DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation & Research

April 13, 2007

Duane Alexander, MD
Director, NICHD
MSC 2425
31 Center Drive, RM 2A03
Bethesda Maryland 20892-2425

RE: Referral of Drugs under section 505A(d)(4)(B)(i) of the Federal Food, Drug and Cosmetic Act

Dear Dr Alexander,

Consistent with the provisions of section 4 of the Best Pharmaceuticals for Children Act (BPCA), FDA is referring hydrocortisone valerate to the Foundation for the National Institutes of Health (FNIH) for the conduct of pediatric studies. It has been determined that there is a continuing need for information relating to the use of this drug in the pediatric population. The attached Written Request has been sent to the holder of the approved application and was declined. The attached Written Request outlines the pediatric studies that need to be conducted to provide the necessary information for the use of hydrocortisone valerate in the pediatric population.

Please feel free to contact our office at 301-796-0700 should you have any questions regarding this Written Request.

Sincerely,

Sandra L. Kweder, MD
Deputy Director
Office of New Drugs
Center for Drug Evaluation and Research

Attachment
cc: Donald Mattison, MD
Senior Advisor to the Directors, NICHD and CRMC

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WRITTEN REQUEST

Dear:

To obtain needed pediatric information on hydrocortisone valerate, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

The purpose of this Written Request is to define the safety of 0.2% hydrocortisone valerate cream and ointment in pediatric patients with atopic dermatitis, specifically with regard to the potential for hypothalamic-pituitary-adrenal (HPA) axis suppression and local cutaneous adverse effects and to compare its safety profile with that of 1% hydrocortisone acetate cream and ointment and to 1% hydrocortisone only cream and ointment (HC, free alcohol base). For additional background information, please see appendix A.

Type of Study:

A randomized, double-blind, active-controlled, parallel group safety study of 0.2% hydrocortisone valerate cream and ointment in pediatric patients aged 3 months to 16 years, with atopic dermatitis.

Study Objectives:

1. To assess the short-term safety of 0.2% hydrocortisone valerate cream and ointment in pediatric patients with atopic dermatitis.
2. To assess the short-term safety of a 1% hydrocortisone cream and ointment OTC product, such as 1% hydrocortisone acetate or 1% hydrocortisone only (free alcohol base), as above.
3. To compare the safety of hydrocortisone valerate cream and ointment to the cream and ointment product specified in objective 2.

Specifically, with regard to safety, the effects on the hypothalamic pituitary axis (HPA) and local cutaneous adverse effects associated with topically applied corticosteroids (telangiectasia, thinning, shininess, striae, bruising, loss of elasticity and loss of normal skin markings) will be assessed.

Study Design:

A randomized, double-blind, active-controlled, parallel group study comparing the safety of 0.2% hydrocortisone valerate (17-valerate ester) cream and ointment to a 1% hydrocortisone cream and ointment OTC product, such as 1% hydrocortisone acetate (21-acetate salt) or 1% hydrocortisone only (free alcohol base).

Patients with atopic dermatitis involving at least 20% BSA will be enrolled. Patients will be randomized to one of the following treatments: hydrocortisone valerate cream, hydrocortisone valerate ointment, a currently marketed 1% hydrocortisone cream OTC product (class VII potency) and a currently marketed 1% hydrocortisone ointment OTC product (class VII potency). The 1% hydrocortisone cream and ointment that are chosen must be chemically identical except for the formulation, i.e., if 1% hydrocortisone acetate cream is chosen then the ointment chosen must be the 1% hydrocortisone acetate ointment.

Patients will be randomized in a 1:1 ratio among the following 4 treatment groups:
Valerate Cream group: Hydrocortisone valerate 0.02% cream,
Valerate Ointment group: Hydrocortisone valerate 0.02% ointment,
Cream control group: 1% hydrocortisone only cream (free alcohol base- class VII) OR 1% hydrocortisone acetate (21-acetate salt- class VII) cream
Ointment control group: The ointment counterpart of the cream control.

Study duration will be 4 weeks in the control groups and up to 8 weeks in the hydrocortisone valerate treatment groups provided there is no evidence of HPA axis suppression by cosyntropin stimulation testing after 4 weeks of treatment with hydrocortisone valerate cream or ointment. The study must include a 2-week post-treatment visit in all patients for evaluation of local cutaneous adverse effects known to be associated with topically applied corticosteroids.

Although this is primarily a safety study, efficacy data will also be obtained (see Study Evaluation).

