CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19958/S008

MEDICAL REVIEW(S)

JUN 17 1999

Medical Officer's Review of NDA
Amendment and Labeling Supplement

NDA #: 19-958 SE5-008 BL
19-958 SLR-011
HFD-540#: 992347

Submission: 12/16/98
CDER stamp date: 12/17/98
Assignment date: 1/11/99
Date review begun: 4/23/99
Date draft completed: 5/24/99
Date final completed: 6/4/99

Drug name:	Cutivate Cream, 0.05%
Generic name:	Fluticasone propionate cream, 0.05%
Proposed trade name:	Cutivate Cream, 0.05%
Chemical name:	[(6α,11β,16α,17α)-6,9,-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy)androsta-1,4-diene-17-carbothioic acid, S-fluoromethyl ester]
Sponsor:	Glaxo Wellcome Inc. P.O. Box 13398 Five Moore Drive Research Triangle Park, NC 27709 919-941-5883
Pharmacologic Category:	Anti-inflammatory
Proposed Indication(s):	For the addition of treatment in children down to the age of 3 months for the current approved indications (eczema and corticosteroid-responsive dermatoses)
Dosage Form(s) and Route(s) of Administration:	cream; topical
Related Drugs:	Cutivate ointment, 0.05%
Related Reviews: Biopharm dated:	Draft – 6/3/99

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ON ORIGINAL

2 Table of Contents

3 Material Reviewed

3.1 NDA Volumes Reviewed

NDA 19-958 SE5-008 BL - Volumes 17.1-17.3

3.2 Regulatory Background

NDA 19-958, SE5-008 was submitted on June 9, 1995 for the treatment of corticosteroid-responsive dermatoses in the pediatric population down to the age of 2 years. The efficacy supplement was issued a "not approvable" letter on June 6, 1996 because adequate safety had not been demonstrated.

A meeting was held on November 24, 1997 to discuss the outstanding safety issues. It was agreed that the sponsor would conduct an open-label study to access the effect on fluticasone propionate cream, 0.05% on the HPA axis. Children with a normally functioning HPA axis would be expected to have a post-stimulation serum cortisol > 18 μg/dL. The study would also assess other systemic safety through monitoring of serum chemistries and hematology. Finally, the study would monitor any cutaneous adverse events that are known to occur with topical steroid use.

It was recommended that the company have 10-15 patients with atopic dermatitis or psoriasis in each age group with at least 35% body surface area involved. The agency agreed that safety data could be extrapolated upward from the youngest well-represented age group.

4 Directions for Use

4.1 Proposed Indication and Usage Section

Indications and Usage: CUTIVATE Cream is a medium potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. CUTIVATE Cream may be used in pediatric patients 3 months of age or older. The safety and efficacy of drug use for longer than 4 weeks in this population or in pediatric patients below 3 months of age have not been established.

4.2 Proposed Pediatric Use Section

4.3 Proposed Dosage and Administration Section

Dosage and Administration: CUTIVATE Cream may be used in adult and pediatric patients 3 months of age or older. Safety and efficacy of CUTIVATE Cream in pediatric patients for more than 4 weeks of use or in pediatric patients below 3 months of age has not been established.

4.4 Proposed Adverse Events Section

Reviewer's Comment: *The above section, 4.1-4.4 are the proposed changes and/or additions to the label as proposed by the sponsor as they relate to the targeted pediatric population.*

5 Description of Clinical Data Sources

Study #FPC4001 – an open-label trial enrolling 51 patients ages 3 months to 5 years with moderate to severe eczema or psoriasis to evaluate the safety, both systemically and locally, after a 3-4 week course of treatment using fluticasone propionate cream, 0.05% bid to at least 35% of the body surface area. This trial was multicentered, involving 10 centers all located in the United States. The study period was from April 27, 1998 – November 3, 1998.

6 Clinical Study

6.1 Sponsor's protocol # 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

6.1.1 Investigators

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6.1.1.1 Objective/Rationale

To evaluate the safety of a 3- or 4-week course of twice-daily fluticasone propionate cream 0.05% in pediatric subjects aged 3 months to 5 years with moderate to severe eczema or psoriasis, by monitoring the following:

1. Plasma levels of fluticasone following twice-daily treatment for 3 or 4 weeks
2. Effect on the HPA axis as determined by response to cosyntropin stimulation tests
3. Hematology and blood chemistries
4. Signs of skin atrophy and pigmentation changes at application site
5. Other adverse events

6.1.1.2 Design

This is a multicenter, open-label trial.

