

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-152

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA Number	21-152
Stamped Receipt Date(s)	March 11 th , 2004
Brand Name	Cutivate 1 [redacted] 0.05 %
Generic Name	Fluticasone propionate
Reviewer	Abimbola Adebowale Ph.D.
Acting Team Leader	Ray Baweja Ph.D.
OCPB Division	DPE III
ORM division	HFD-540
Applicant	GlaxoSmithKline Consumer Healthcare, L.P. NJ 07054
Relevant IND(s)	54,894
Submission Type; Code	3S (Re-activated NDA)
Formulation; Strength(s)	[redacted] 0.05 %
Indication	For the relief of the inflammatory and pruritic manifestations of atopic dermatitis.

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1. Executive Summary

This NDA is a re-submission for fluticasone propionate [redacted] 0.05 %. It was originally submitted to the FDA by Glaxo Wellcome (GW) on December 13, 1999. It was then voluntarily

withdrawn on May 25th, 2000 six months into the review process. The applicant stated that this withdrawal was related to their Company's decision not to market this product.

Cutivate (fluticasone propionate) is currently marketed as Cutivate[®] 0.005% ointment (NDA 19-957, approved Dec. 14th, 1990) and, Cutivate[®] 0.05 % cream (NDA-19-958, approved Dec.18th, 1990). Both the cream and ointment are currently indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in adults. The ointment is labeled to be applied twice daily. The cream is labeled to be applied once or twice daily for atopic dermatitis and twice daily for other corticosteroid-responsive dermatoses. In addition Cutivate cream is approved for treatment of atopic dermatitis in children as young as three months (S-008, NDA 190958, approved June 17, 1999).

The applicant's proposed fluticasone propionate [redacted] is intended to be applied to the affected skin areas once daily for adult and pediatric patients [redacted] of age or older. The applicant also stated that fluticasone propionate [redacted] formulation is not yet commercially available in any country.

1.1 Recommendation (s):

The clinical pharmacology and biopharmaceutics data submitted for topical application of fluticasone [redacted] demonstrated that its systemic exposure was minimal and variable in pediatric patients [redacted] and older. The systemic exposure obtained was within the range of the systemic exposure obtained for currently marketed topical products of fluticasone propionate and therefore may not be a safety concern. No clinically relevant HPA axis suppression was observed in pediatric patients [redacted] years old following extensive application of fluticasone propionate [redacted]. In addition a correlation between the systemic exposure of fluticasone and serum cortisol levels following cosyntropin stimulation testing was not demonstrated. The applicant has met the requirements outlined in 21 CFR 320 and, their application is acceptable from a clinical pharmacology and biopharmaceutics perspective. ✓ OK

1.2 Phase IV Commitments:

None were identified

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The applicant included the reports of three clinical pharmacology studies to characterize the systemic availability of fluticasone propionate [redacted] 0.05 %, in this application. The studies were as follows: 1) FPLA1001: A vasoconstrictor assay study in healthy volunteers 2) FPL10002: A bioequivalence vasoconstrictor assay study in healthy volunteers and 3) FPL10005: A HPA axis suppression study in pediatric patients with eczema. In this submission the applicant used the following terms as synonyms "[redacted]" and, "lotion [redacted]"

Plasma Fluticasone Concentrations:

In study FPL10005, 42 pediatric patients (Aged: 4 months to < 6 years old) with moderate to severe eczema received topical application of fluticasone propionate treatment twice daily for 3-4 weeks. At baseline, the % body surface area treated ranged from 35-92 %. Quantifiable

plasma concentrations of fluticasone were obtained in thirteen of the 21 subjects (2 years and older) at the end of treatment after 3-4 weeks application period. Systemic exposure from topical application of fluticasone emulsion was variable. Plasma fluticasone concentrations ranged from 20.46-819.81 pg/mL. Majority of the patients had concentrations < 115 pg/mL. However, three patients (aged 3-4 years old, % BSA treated of 35 to 65%) had levels exceeding 300 pg/mL. The highest value obtained was 819.81 pg/mL, reported for Subject 6001 (baseline value 446.3 pg/mL). None of these subjects indicated adrenal suppression based on an end of treatment post-stimulation cortisol level of > 31 mcg/dL (i.e. > 18mcg/dL the pre-defined criteria for normal response). In addition, a correlation analysis to determine the relationship between plasma fluticasone and serum cortisol levels indicated that that there was no correlation ($r = 0.14$) between the two variables.