Inclusion and Exclusion Criteria:

Inclusion criteria:

- clinical diagnosis of atopic dermatitis established by the investigator
- age range: 3 months to 16 years
- ≥20% BSA disease involvement treatable with the study medication
- normal baseline cosyntropin stimulation test (peak stimulated plasma cortisol level >18 ug/dl)
- parents/legal guardian(s) must have signed the statement of parental permission/child assent

Exclusion criteria:

- abnormal baseline cosyntropin stimulation test (peak stimulated plasma cortisol level ≤18 ug/dl)
- known immunodeficiency syndromes associated with atopic dermatitis (e.g., Ataxia- telangiectasia, Hyper-IgE syndrome and Wiskott-Aldrich syndrome)
- significant or chronic disease that would affect the HPA axis or interfere with interpretation of the study results
- requirement for any other medication (topical or systemic) that can affect the HPA axis, the course of the disease or safety assessment in treatment areas
- severe side effects from corticosteroid use
- clinical signs of cutaneous infection (i.e., oozing or crusting) requiring treatment
- fever ≥102^{0}F
- known hypersensitivity to any of the components of the study medications
- use of topical or inhaled corticosteroids or topical calcineurin inhibitors within 14 days of study enrollment and use of systemic corticosteroids within 28 days of study enrollment

Ages and Number of patients to be studied:

Pediatric patients of both genders, aged 3 months to 16 years, will be enrolled. The age distribution of evaluable patients (i.e., those with a normal baseline cosyntropin test who have a repeat test at the end-of-treatment) will be as follows:

Ages (years)	Minimum Number of Evaluable Patients/Treatment Group
3 months to <2 years	40 with approximately 50% of the patients ≤1 year of age
2 to <6 years	30
6 to <12 years	30
12 to 16 years	20

Patients must be approximately equally distributed across the age range within each age group. With at least 120 evaluable pediatric patients, aged 3 months to 16 years, enrolled in each treatment group, the total study sample size will be at least 480 evaluable patients.

Study Endpoints:

The primary clinical endpoint will be the cosyntropin-stimulated peak plasma cortisol level at week 4.

Secondary endpoints will be the cosyntropin-stimulated peak plasma cortisol level at week 8 and local cutaneous adverse effects at the end-of-treatment and two weeks after treatment is discontinued.

Additional secondary endpoints include the proportion of patients demonstrating clearance of atopic dermatitis (active disease no longer evident), the proportion of patients demonstrating excellent improvement from baseline (75-99% improvement in active disease) and the mean percent reduction in BSA involvement from baseline.

Study Evaluation:

The total volume of blood to be drawn should also be determined a priori and stated in the protocol.

Clinical assessments should include medical history/baseline disease, medications, physical examination, dermatological evaluations (e.g., signs of skin atrophy, skin pigmentation changes, telangiectasia), and assessment of compliance with treatment and routine clinical laboratory tests.

The proportion of patients demonstrating clearance of atopic dermatitis (active disease no longer evident) and the proportion of patients demonstrating excellent improvement from baseline (75%-99% improvement in active disease) will be assessed by the investigating physician on study days 4 and 7 and weekly thereafter until treatment is discontinued. At these same time points, the mean percent reduction in BSA involvement from baseline will also be assessed. These analyses will be performed for each treatment and treatment group and the results compared among the treatment groups.

A 30 minute Cosyntropin Stimulation Test will be performed at baseline and at 28 $\pm$ 4 days in all patients. This test will be repeated at 56 $\pm$ 4 days in patients who continue treatment with 0.2% hydrocortisone valerate cream or ointment. The test will be performed as specified in the Cosyntropin package insert with administration of cosyntropin 0.25mg IM/IV to patients older than 2 years and 0.125mg to those aged 2 years or younger. Plasma cortisol levels should be measured using a single validated assay. In patients with an abnormal response ($\leq$18 ug/dl), the cosyntropin stimulation test will be repeated at approximately 4-week intervals until the peak stimulated cortisol level is normal (i.e., >18ug/dl).

Total body evaluation for local cutaneous adverse effects (e.g., whole body to include telangiectasia, thinning, shininess, striae, bruising, loss of elasticity and loss of normal skin markings) will be performed every 2 weeks during treatment and approximately 2 weeks post-treatment to assess changes from baseline.

Patients should receive adequate information regarding topical corticosteroid use, associated adverse events and protection against adrenal crisis under conditions of stress should they be suppressed from 0.2% hydrocortisone valerate cream or ointment, 1% hydrocortisone only cream or 1% hydrocortisone only ointment.