6.1.1.3 Protocol

Methodology

This study was an open-label trial of a 3-4 week course of twice-daily treatment with fluticasone propionate cream, 0.05%. Six clinic visits (Screening, Days 1, 8, 15, 22, 29) were scheduled, with a conditional seventh visit 1 or 2 weeks post-treatment if needed for repeat

laboratory tests or adverse events assessments. Thus, the maximum total time a subject could be in the study, after screening, was 6 weeks.

Patients had a cosyntropin stimulation test (CST) performed at the baseline visit and end-treatment visit. The CST was to be repeated at the follow-up visit if the results at end-treatment were abnormal. Immediately after obtaining the pre-stimulation sample, cosyntropin was to be administered intravenously and the post-stimulation value was scheduled to be collected 30 minutes later. The dose to be used in the younger age group (ages 3 months – 2 years) was 0.125mg and in the older age group (3 – 5 years) was 0.25 mg.

Patients also had serum chemistry and hematology samples drawn at the baseline and end-treatment visits.

Cutaneous signs or lack thereof, were recorded at the baseline visit. These included signs of telangiectasia, loss of elasticity, purpura, dusky erythema, striae, or any other signs of atrophy. These were evaluated at each visit.

Diagnosis and Criteria for Inclusion

Males and females 3 months to 5 years 11 months of age, with a diagnosis of moderate to severe eczema or psoriasis showing extensive body surface area (BSA) involvement of at least 35% were screened. Subjects were not to have been treated with topical steroids for at least 1 week or systemic steroids for at least 6 months prior to beginning treatment with the study drug.

Parents were to apply study drug to a minimum of 35% BSA throughout the treatment period. All lesions were to be treated except lesions that may have been present on the eyelids, perioral area, perinasal area, or in the diaper area of subjects who wore diapers. Up to 120 grams per week were allowed for subjects age 3 months to 2 years, and up to 180 grams per week were allowed for subjects age 3 years to 5 years.

6.1.1.3.1 Population

A total of 66 subjects were screened, 51 were enrolled and 49 were started on study treatment. All subjects enrolled had a diagnosis of eczema. A total of 32 subjects 3 months to 2 years of age received treatment. Seventeen subjects 3 to 5 years of age were treated.

6.1.1.3.2 Endpoints

The endpoints of this trial were safety endpoints. Patients were to be assessed for adrenal suppression by testing HPA axis function via the Cortrosyn® Stimulation test (CST). The serum cortisol values were determined using the

all subjects] and the assay (subjects 2 years old and older) at baseline and end-treatment. The results based on the were considered the primary outcome measure, and assay results were used as confirmatory data. The was chosen as the primary outcome measure because the turn around time was within 24 hours versus one week for the assay. Patients were to have the CST at baseline and at end-treatment, which consisted of a pre-stimulation blood drawing and then a blood drawing 30 minutes post-stimulation. The following definitions of expected responses for non-suppressed adrenal function were used as endpoints as provided by the Cortrosyn® package insert:

- Post-stimulation cortisol > 18.0μg/dL
- Post-stimulation cortisol at least 7μg/dL greater than pre-stimulation cortisol value
- Post-stimulation cortisol approximately double pre-stimulation cortisol value, provided pre-stimulation cortisol value does not exceed the normal range

The post-stimulation cortisol for the [redacted] assay is [redacted] μg/dL.

Reviewer's Comment: *The primary variable to be used to determine adrenal suppression will be the post-stimulation cortisol value of [redacted] μg/dL in the [redacted] assay, when a patient fails to meet all three criteria. Since the adrenal gland secretes maximally in the morning, and all samples were to be drawn at 8:00 am, when the endogenous stimulation of the adrenal gland is maximum, post-cortisol levels would not necessarily be expected to double or increase by μg/dl.*

Other safety parameters to be assessed included local cutaneous effects (skin atrophy, telangiectasias, pigmentary changes) and other systemic effects, particularly glucose and electrolyte homeostasis.

6.1.1.3.3 Statistical considerations

Analysis of the data is to be descriptive, as this is an open-label study designed to evaluate safety in pediatric subjects down to the age of 3 months.

6.1.1.4 Results

6.1.1.4.1 Populations enrolled/analyzed

Fifty-one subjects were enrolled at 10 centers, including 32 subjects (63%) 3 months to 2 years, 11 months of age at screening, and 19 subjects (37%) 3 to 5 years, 11 months of age. Forty-nine subjects (32 in the younger age group and 17 in the older age group) received treatment with study medication.