HPA Axis Suppression:

All 42 subjects who completed the study had end of treatment post-stimulation cortisol levels > 18 mcg/dL indicative of a normal adrenal response. However, an evaluation of the responsiveness of individual patients by the Sponsor's consulting endocrinologist identified 2 patients with pre-and post-stimulation serum cortisol levels that were lower at end of treatment compared with baseline. A summary table of the cortisol levels for these two patients is inserted below:

Table: Cortisol Values for Subjects Noted by the Endocrinologist

Subject		Pre-stimulation (mcg/dL)	Post-stimulation (mcg/dL)
5008	Baseline	23.1	32.9
	End-Treatment	8.9	21.1
6029	Baseline	9.1	29.1
	End-Treatment	4.5	22.5

Although the cortisol levels were within the normal response definition (i.e. > 18 mcg/dL), the Sponsor's consultant endocrinologist concluded that these two patients may have developed mild, partial suppression of the HPA axis as a consequence of fluticasone propionate emulsion exposure. However, he also concluded that these findings were not clinically relevant. This data was consulted to the Division of Metabolic and Endocrine Drug Products (DMEDP, HFD-510). The medical reviewer (Dr. R. Perlstein) of the consult agreed with the Sponsor's endocrinology consultant that these findings are not clinically significant.

Vasoconstrictor Assay:

Using the corticosteroid-induced skin blanching in the vasoconstrictor assay (FPL1001), it can be concluded that fluticasone is absorbed through the skin of healthy volunteers. Fluticasone propionate emulsion ranked close in potency to the currently marketed Cutivate® cream, a mid-potency topical corticosteroid.

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2. QBR

2.1 General Attributes

Physicochemical Properties of the Drug Substances

Fluticasone propionate is a synthetic fluorinated 17-carbothioate corticosteroid. Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

Therapeutic Indications and Mechanism of Drug Action

Cutivate  is indicated for the relief of the inflammatory and pruritic manifestations of atopic dermatitis. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. Fluticasone propionate is believed to have a high specificity for glucocorticoid receptor which could be related to its anti-inflammatory activity. Glucocorticoids have been shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages and neutrophils) and mediators (histamine, eicosinoids, leukotrienes, and cytokines) involved in inflammation.

Proposed Dosage and Route of Administration

Cutivate  is to be applied as a thin film to the affected skin areas once daily.

2.2 General Clinical Pharmacology

Q. What were the design features of the clinical pharmacology and clinical studies used to support dosing or labeling?

The applicant obtained the important safety and efficacy information from the following studies:

Clinical Pharmacology Studies (Phase I studies):

FPLA1001: Vasoconstrictor assay in healthy adult subjects (N = 33, Aged 20-66 years old).
Treatments administered as a single dose were: 0.05 % fluticasone propionate lotion 1, lotion 1

vehicle, 0.05 % fluticasone propionate lotion 2, lotion 2 vehicle, mometasone (Elocon[®] lotion), fluticasone propionate 0.05 % (Cutivate[®]) cream, clobetasol (Temovate[®]) cream, hydrocortisone (Hytone[®]) lotion.

FPL10002: Bioequivalence Vasoconstrictor assay in healthy adult subjects (N = 15, Aged 22-50). Treatments administered as a single dose were 0.05 % fluticasone propionate lotion 1, 0.05 % fluticasone propionate lotion 2 and fluticasone propionate 0.05 % (Cutivate[®]) cream. This study was terminated because an acceptable dose-response model could not be determined for the fluticasone 0.05 % reference cream.

FPL10005: Systemic safety HPA axis suppression study in pediatric patients (n = 44) aged 4 months to < 6 years with moderate to severe eczema. Fluticasone propionate 0.05 % lotion # 2 was applied twice daily over ≥ 35 % body surface area for 3-4 weeks

FPL 10003: Allergenicity/Irritation double-blind randomized site vehicle-controlled study in healthy volunteers (N = 231, Aged 18-75 years old). Fluticasone propionate 0.05 % lotion # 2 and vehicle were applied to individual patch areas on each subject's back for a total of 25 days. The medical reviewer is reviewing this study.

Phase III pivotal Clinical trials:

Two replicate studies with identical designs were conducted. They were FPL30003 (N = 220, (Ages 3 months to 77 years) and FPL 30004 (N = 219, Ages 3 months to 87 years): Both were conducted as multi-center, double-blind, randomized, vehicle-controlled, parallel group comparison of patients with a diagnosis of moderate to severe atopic dermatitis. Study drug was applied in the evening on a daily basis. Subjects were evaluated at Day 1 (baseline), Day 15, and Day 29. Subjects were scheduled for 4 weeks of treatment; however any subject whose lesions were 100 % clear at Day 15 had end-treatment evaluations performed at that time.