Study medication should be interrupted or discontinued if there is no improvement or if there is worsening of atopic dermatitis or if safety concerns develop (e.g., HPA axis suppression by cosyntropin stimulation testing). Study medication should be discontinued when the integrity of the skin barrier has been restored. Efficacy and safety data as stated in the "Study Evaluation" section of this Written Request should be reported for all patients in whom study medication is interrupted or discontinued. If treatment duration is less than 4 weeks, efficacy and safety information collected in these patients should be recorded and analyzed separately from the study patients (study patients are those completing at least 4 weeks of treatment). Patients treated for less than 4 weeks should

return for repeat cosyntropin stimulation testing no sooner than 4 weeks from their baseline evaluation.

Drug information:

Test Drug:
Dosage form: 0.2% hydrocortisone valerate cream and ointment (17-valerate ester)
Route of administration: topical
Regimen: apply to areas of skin affected with atopic dermatitis three times per day for up to 8 weeks.

Active Control:
Dosage form: currently marketed 1% hydrocortisone cream and ointment (free alcohol base- class VII potency) OR 1% hydrocortisone acetate (21-acetate salt- class VII) cream and ointment
Route of administration: topical
Regimen: apply to areas of skin affected with atopic dermatitis three times per day for 4 weeks

Drug specific safety concerns:

For the topical corticosteroids, the safety concerns include secondary adrenal insufficiency and other systemic adverse effects associated with corticosteroids (HPA axis suppression) as well as local cutaneous adverse effects (telangiectasia, thinning, shininess, striae, bruising, loss of elasticity and loss of normal skin markings)

Statistical information, including power of study and statistical assessments:

Number (percentage) of evaluable patients in each treatment group with abnormal (i.e., $\leq$18 ug/dl) cosyntropin-stimulated peak plasma cortisol levels at week 4 in all patients and, also, at week 8, in patients who continue treatment with 0.2% hydrocortisone valerate cream or ointment. The relationship between age, the amount of drug used, percent of body surface area involved and the presence of HPA axis suppression will be assessed.

Standard descriptive statistical analyses must be performed for adverse events and other safety measures.

Labeling that may result from the study(ies): Appropriate sections of the label may be changed to incorporate the findings of the studies.

Format of reports to be submitted: Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian

or other Pacific Islander or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

Timeframe for submitting reports of the study(ies): Reports of the above studies must be submitted to the Agency on or before December 1, 2009. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request: As per the Best Pharmaceuticals for Children Act, section 3, within 30 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a New Drug Application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e., approval, approvable, not approvable); or
4. the exclusivity determination (i.e., granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

If you have any questions, call

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation
and Research

APPENDIX A

Background and Rationale:

Atopic Dermatitis

Atopic dermatitis is a chronic inflammatory disease of the skin that is characterized by dry skin and pruritus in all stages of the disease. It is primarily seen in the pediatric age group, occurring in 10-20% of children in industrialized countries. In 50-75% of cases, the age of onset is $\leq$ 6 months. It is a condition characterized by exacerbations and remissions. However, the condition clears in 60% of children by age 16 years.

Treatment of atopic dermatitis must be individualized, taking into account such factors as the patient's age and severity of the disease. Moisturizers are the cornerstone of therapy because atopic dermatitis is characterized by dry skin. The mainstays of pharmacological therapy are the topical corticosteroids, which have been used for more than 50 years in the treatment of this condition. The weakest topical corticosteroid that adequately controls the disease should be used and treatment should be discontinued when control is achieved. This is because although topically applied, these products may be systemically absorbed, thus potentially placing the patient at risk for corticosteroid adverse effects. These adverse effects include hypothalamic-pituitary-adrenal (HPA) axis suppression and local cutaneous adverse effects (telangiectasia, thinning, shininess, striae, bruising, loss of elasticity and loss of normal skin markings).

State of Armamentarium

The least potent topical corticosteroids (i.e., those that are class VII), are those containing hydrocortisone (HC, free alcohol base) or hydrocortisone acetate (21-acetate salt) at concentrations of 0.25-1.0%. These preparations are available over-the-counter (OTC). They are labeled for the "temporary relief of itching associated with minor skin irritations, inflammation and rashes" in individuals 2 years of age and older. The OTC labels for these products state not to use more than 3-4 times/day and to stop use and see a doctor if symptoms persist for more than 7 days.

