averaged 11.40% lower than values; and post-stimulation values by averaged 16.28% lower than values. At end treatment, results averaged 10-57% (pre-) and 19.11% (post-) lower than those obtained by As supported by the literature also, a post stimulation value used to denote a normal adrenal response based on assay was adjusted downward to >14.5 µg/dL (compared to 18.0 µg/dL by method)

*IV.1 Serum Cortisol levels by assay*

The mean ± SD baseline pre-stimulation cortisol values based on and mean end-treatment pre- and post-stimulation values are tabulated below. A table showing the results broken down by age group is attached in the Appendix on page 15. This table also shows the cortisol values on other specific days (eg. Day 11, 25, 33 and 36 days, for one subject each)

| Serum Cortisol µg/dL | Visit Day | n | At Pre-Stimulation All Subjects | At Post-Stimulation All Subjects |
|---|---|---|---|---|
| Baseline | 1 | 48 | 13.76±6.94 | 30.53±7.23 |
| End-treatment (all visits) | | 44 | 12.32±6.92 | 28.84±7.16 |
| End-treatment | 22 | 8 | 12.80±6.07 | 28.83±4.96 |
| End-treatment | 29 | 32 | 12.85±7.22 | 29.42±7.16 |

*IV.1.1* *Baseline Pre- and Post stimulation*

There were two subjects with baseline post-stimulation cortisol values not >18.0 µg/dL. One of these subjects (A143) had been treated with alclometasone dipropionate 0.05% for 10 weeks ending 7 days prior to baseline visit, thus violating the exclusion criterion for chronic use of steroid within 4 weeks of the study start date. After 5 day interruption the subject continued and completed the study. Another subject (B242) had taken a 12 week course on alclometasone dipropionate and hydrocorisone and stopped 11 days prior to baseline visit. The subject took study drug for 4 days. 5 days after discontinuing the drug the CST values were normal. These results are tabulated in the Appendix on page 13.

*IV.1.2* *End-treatment Pre- and Post-stimulation*

There were two subjects (B201 and B202) who did not have end treatment post-stimulation values >18 µg/dL. Results from these subjects are tabulated below. Both of these subjects had evidence of adrenal suppression based on results.

**End-treatment CST**
**Subjects Who Did Not Have Post-Stimulation Cortisol Value >18 µg/dL**

| | | | | | | Serum Cortisol (µg/dL) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Baseline | | End-treatment | | Follow-up | |
| Sub-ject | Age/Sex | % BSA* | Severity† | Duration | Amount Used | Pre-stim. | Post-stim. | Pre-stim. | Post-stim. | Pre-stim. | Post-stim. |
| B201 | 5 years/M | 95 (95) | 22 (9) | 4 weeks | 561.0 grams | 22.1 | 33.9 | 7.1 | 11.8 | 2.1[1] | 19.8[1] |
| B202 | 2 years/M | 35 (35) | 17 (7) | 5 weeks | 176.5 gram | 10.8 | 28.6 | 2.1 | 9.4 | LTF | LTF |

* at the Baseline Visit: affected (treated)
† total (total of 3 worst scores)
[1] 12 days after end-treatment
LTF = lost to follow-up

Subject 201 was treated in a large BSA. Over the 4-week course of treatment the BSA affected decreased to over 20 %, but the parent continued to treat 95% BSA throughout the treatment period (protocol specified that at least 35% BSA to be treated throughout). This subject had a plasma fluticasone level of 116.5 pg/mL at end-treatment. 12 days after treatment the CST returned to normal.
Subject 202 was incorrectly assigned prefix B. His end treatment visit was 7 days late and hence was treated for 5 weeks. The results of plasma fluticasone assay were below the limit of detection. The subject left town and never returned for follow up.

*Reviewer's Comment*

*There was clear evidence of suppression in these two subjects. However, these subjects were either treated on an exaggerated surface area or for an extended period of time (5 weeks).*

*IV.2 Serum Cortisol levels by assay*

The mean baseline pre- and post-stimulation cortisol values and end-treatment pre and post-stimulation values as assayed by method are shown in the following table. The results broken down by age group are attached in the Appendix on page 16.

| Serum Cortisol µg/dL | Visit Day | N (pre-) | At Pre-Stimulation All Subjects | N (post-) | At Post-Stimulation All Subjects |
|---|---|---|---|---|---|
| Baseline | 1 | 37 | 12.39±5.96 | 36 | 24.26±6.17 |
| End-treatment (all visits) | | 30 | 10.60±5.60 | 28 | 22.78±6.23 |
| End-treatment | 22 | 6 | 12.30±5.72 | 5 | 24.46±4.47 |
| End-treatment | 29 | 21 | 10.77±5.70 | 21 | 22.13±6.76 |

*IV.2.1 Baseline Pre- and Post stimulation*

Two subjects (B242 and B272) did not have baseline post-stimulation values >14.5 µg/dL. Subject B242 also had adrenal suppression based on method. Subject B272 had been chronically treated with hydrocortisone 1% twice daily for 17 weeks, ending 7 days before the baseline visit (protocol violation). The results from these two subjects are tabulated below.