Forty-six (90%) of the subjects completed the study, 32 (100%) in the 3 months to 2 years, 11 months of age group and 14 (74%) in the 3 years to 5 years, 11 months age group. In the latter group, one patient was lost to follow-up, one patient's baseline cortisol levels were clinically low, and one patient did not meet the severity score for disease severity. Table 1 shows the baseline demographics for patients enrolled in the study.

Table 1
Summary of Baseline Demographics

		Age 3 mos-2yrs.	Age 3-5yrs	Total
Age (years)	N	32	19	51
	Mean	1.7	4.4	2.7
	SD	0.84	0.98	1.59
	Median	1.7	4.2	2.5
	Minimum	0.25	3.12	0.25
	Maximum	2.99	5.86	5.86
Sex	N	32	19	51
	Female	14 (44%)	10 (53%)	24 (47%)
	Male	18 (56%)	9 (47%)	27 (53%)
Race	N	32	19	51
	White	13 (41%)	7 (37%)	20 (39%)
	Black	10 (31%)	5 (26%)	15 (29%)
	Asian	5 (16%)	3 (16%)	8 (16%)
	Amer. Hispanic	1 (3%)	3 (16%)	4 (8%)
	Other	3 (9%)	1 (5%)	4 (8%)
Height (cm)	N	28	18	46
	Mean	81.4	103.5	90.0
	SD	11.60	9.29	15.24
	Median	84.0	102.5	90.5
	Minimum	64	79	64
	Maximum	101	122	122
Weight (kg)	N	32	18	50
	Mean	11.7	18.1	14.0
	SD	2.86	3.23	4.28
	Median	12.0	18.2	14.0
	Minimum	7	12	7
	Maximum	17	26	26

Table 2 is a summary of the dermatologic characteristics of the patients at baseline.

Table 2
Summary Of Dermatologic Characteristics At Baseline

	Age 3 mos-2 yrs	Age 3-5 yrs	Total
%BSA *			
N	32	19	51
Mean	65.3	71.7	67.7
SD	20.51	21.57	20.93
Median	66.0	76.0	71.0
Minimum	35	36	35
Maximum	100	100	100
%BSA to be Treated			
N	32	17	49
Mean	62.3	67.2	64.0
SD	17.81	20.15	18.59
Median	61.0	71.0	68.0
Minimum	35	36	35
Maximum	94	95	95
Sum of all Signs/Symptoms			
N	32	18	50
Mean	14.9	16.6	15.5
SD	3.88	4.68	4.21
Median	16.0	17.0	16.0
Minimum	9	8	8
Maximum	22	23	23
Sum of 3 Worst Signs/Symptoms			
N	32	18	50
Mean	7.4	7.6	7.5
SD	1.29	1.54	1.37
Median	7.0	8.0	7.0
Minimum	5	4	4
Maximum	9	9	9

*BSA covered by study disease

Reviewer's Comment: *The sponsor included all 51 patients in the safety analysis, even though only 49 were started on study medication. This was to comply with ICH guidelines for defining the intent-to-treat population, namely that this population is comprised of any subject who had an invasive procedure at the Baseline visit and/or received study drug.*

Cutaneous atrophy was not reported for any subject at baseline. One subject had mild telangiectasia of the face at baseline, which was not assessed as atrophy. Abnormal pigmentation was reported at baseline in 8 subjects (25%) in the younger age group and 3 subjects (16%) in the older age group.

The most frequent concurrent medication used was EMLA, used as a topical anesthetic at venipuncture sites (39 subjects, 76%). The use of this drug was more common in the younger

age group (28 subjects, 88% than in the older subjects (11 subjects, 58%). The second most common drug used was hydroxyzine hydrochloride, used by 28 subjects (55%). The concomitant use of this drug was slightly more common in younger subjects (19 subjects, 59%) than in older subjects (9 subjects, 47%). There were 2 subjects, both in the younger age group with a corticosteroid listed as a concomitant medication, in violation of the protocol restriction on these drugs. Subject A176 was given alclometasone dipropionate 3 days before the follow-up visit for relapsing eczema. Subject A189 was given oral prednisolone 1 day before the end-treatment visit for an adverse event, wheezing.

Most subjects (96%) missed less than 10% of scheduled applications. Only 2 subjects (4%) missed more than 10% of scheduled applications. No subject missed more than 20% of scheduled applications. The mean percentage of missed applications was 2.8% in the younger age group and 2.2% in the older age group.