Of prescription medications, only fluticasone propionate cream (Cutivate), 0.05%, has been specifically approved for use in infants less than 1 year of age. It is a medium potency (class V) corticosteroid and is approved for the treatment of corticosteroid-responsive dermatoses in infants as young as 3 months of age.

Adverse Events

While local cutaneous adverse events associated with topical corticosteroids are of concern, systemic effects, such as HPA axis suppression, can be life-threatening. HPA axis suppression may be determined in several ways; the cosyntropin (synthetic subunit of ACTH) stimulation test is a widely used test for this purpose. Although variations may be performed in several ways, the 30 minute test is most commonly used. It is a simple test that can be performed as an outpatient at any time of day. Use of the 30 minute cosyntropin stimulation test to determine the effect of topical corticosteroids on the HPA

axis and the criterion to define a normal response as a peak cortisol level at 30 minutes of >18 ug/dl (>500 nmol/L), was endorsed by the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee on October 29, 2003.

Low potency products

The effect of topical 1% hydrocortisone on the HPA axis as determined by the cosyntropin stimulation test has been studied in pediatric patients with atopic dermatitis [1,2,3,4,5]. Although a 30 minute cosyntropin stimulation test was performed, the early reports lacked a control group and used outmoded assays to measure plasma cortisol[1,2]. One of these early reports reported no HPA axis suppression by the criteria specified (increment in plasma cortisol ≥7.5 ug/dl and peak cortisol ≥20 ug/dl) in 9 of 9 patients (mean age 3.9 ± 2.6 years) after an average of approximately 16 days of treatment with 1% hydrocortisone acetate ointment[1]. However, the other early article, which defined a normal cosyntropin response based on three criteria (basal cortisol >5 ug/dl, increment >7 ug/dl and peak >18 ug/dl) reported HPA axis suppression after 4 weeks of treatment with 1% hydrocortisone ointment in 3/7 patients with a normal baseline test[2]. It is not clear which of the three criteria were failed by each of these 3 patients.

In contrast to the early studies, more recent reports included concomitant controls of children who had never received corticosteroids by any route and plasma cortisol levels were measured by RIA or IRMA. A summary of these studies and results follows[3,4,5]:

- In two of the recent studies, 5 and 7 children, respectively, aged >3 years, had received only 1% hydrocortisone regularly since infancy (median duration of use: 6.5 and 6.9 years, respectively) to treat atopic dermatitis (median BSA 58% and 36%, respectively)[3,4]. In these children, a lower intravenous (IV) dose of cosyntropin (500 ng/1.73m^2) than recommended in the label (low-dose ACTH test) was administered and the plasma cortisol response was measured periodically for 60 minutes. In both studies, the results of HPA axis testing in these children were comparable to controls. In one of the studies which specified criteria for a normal response (peak stimulated cortisol ≥500 nmol/L= ≥18 ug/dl, and/or increment ≥200 nmol/L= ≥7 ug/dl at 60 minutes), there was no evidence of HPA axis suppression in either the control group or the 1% hydrocortisone group[4]. It should be noted that there is no consensus regarding either the performance of the low-dose ACTH test [i.e., the dose of ACTH to be administered or the timing of the blood samples to be obtained post-ACTH administration) or the criteria to define a normal response].
- Another recent study evaluated the effect of topical 1% hydrocortisone cream on the adrenal response using the 2 hour ACTH test[5]. The control group consisted of 3 infants, ages 2, 7 and 15 months old who had never received corticosteroids by any route. The treatment group consisted of 17 patients, aged 2 months-14.4 years (mean age: 3.6 years) with acute dermatitis (mean BSA 74%) who had received 1% hydrocortisone cream for 1 month to 14 years (median duration of use: 3 months). HPA axis suppression was defined as a peak stimulated plasma cortisol <830 nmol/L= <29 ug/dl in response to 0.25mg/1.72m^2 ACTH, IV. HPA axis suppression was reported in 1 of 3 (33%) patients in the control group (patient's