**Baseline CST Results**
**Subjects Who Did Not Have Post-Stimulation Cortisol Values >14.5 µg/dL**

| | | | | Serum Cortisol | | Repeat CST few days later | |
|---|---|---|---|---|---|---|---|
| Subject | Age/Sex | % BSA* | Severity† | Pre-stimulation (µg/dL) | Post-stimulation (µg/dL) | Pre-stimulation (µg/dL) | Post-stimulation (µg/dL) |
| B242 | 3/Female | 85 (80) | 18 (8) | QNS | 4.9 | 18[2] | 40[2] |
| B272 | 3/Male | 76 (71) | 18 (8) | 6.4 | 14.5 | ND | ND |

[1] methodology, except for B242 repeat CST, unknown methodology
[2] 60-minute CST performed by a referral endocrinologist 5 days after discontinuing study drug at a non-study laboratory
* at the Baseline Visit: affected (treated)
† total (total of 3 worst scores)
QNS = Quantity not sufficient to run assay
ND = not done

However, subject B272 had a baseline post-stimulation value of 32.2 µg/dL based on assay. The subject continued the study for 4 weeks and his end treatment CST results by were, pre-stimulation 12.2 µg/dL and post-stimulation 23.0 µg/dL.

*IV.2.2 End-treatment Pre- and Post-stimulation*

The end treatment CST results based on assay showed that three subjects (A171, A176 and B201) had cortisol values not >14.5 µg/dL. These are tabulated in the following table.

**End-treatment CST**
**Subjects Who Did Not Have Post-Stimulation Cortisol Values >14.5µg/dL**

| | | | | | | Serum Cortisol (µg/dL) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Baseline | | End-treatment | | Follow-up | |
| Subject | Age/ Sex | % BSA* | Duration | Severity† | Amount of Drug Used | Pre-stim. | Post-stim. | Pre-stim. | Post-stim. | Pre-stim. | Post-stim. |
| A171 | 2/F | 86 (81) | 4 weeks | 22 (9) | 355.7 grams | 13.9 | 20.3 | 8.1 | 12.4 | 12.9[1] | 15.5[1] |
| A176 | 2/F | 100 (75) | 4 weeks | 13 (7) | 126.9 grams | 28.9 | 24.2 | 17.8[2] | 8.5[2] | 11.9[3] | 17.0[3] |
| B201 | 5/M | 95 (95) | 4 weeks | 22 (9) | 561.0 grams | 18.4 | 26.3 | 7.3 | 10.8 | 3.6[4] | 18.2[4] |

* at the Baseline Visit: affected (treated)
† total (total of 3 worst scores)
[1] 2 weeks after end-treatment
[2] Samples may have been reversed
[3] 1 week after end-treatment
[4] 12 days after end-treatment

Subject B202, who had evidence of adrenal suppression by method, was not evaluated assay. Subjects A171 was also on hydrocortisone 1% twice daily for 17 weeks, ending 10 days before the baseline value. This subject also had a fluticasone level of 122 pg/mL. Subject A176 had lower post-stimulation CST values as compared to the pre-stimulation values, suggesting samples could be reversed. The were fine for this subject and had no detectable levels of fluticasone. Subjects B201 is also discussed in the assay.

There was very little correlation between subject's age and either generated cortisol data as shown in the following table.

**Correlation between CST Results and Age**

| Cortisol Data vs Age | | Cortisol Data vs Age | |
|---|---|---|---|
| Baseline | End-treatment | Baseline | End-treatment |
| r = -0.20181 | r = -0.17234 | r = -0.15547 | r = -0.19036 |
| p = 0.1737 | p = 0.2691 | p = 0.3652 | p = 0.3319 |

*IV.3 Fluticasone plasma concentrations*

29 subjects had plasma samples taken at either baseline and/or at the end treatment for the measurement of plasma fluticasone levels. There were 27 of 29 subjects who had plasma fluticasone values taken at baseline and 25 out of 29 at end-treatment.

No subject had measurable fluticasone values at baseline. 6 out of 25 subjects had measurable plasma levels at end-treatment. The mean fluticasone plasma values were 112.1 pg/ml in the younger group (Group A) and 163.1 pg/ml in the older group (Group B). Median values were 122 pg/ml and 116.5 pg/ml, respectively. The highest value was 263.8 pg/ml, but this subject was not suppressed.