6.1.1.4.2 Efficacy endpoint outcomes

Severity of signs and symptoms of the study disease and percent BSA affected and treated were collected in order to augment safety assessment in any individual who showed adrenal suppression by comparing adrenal function to severity of skin disease and extent of BSA involvement. No efficacy analyses were planned or implemented.

Reviewer's Comments: *It is important to note that of the 46 patients who completed the per-protocol specified time frame, 23 (50%) had a 50% decrease in the BSA involved by 2 weeks of treatment, 9 (20%) had a 50% decrease of BSA involvement by 3 weeks of treatment, and another 4 (9%) had the same improvement occur by 4 weeks of treatment.*

6.1.1.4.3 Safety outcomes

Forty-six subjects (90%) were treated per the protocol-specified time frame (16 [31%] for 3 weeks; 30 [59%] for 4 weeks). In the 3 month – 2 year age group 13 (41%) were treated for 20-26 days and 19 (59%) were treated for > 26 days. In the 3 year – 5 year age group 3 (16%) of subjects were treated between 20-26 days and 11 (58%) were treated for > 26 days. The overall mean number of days a subject was treated was 25.5 and the overall median number of days a subject was treated was 27.0.

The older group, being larger in body size, used more drug than the younger group. In the first week, the younger group used a mean of 28.2 grams/week (range 3.0-85.4 grams) and the older group used a mean of 62.1 grams/week (range, 6.4-143.3 grams). In the 4th week, means were 24.5 grams (range 6.7-84.3 grams) in the younger group and 58.9 grams (range 9.6-133.2 grams) in the older group. The average amount of drug used per day over the course of the study was 3.8 grams (range, 0.3-12.7 grams) in the younger age group and 7.7 grams (range, 1.0-20.0 grams) in the older age groups.

No subjects discontinued study drug permanently due to adverse events. One subject had a temporary interruption in study medication due to an adverse event. This is discussed under the section entitled "Secondary Safety Parameters".

Safety Parameters

Cosyntropin Stimulation Test

The most important safety parameter was the Cosyntropin Stimulation Test. This was done at the baseline visit and at the end-treatment visit. The time between the cosyntropin injection and the post-stimulation sample collection was close to that specified by the protocol (30 minutes) and was similar in the two age groups. Specifically, the mean time between cosyntropin administration and the post-stimulation blood draw was 32.8 minutes at baseline (range 28-55 minutes) and 32.4 minutes at end-treatment (range 25-45 minutes). The majority of subjects (37) were fasted prior to cosyntropin injection at all visits. Thirty-seven subjects consumed some food and/or drink prior to post-stimulation sampling at all visits.

The number of subjects with CST results based on the [ ] assay were as follows: 49 – baseline pre-stimulation, 47 – baseline post-stimulation, 44 – end-treatment pre-stimulation, 43 – end-treatment post-stimulation. Thirty-two of the 43 patients (74%) who had end-treatment post-stimulation cortisol levels drawn were in the 3 months – 2-year age group. The number of subjects with CST results based on the [ ] assay were as follows: 37 – baseline pre-stimulation, 36–baseline post-stimulation, 30 – end-treatment pre-stimulation, 28 – end-treatment post-stimulation. Fifteen of the 28 patients (54%) who had end-treatment post-stimulation cortisol levels drawn were in the 3 months – 2 years age group.

Forty-three subjects had complete per-protocol CST results, 29 aged 3 months to 2 years and 14 aged 3 to 5 years. Overall, the mean baseline pre-stimulation cortisol level was 13.76 μg/dL compared to the mean end-treatment pre-stimulation cortisol level of 12.3 μg/dL. The mean baseline post-stimulation cortisol level was 30.53 μg/dL compared to the mean end-treatment post-stimulation level of 28.84μg/dL.

Two subjects, 5 and 2 years of age, had end-treatment post-stimulation cortisol levels below the minimum level of 18.0μg/dL as noted in table 3:

Table 3
End-treatment CST (FPIA)
Subjects Who Did Not Have Post-Stimulation Cortisol Value > 18μg/dL
N=43

						Serum Cortisol (μg/dL)					
						Baseline		End-treatment		Follow-up	
Subject	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 grams	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 B201 was treated with an average of 20.0 grams of fluticasone per day and received 561.0 grams over the 4-week treatment course. The patient began treatment to 95% of his BSA. By day 15, the BSA affected decreased to 21%, worsened to 26% by day 22, and by the 4th week, had decreased to 20% BSA affected. The patient's parent, however, continued to treat 95% of the BSA throughout the treatment period (protocol specified at least 35% BSA to be treated throughout). The subject had a plasma fluticasone level of 116.5 pg/mL at end-treatment. The subject returned for a follow-up visit 12 days after the end of treatment and his CST results returned to >18μg/dL.