Q. What is the basis of selecting the pharmacodynamic response endpoints?

The pharmacodynamic endpoints selected were the vasoconstrictor bioassay and the cortisol serum concentrations following cosyntropin stimulation tests. The vasoconstrictor bioassay is based on the property of corticosteroids to produce blanching or constriction of the blood vessels in the skin. Following topical application of the drug product for a period of ~16 hours, the degree of skin-blanching was visually assessed using a 4 point scale at 2, 3, 6, 8 and 24 hrs after removal of the drug. This property presumably relates to the amount of drug entering the skin. The vasoconstrictor assay is used as a surrogate test to assess the potency of topical formulations of corticosteroids.

The adrenocorticotropin (ACTH)/cosyntropin stimulation test was the primary safety parameter used to assess the integrity of the HPA axis. A rise in serum cortisol concentrations following adrenal stimulation with synthetic ACTH (cosyntropin, 1-24 ACTH, or Cortrosyn[™]) can be used to assess HPA axis suppression. For this study the post-stimulation (30 minutes post-injection) serum cortisol levels > 18 mcg/dL was chosen to represent the ability of the adrenal glands to produce adequate levels of cortisol and was selected as the pharmacological endpoint. The basis

of this endpoint is that exogenous corticosteroids can suppress the HPA axis, resulting in decreased circulating (ACTH) levels, atrophy of glucocorticoid-secreting cells in the adrenal cortex, and secondary adrenal insufficiency. Measurement of serum cortisol levels in response to intravenous injection of cosyntropin as the primary assessment for adrenal responsiveness is considered representative of systemic corticosteroid effect.

Q. What is the systemic exposure of fluticasone propionate _____ ?

Plasma Fluticasone Concentrations:

In pediatric patients (2 years of age and older) with moderate to severe eczema, systemic exposure from topical application of fluticasone emulsion was variable. Quantifiable plasma concentrations of fluticasone were obtained in thirteen of the 21 subjects at the end of treatment after 3-4 weeks application period (Study FPL10005) as shown in the table below:

Table 2.2.1 Demographic, Disease and Treatment Characteristics and CST Results for Subjects with Detectable Fluticasone in Plasma at End of Treatment (N = 13 of 21 Tested)

Subject	Age (y-mo)/ Sex	Fluticasone Plasma Level (pg/mL)	% BSA Treated at Baseline	Sum of Severity Scores at Baseline ^a	Total Drug Used (g)	Duration of Treatment (weeks)	End-treatment Post-stimulation Cortisol (µg/dL)
6001	3-6 / M	819.81	35	17 (8)	unk ^b	4	32.3
6020	2-3 / M	25.24	92	19 (9)	277.2	4	27.0
6003	4-2 / F	309.63	60	14 (6)	unk	4	32.7
6004	3-8 / F	115.15	60	12 (6)	156.2	4	33.9
6005	5-11 / F	59.68	51	14 (6)	208.5	4	35.5
6006	4-6 / F	42.82	83	14 (6)	328.4	4	32.6
6007	4-4 / F	36.39	43	14 (6)	207.5	4	40.5
6008	4-10 / F	67.30	70	14 (8)	258.4	3+	23.8
6011	2-2 / F	70.13	60	16 (8)	245.8	4	28.8
6015	4-0 / M	366.67	65	17 (8)	unk	5	31.7
6016	3-10 / M	34.14	85	18 (8)	unk	4	25.1
6017	5-2 / M	20.46	38	10 (6)	177.7	3+	27.3
6027	3-3 / M	57.99	85	14 (7)	190.7	4	31.8

^aTotal of all signs and symptoms (worst 3 signs/symptoms)

^bunk = unknown; all bottles not returned

Three patients (aged 3-4 years old, % BSA treated of 35 to 65%) had levels exceeding 300 pg/mL. The highest value obtained was 819.81 pg/mL, reported for Subject 6001 (baseline value 446.3 pg/mL). None of these subjects indicated adrenal suppression based on an end of treatment post-stimulation cortisol level of > 31 mcg/dL (i.e. > 18mcg/dL the pre-defined criteria for normal response).

Although there were limited number of subjects with plasma fluticasone data, a correlation analysis to determine the relationship between plasma fluticasone and serum cortisol levels indicated that there was no correlation (r = 0.14) between the two variables. This is

consistent with the observation that adrenal suppression was not observed in the patients with high plasma fluticasone concentrations.

Apart from adrenal suppression, these observed values of plasma fluticasone obtained may not represent a safety concern because they are within the range of the peak plasma concentrations (0.1 to 1.0 ng/mL) obtained following administration of recommended doses of inhaled fluticasone propionate drug products.