age: 7 months) and in 7 of 17 patients (41%) with acute dermatitis. Three of the 7 dermatitis patients with evidence of HPA axis suppression were infants ≤1 year of age who received 1% hydrocortisone cream daily for 3-5 months. The remaining 4 patients who suppressed had received topical hydrocortisone for 1 month, 2 months, 6 years and 14 years. The authors report that in this study, there was no significant correlation between the duration of hydrocortisone use beyond one month, the minimum treatment duration in this study, and the adrenocortical response to ACTH. The 2 hour plasma cortisol levels in the 3 infants (infants: 356, 394 and 606 nmol/L) were markedly lower than in the 4 children who suppressed (range in the children: 705-788 nmol/L). The article states that when hydrocortisone cream was applied only in the morning (note: initial frequency of use was not stated) and factors aggravating the dermatitis were treated (e.g., skin infection and food allergy), recovery of the HPA axis was found at retesting in two of the three infants after 3 and 18 months. Improvement in the 2 hour plasma cortisol response was noted in the third infant (395 to 780 nmol/L). Reversibility of HPA axis suppression was not addressed in the 4 children. Compared to the low dose ACTH studies, this study had a larger sample size, and patients were younger and had a larger BSA involved with atopic dermatitis.

In conclusion, there are only a few published studies that investigated the potential for topical 1% hydrocortisone products to suppress the HPA axis. The recent studies, which included a control group and updated plasma cortisol assays did not use the 30 minute cosyntropin test for which generally accepted criteria have been developed to define a normal response. In addition, data interpretation is hampered by small sample sizes. Nevertheless, HPA axis suppression was reported in one of these studies with at least one month of application and infants were the most susceptible.

Medium potency products

The effect of fluticasone propionate (Cutivate) cream, 0.05%, on the HPA axis has also been studied in pediatric patients. Of 43 evaluable patients, aged 3 months to 5 years, with atopic dermatitis involving at least 35% BSA, two (4.7%) patients demonstrated HPA axis suppression (peak plasma cortisol level ≤ 18ug/dl, standard 30 minute cosyntropin stimulation test), after 3-4 weeks of treatment.

0.2% hydrocortisone valerate (the 17-valerate ester) cream and ointment are medium potency (class V) corticosteroids. Although 0.2% hydrocortisone valerate is being used in pediatric patients (see below), safety information has been obtained only in adult patients and it has been approved only in adult patients for the relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses.

The PRECAUTIONS section of the package insert for hydrocortisone valerate cream and ointment, 0.2%, states that these products have produced mild, reversible adrenal suppression in adult patients when used under occlusion for 5 days, 15 grams twice a day over 25% to 60% body surface area (BSA) or when used three times a day over 20% to 30% BSA to treat psoriasis for 3-4 weeks.

The efficacy and safety of hydrocortisone valerate 0.2% cream compared to mometasone furoate (Elocon) 0.1% cream was studied in pediatric patients, aged 2-12 years, with atopic dermatitis who failed to respond to a topical hydrocortisone preparation[6]. The study was a multicenter, randomized, evaluator-blind parallel-group study with duration up to 3 weeks. The safety profile was comparable between the two treatments, with 19.3% of patients in the mometasone furoate treatment group reporting adverse events compared to 17.3% in the hydrocortisone valerate group. Of these, only application site reactions, all mild, were judged by the investigators to be treatment-related (3.7% in the mometasone furoate group and 1.8% in the hydrocortisone valerate group). However, an effect on the HPA axis was not evaluated in this study nor was safety compared to 1% hydrocortisone acetate.

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[1] Munro DD. The effect of percutaneously absorbed steroids on hypothalamic-pituitary-adrenal function after intensive use in in-patients. British Journal of Dermatology 1976: 94(Suppl. 12): 67-76.

[2] Marten RH, Byrne JPH, et al. Study of the Effects of Hydrocortisone and Hydrocortisone 17-Butyrate Ointments on Plasma ACTH Levels and Synacthen Responses in Children with Eczema. Dermatologica 1980: 160: 261-269.

[3] Patel L, Clayton PE, et al. Adrenal function following topical steroid treatment in children with atopic dermatitis. British Journal of Dermatology 1995: 132: 950-955.

[4] Ellison JA, Patel L, et al. Hypothalamic-Pituitary-Adrenal Function and Glucocorticoid Sensitivity in Atopic dermatitis. Pediatrics 2000: 105(4): 794-799.

[5] Turpeinen M. Adrenocortical response to adrenocorticotropic hormone in relation to duration of topical therapy and percutaneous absorption of hydrocortisone in children with dermatitis. Eur J Pediatr 1989: 148: 729-731.

[6] Lebwohl M. A comparison of once-daily application of mometasone furoate 0.1% cream compared with twice-daily hydrocortisone valerate 0.2% cream in pediatric atopic dermatitis patients who failed to respond to hydrocortisone. International Journal of Dermatology 1999: 38: 604-606.