Subject B202 was treated with an average of 5 grams per day and received 176.5 grams over the course of the study. His end-treatment visit was 7 days late, thus the patient was treated continuously for 5 weeks. The patient began treatment to 35% of his BSA and continued treating this amount throughout the study period. By day 8, the BSA affected decreased to 21%, by day 22, BSA affected had decreased to 7%, but increased by day 29 to 17%. The result of this patient's plasma fluticasone level was below the limit of quantification at end-treatment. This patient was lost to follow-up despite extensive efforts to get him back in for testing, therefore, reversibility of his suppression is unknown.

Table 4 shows the results of patients that were suppressed by [ ] assay.

Table 4
End-treatment CST (HPLC)
Subjects Who Did Not Have Post-Stimulation Cortisol Values > 14μg/dL
N=28

						Serum Cortisol (μg/dL)					
						Baseline		End-treatment		Follow-up	
Subject	Age/Sex	%BSA*	Severity+	Duration	Amount Used	Pre-stim.	Post-stim.	Pre-stim.	Post-stim.	Pre-stim.	Post-stim.
A171	2years/F	86 (81)	22 (9)	4 weeks	355.7 grams	13.9	20.3	8.1	12.4	12.9[1]	15.5[1]
A176	2 years/F	100 (75)	13 (7)	4 weeks	126.9 grams	28.9	24.2	17.8[2]	8.5[2]	11.9[3]	17.0[3]
B201	5years/M	95 (95)	22 (9)	4 weeks	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)
[2]Samples may have been reversed
[3]1 week after end-treatment
[4]12 days after end-treatment

Reviewer's Comments: *It is agreed that the results for patient A176 was probably due to laboratory error and that the end-treatment cortisol values were mislabeled as the results are non-physiologic. This patient did not demonstrate suppression by [ ] assay in that at end-treatment the pre-stimulation cortisol value was 12.7 μg/dL and the post-stimulation cortisol value was 24.1 μg/dL. A171 had 81% of BSA treated throughout the study for 4 weeks, only improving to 71% BSA involved. Her end-treatment results by [ ] assay did not show suppression, 12.0 μg/dL pre-stimulation and 19.8 μg/dL post-stimulation. Her repeat test on follow-up was normal for both [ ] although the rise was not at least 7μg/dL (approximately 3 μg/dL). This was attributed to the fact that the patient had begun mometasone*

and hydrocortisone since the end-treatment status of this study. Therefore, in this reviewer's opinion, this patient did not demonstrate adrenal gland suppression after treatment with fluticasone propionate.

Subject B202 did demonstrate suppression by both assays and also returned to normal function at follow-up by both assays. Subject B201, the other subject who demonstrated adrenal suppression by [ ] assay, was not included in this table for [ ] assay because the laboratory mishandled his specimen during analysis. What is known is that his baseline result by [ ] was 10.4 µg/dL pre-stimulation and 21.8 µg/dL post-stimulation. After treatment at the 4 week mark (day 29), his end-treatment pre-stimulation result was 3.7 µg/dL. This is almost 3 times lower than his baseline pre-stimulation value. In this reviewer's opinion, if the end-treatment post stimulation specimen had been handled properly, it would probably have shown results consistent with adrenal suppression; thus confirming the results of the [ ] assay.

There was also one patient, B214, a 5-year-old, whose pre-stimulation cortisol was 22.3 µg/dL (upper limit of normal, 22.9µg/dL), who also did not exhibit a 7 µg/dL rise from baseline post-stimulation (28.3 µg/dL). This patient, like patient A171, was trending toward suppression.

Plasma Fluticasone Levels

Twenty-nine subjects had plasma samples taken at either baseline and/or at the end of treatment who were 2 years of age or greater. There were 27 of 29 (93%) subjects with plasma fluticasone samples drawn at baseline and 25 of 29 (86%) subjects with plasma fluticasone samples drawn at end-treatment. No subject had measurable fluticasone values (limit of quantification 50 pg/mL) at baseline. Six of 25 (24%) subjects had measurable fluticasone values at end-treatment; the remaining samples were below the assay's limit of quantification. The mean fluticasone plasma values for the six subjects were 112.1 pg/ml in the younger age group and 163.1 pg/ml in the older group (137.6 pg/mL). Median values were 122.0 pg/ml and 116.5 pg/ml, respectively. The highest value was 263.8 pg/mL, reported for subject B282. This subject did not have adrenal suppression, with end-treatment post-stimulation cortisol results > 18µg/dL (23.3 µg/dL by [ ] 22.9 µg/dL by [ ] Table 5 shows the subjects who had detectable plasma fluticasone levels at end-treatment.