With few subjects having detectable levels, no relationship between response and drug concentration of drug dose could be obtained. Only one subject (B201) who was considered to have adrenal suppression showed detectable levels of plasma fluticasone as well. B202 was also suppressed but did not show any plasma fluticasone levels. Subject A171 had lower trending end-treatment cortisol level, but was not suppressed by method, but showed suppression by assay. The following table shows the detectable fluticasone levels.

**Subjects with Detectable Fluticasone in Plasma at End-treatment**

| Subject | Age (y-m)/Sex | Fluticasone plasma levels (pg/mL) | % BSA Treated at Baseline | Severity Score at Baseline total (worst 3)* | Total Amount of Drug Used (g) | Duration of Treatment (weeks) | End-treatment CST Results (µg/dL) >18.0; >14.5) |
|---|---|---|---|---|---|---|---|
| A171 | 2-4/F | 122.0 | 81 | 22 (9) | 355.7 | 4 | 19.8/12.4 divergent |
| A189 | 2-1/M | 155.1 | 88 | 18 (9) | Missing[1] | 4 | 34.2/23.8 normal |
| A190 | 2-0/F | 59.2 | 77 | 12 (6) | Missing[1] | 4 | 29.2/26.2 normal |
| B201 | 5-1/M | 116.5 | 95 | 22 (9) | 561.0 | 4 | 11.8/10.8 suppressed |
| B281 | 4-2/F | 109.1 | 92 | 23 (9) | 259.4 | 4 | 31.1/29.3 normal |
| B282 | 3-11/M | 263.8 | 56 | 12 (6) | 355.7 | 4 | 23.3/22.9 normal |
| B202 | 2-4/M | BQL | 35 | 17 (7) | 176.5 | 5 | 9.4/NA suppressed |
| A176 | 2-8/F | BQL | 75 | 13 (7) | 126.9 | 4 | 24.3/8.5[2] divergent |

*Minimum score of 6 for worst three required to enroll
[1]Incomplete data available
[2]Samples may have been reversed
BQL - Below quantification limits
NA - Not applicable (sample mishandled by lab)

## V. Overall Conclusions

- Fluticasone cream has potential to suppress HPA axis function in pediatric patients as young as 3 months. Two of the 43 subjects showed end-treatment stimulation cortisol levels indicating adrenal suppression. One subjects at the end of 2 weeks post treatment showed normal function and the second subject was lost to follow up. These subjects were either treated on a very large surface area or were treated for

extended duration (than required in the protocol-3-4 weeks). A third subject showed a trend towards lower cortisol levels.

- Systemic absorption of fluticasone was seen in 6 out of 25 subjects at end-treatment.

*Reviewer's Comment*

*Although clear evidence of suppression was seen in only two subjects (2 out of 43), a downward trend in cortisol levels was seen in some subjects comparing the baseline pre-stimulation levels to end-treatment pre-stimulation levels (e.g. subjects A101, B201, B202, A111, A112, B271, A189, B282, A122 by assay and B201, B202, A111, B252, A171, , B282 by method). However, these subjects were able to respond to ACTH stimulation (with the exception of B201, B202 and A171-all these were suppressed at end-treatment post-stimulation as well). The individual subject listing is attached in the Appendix on pages 17-26.*

## VI. Label

The labeling changes regarding the pediatric HPA axis suppression study has been discussed with the medical officer and will be incorporate din the labeling meeting. The Clinical Pharmacology section of the label as submitted in the supplement S011 has been reviewed separately [see the labeling review for NDA 19-958 (S011) signed off on]

## VII. Comments to the sponsor

- It was observed that the assay validation range mentioned in the report was not the same as that mentioned in the assay validation report. For future submissions, the sponsor should be consistent in reporting the data, and any discrepancy, if observed, should be explained well.

- For future submissions, the sponsor should submit a detailed validation report for all the analytical methodologies used in a particular study.

## VIII. Recommendation

The sponsor has conducted an HPA-axis suppression study to assess the safety of CUTIVATE® in children aged 3 months to 5 years. There is clear evidence of suppression of adrenal response in 2 subjects. There was also a downward trend in the cortisol levels in some subjects, suggesting adrenal suppression upon treatment with CUTIVATE®. The results indicate that adequate consideration should be given to the body surface area of application as well as the duration of treatment and the dosing regimen as in the label should be followed.

The reviewer recommends approval of the use of CUTIVATE® cream in children 3 months in age and older. The two comments regarding future submissions should be conveyed to the sponsor.

/S/ 6/9/99

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CC: NDA 19-958 (SE5-008)
HFD-540/Div File
HFD-540/CSO/Wright
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-344(Viswanathan)
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