***Reviewer's Comment:** According to the clinical pharmacology/biopharmaceutics review, the limit of quantification for plasma fluticasone levels is 20pg/mL. This will not, in this instance as will be seen from below, make a difference in the correlation of plasma fluticasone levels and adrenal suppression.*

It was agreed between the Agency and Sponsor that for ethical reasons plasma fluticasone levels would not be drawn in infants (ages 3 months-1 year, 11 months).

Table 5
Subjects with Detectable Fluticasone in Plasma at End-treatment
N=29

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) (FPIC>18; HPLC>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)	177.4	4	34.2/23.8 normal
A190	2-0/F	59.2	77	12 (6)	67.1	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	23.2/22.9 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[1] divergent

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

Reviewer's Comment: *This study did not demonstrate any reliable correlation between plasma fluticasone levels and adrenal suppression. Only one (B201) of the two subjects (B201, B202) who had adrenal suppression at end-treatment had detectable plasma fluticasone levels at end-treatment. Only one (A171) of the two other subjects (A171, A176) with lower trending end-treatment cortisol levels, but not considered suppressed, had detectable fluticasone plasma levels. Again, the patient with the highest fluticasone plasma level did not demonstrate adrenal gland suppression.*

Cutaneous Safety Parameters

Other safety parameters monitored in the trial were cutaneous events. There were two patients with mild telangiectasia, assessed as atrophy (B201 and B213). Patient B201, a 5-year-old boy, had mild telangiectasia first documented on Day 22 in the popliteal and antecubital areas. The subject also had dusky erythema. On day 29, the same signs were persistent but the patient also had mild telangiectasia on the face. Both signs were still present at a follow-up visit 12 days later. One month later the atrophic signs had regressed in the antecubital area and on the face, with the telangiectasia improved in the popliteal fossae.

The second patient B213, a 3-year-old boy, had mild telangiectasia on the face first documented on Day 29 and assessed as atrophy. At a follow-up visit, 1 week later, the face was unchanged. Three months later, the telangiectasias of the face had resolved. The investigator reported that due to the severity of the eczema on the face at screening, it was not possible to determine if they had been present at baseline, but as the eczema improved, they became visible.

One other patient, a 1-year-boy, had facial telangiectasias at screening and throughout the study. The investigator also reported some thinning of the skin in the facial area,

but did not consider this atrophy. The patient's face was treated throughout the study and the signs did not worsen during the study.

Reviewer's Comment: *The protocol did not specify that the face was to be specifically treated. So it is unknown how many children had their faces included in the at least 35% BSA to be treated. What is known is that 41 of 51 patients had atopic dermatitis of the face recorded at baseline. If one assumes that given the location, most parents would have wanted their children's face treated, then the denominator for the adverse events occurring on the face would be 41.*

The course of these events described above would suggest that the telangiectasias that occurred in these 2 patients (2/41 or 4.9%) and the dusky erythema, which occurred in one individual (1/51 or 2%), were secondary to the use of fluticasone propionate cream, 0.05%.

Table 6 shows the patients who had new onset pigmentary changes after beginning study medication.

Table 6
New Onset Pigmentary Changes

Pt. No.	Ethnicity	Day First Recorded	Type of Change
B202	African-Amer.	22	Post-inflammatory Hyperpigmentation
B251	African-Amer.	8	Hyperpigmentation
B272	Amer.-Hispanic	15	Slight Hyperpigmented Areas
A186	Asian American	22	Post-inflammatory Hypopigmentation
A187	Euro.-American	8	Post-inflammatory Hypopigmentation
B285	Asian American	15	Post-inflammatory Hypopigmentation
B286	Asian American	15	Post-inflammatory Hypopigmentation

Reviewer's Comment: *These pigmentary changes appear to be secondary to the inflammation caused by the disease itself and not secondary to fluticasone propionate. If it had been secondary to the drug product, hypopigmentation should have been seen in the African American population.*

Other drug-related adverse events of the skin included a 2-year-old who experienced a moderate burning of the skin, which was documented to be a local application site reaction. The condition resolved the same day. A 5-year-old experienced mild urticaria and it also resolved the same day it occurred. A 3-year-old developed a severe erythematous rash that required temporary interruption of treatment. It was determined the patient applied the medication too soon after bathing. The condition resolved and the patient completed the study.

Laboratory Parameters

The majority of the analytes shifted to normal values or did not change between baseline and end-treatment. Shifts to low or high hematology values reported in more than 5% of subjects included shifts to high values for total white blood cell counts (three subjects, 8%), shifts to low values for platelet counts (five subjects, 14%), shifts to low values for total

neutrophil count (two subjects, 6%), shifts to low values for % neutrophils (nine subjects, 24%), and shifts to high values for eosinophil counts (two subjects, 6%). The most common shifts were to high values for % lymphocytes (13 subjects, 34%) and shifts to low values for % neutrophils (nine subjects, 24%). Colds and upper respiratory infections (which may be viral in etiology, and associated with neutropenia) were relatively common in this population.

Among clinical chemistry analytes, shifts reported by more than 5% of subjects included shifts to high AST values (four subjects, 11%), shifts to high total protein (four subjects, 11%), shifts to low glucose 93 subjects, 9%), shifts to low uric acid (two subjects, 6%), and shifts to high calcium (two subjects, 6%). All shifts to high AST values were reported in older children. With this exception, there were no notable differences between the age groups.

Reviewer's Comment: *It should be noted that there was little variation in the total percentage of patients with laboratory abnormalities when baseline was compared to end-treatment values.*

There were five laboratory results that were considered significantly abnormal, none of which were drug-related. There was a 2 year old with a low fasting blood glucose of 53mg/dL; an 11 month old who at baseline had mild neutropenia (3.17x10^3/uL), which then decreased to 1.90x10^3/uL but rose on follow-up to 2.25x10^3/uL; a 1 year old whose total WBC rose to 16.78x10^3/uL and was felt to be secondary to a concurrent disease; a 7 month old that had a low hemoglobin and hematocrit at baseline (8.6g/dL and 29%) and it remained so at end-treatment (7.7 g/dL and 29%); and a 9 month old with an elevated platelet count of 7450,00/μL, which was thought to be a laboratory error. The other laboratory abnormalities were not of clinical significance and some were within the acceptance of laboratory variance.

Significantly, there were no abnormalities consistent with glucose intolerance or electrolyte imbalance. Therefore, in this reviewer's opinion, treatment of these age groups with fluticasone propionate cream did not result in any significant laboratory abnormalities that could be attributed to the drug product.

7 Overview of Safety

Forty-three subjects had complete per-protocol CST results, 29 aged 3 months to 2 years and 14 aged 3 to 5 years. There were 2/43 patients in this study, one 2-year-old and one 5-year-old who experienced adrenal suppression. These patients were treated with fluticasone propionate cream, 0.05% over 35% and 95% BSA, respectively for four and five weeks, respectively. On follow-up 12 days later, the 5-year-old's adrenal gland was responding appropriately. No conclusions can be made concerning the 2-year-old, who was lost to follow-up.

Two patients (4.6%), aged 2 years old and 5 years old, trended toward adrenal suppression in that the change in post stimulation cortisol was not 7 μg/dL greater than the pre-stimulation value although the total post-stimulation serum cortisol was >18 μg/dL.

Only one of the two subjects who demonstrated adrenal suppression had a measurable fluticasone plasma level. Only one of the two patients that trended toward adrenal suppression had a measurable fluticasone plasma level. The patient in the study

with the highest fluticasone plasma level did not show any trend toward adrenal suppression.

Two patients had mild telangiectasias that were not documented at baseline, a 3-year-old and a 5-year-old. Both had telangiectasias of the face that resolved within one to three months. The 5-year-old had telangiectasias in the antecubital and popliteal areas that also were not documented at baseline. In one month, he had resolution of the former and improvement of the latter.

There was one incident each of dusky erythema, urticaria, application site reaction, and erythematous rash. Each of these reactions resolved and the patients were able to complete the study. There were not any pigmentation changes that could be attributed to the use of fluticasone cream.

There were not any significant laboratory abnormalities that could be attributed to fluticasone cream; particularly, there was not any evidence of either glucose intolerance or electrolyte imbalance.

There were not any deaths during this study and no patient was discontinued due to an adverse event secondary to fluticasone propionate cream, 0.05%.

Note: *This label is the currently approved label of 9-5-97 with the changes incorporated by the sponsor for this amendment involving an additional population for the approved indications. It also includes a review of the labeling supplement SLR-011 for the clinical portions of the label. Recommendations by the reviewer are shadowed and/or marked by ~~strikeout~~ unless otherwise noted.*

8 Labeling Review

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9 Conclusions

Cutivate (fluticasone propionate cream) Cream, 0.05% has a safety profile that would allow its use in the pediatric population down to the age of 3 months. Although 2 patients developed HPA axis suppression, it was under conditions of exaggerated use. One patient had 95% of his BSA treated for 4 weeks, although at day 15, total BSA involved had dropped to 21%. The other patient had 35% BSA treated for 5 weeks, 1 week longer than the protocol specified. All patients had to continue treatment to at least 35% of their BSA throughout the trial, either for 3 or 4 weeks. Twenty-three of forty-six patients (50%) had at least a 50% reduction in BSA affected by disease by 14 days of treatment. Another 9 (20%) had at least a 50% reduction in BSA affected by disease by 21 days. Only 3 (7%) patients took 4 weeks to obtain a 25% reduction in BSA affected by disease. This is to say that under conditions of normal use, a patient would decrease the amount of drug used as the disease clears, thus decreasing the risk for developing suppression of the adrenal gland.

There was not a direct correlation between fluticasone plasma levels (FPL), amount of fluticasone cream used, BSA treated, or age and adrenal suppression. All but one of the patients who had a detectable plasma fluticasone level (6 patients), who were suppressed (2 patients), or trended toward suppression (2 patients) used the drug for 4 weeks. The one outlier used the drug for 3 weeks. The two year-4-month old who became suppressed did not have a detectable fluticasone plasma level after treating 35% of BSA with a total of 176 grams. Yet a 2 year-4 month old who treated 81% BSA throughout, used 355.7 grams, and had a detectable FPL, only trended toward suppression. There were 6 other toddlers who used approximately the same amount of drug as the toddler who became suppressed over a 3-4 week period and they had neither a detectable FPL nor adrenal suppression.

There was not a good correlation between these variables and the older age group. The other patient who became suppressed was a 5 year old who treated 95% of BSA for 4 weeks, used 561.0 grams of study drug and did have a FPL of 116.5 pg/mL. Yet a 3 year-11 month old who had a higher FPL (263.8 pg/dL), treated as high as 56% BSA over 4 weeks, and used 355.7 grams of study drug, did not exhibit adrenal suppression. There were 3 patients who used over 300 grams in this age group but did not have a detectable FPL or evidence of adrenal suppression. One patient who used 259 grams of study drug had a detectable FPL (109.1 pg/mL) but did not exhibit adrenal suppression.

Finally, in the 2 patients that exhibited HPA axis suppression, for the one patient that returned for follow-up and had 95% BSA treated for 4 weeks, after 12 days his HPA axis was functioning normally, thus exhibiting reversibility.

Although some patients had a decrease in their pre-stimulation end-treatment cortisol value compared to the baseline pre-stimulation cortisol value, the majority of these patients were able to attain an appropriate post-stimulation cortisol value at end-treatment. For some of them, the post-stimulation cortisol value was greater than the baseline post-stimulation cortisol value. These patients also did not have any evidence of distant organ suppression by laboratory values. Therefore, clinical significance from this observation cannot be ascertained from the data presented.

Therefore, in reference to HPA axis suppression and fluticasone propionate cream, the study was able to demonstrate that fluticasone propionate cream, 0.05% has the potential to cause suppression of the HPA axis when used over a large body surface area (≥ 35%) twice a day for 4 weeks. It did not establish a good correlation between adrenal gland suppression and the other variables. Importantly, the study demonstrated that the suppression is reversible upon cessation of the drug product.

Fluticasone propionate cream, 0.05%, after 4 weeks of use, also has the potential to cause telangiectasia and dusky erythema, both of which are reversible upon cessation of the drug product.

Fluticasone propionate cream, 0.05% did not cause any other laboratory abnormalities.

10 Recommendations

It is recommended that Cutivate (fluticasone propionate cream), 0.05% Cream be approved for use in the pediatric population down to the age of 3 months with the labeling changes as suggested above. There may be additional changes to the label proposed by clinical pharmacology/Biopharmaceutics as the final review is pending.

/S/

Denise Cook, M.D.
Medical Officer, Dermatology 6/8/99

cc: IND
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