Cosyntropin Stimulation Tests-Serum Cortisol Levels:

The results of the cosyntropin stimulation tests demonstrated that the potential for suppression of the HPA axis when relatively large amounts of cutivate emulsion 0.05 % are applied to large body surface areas (BSAs) for 21-28 days in children (aged 4 months to < 6 years) with moderate to severe eczema is minimal.

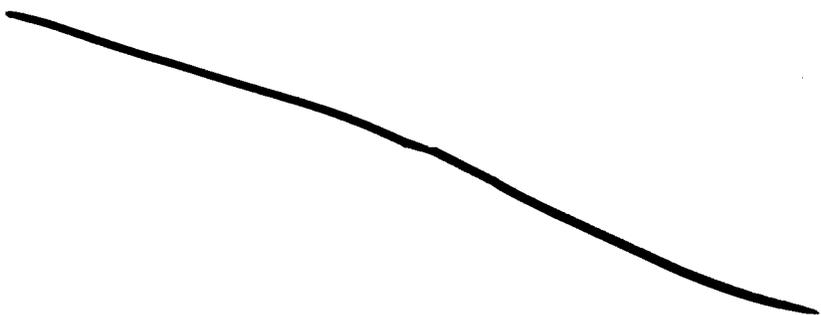
This was shown in study FPL 10005, where all 42 subjects who completed the study had end of treatment post-stimulation cortisol levels > 18 mcg/dL indicative of a normal adrenal response. Fluticasone emulsion was applied twice daily for 3 to 4 weeks over an extensive % BSA (ranging from 35 to 94 %) at baseline. The mean amount of drug used during the study was ~ 195-200 grams. A summary table of the serum cortisol levels obtained for all the subjects tested is inserted below:

Mean (± Standard Deviation) Serum Cortisol Levels of Subjects

Baseline	4 months to < 3 years * (N=26)	3 years to < 6 years (N=18)	All Subjects (N = 44)
Pre-stimulation (µg/dL)	13.36 (± 5.96) [6.0-30.4]	13.03(± 6.45) [5.6-29.6]	13.22 (± 6.09) [5.6-30.4]
Post-stimulation (µg/dL)	37.23 (± 5.75) [29.3-51.8]	32.61 (± 5.44) [19.1 -41.0]	35.3 (± 6.02) [19.1-51.8]
End of Treatment			
Pre-stimulation (µg/dL)	11.98 (± 5.52) [2.9-28.4]	12.86 (± 7.37) [3.8-31.2]	12.35 (± 6.31) [2.9-31.2]
Post-stimulation (µg/dL)	35.21 (± 9.40) [21.1-59.7]	30.83 (± 5.02) [22.5-40.5]	33.33 (± 8.05) [21.1-59.7]

a: Baseline, N= 26 pre-stimulation and 25 post-stimulation; End of Study, N=24 pre-and post-stimulation

The data in the stratified table above shows that all patients had end of treatment post-stimulation serum cortisol levels > 18 mcg/dL indicative of a normal adrenal response. The mean pre-stimulation serum cortisol levels (~13 mcg / dL) and post-stimulation serum cortisol levels (~ 33 mcg / dL), at baseline and end of treatment, between groups, were also comparable.



Following discussions with the dermatology medical reviewer (Dr. M. Albert) and an evaluation of the Sponsor's proposed label, it appears that some of the recommendations above are already reflected in the label. Any modifications to the Sponsor's proposal based on the above recommendations will be incorporated into the label by the clinical division as appropriate.

Vasoconstrictor Assay:

The corticosteroid-induced skin blanching in the vasoconstrictor assay (FPLA1001), demonstrated that the two formulations of fluticasone emulsion (0.05%) investigated in this study were absorbed percutaneously through the skin of healthy volunteers. Both fluticasone propionate emulsions were ranked close in potency to each other and to the currently marketed cutivate cream, a mid-potency topical corticosteroid. The two emulsions differed in the composition of the vehicle used (emulsion # 1 was diluted cutivate cream and emulsion # 2 used Temovate cream vehicle). The results of the vasoconstrictor study was used to guide the selection of fluticasone emulsion #2, which was the formulation used in the pivotal clinical trials and was also that which was selected for marketing.

Q. What are the characteristics of the exposure-response relationships for efficacy?

The sponsor did not characterize the exposure-response curve for efficacy for fluticasone propionate in this submission.

Q. What are the characteristics of the exposure-response relationships for safety?

The applicant used plasma fluticasone values to assess the degree of exposure and to determine whether or not there was any relationship between end-treatment post-stimulation cortisol values and exposure, particularly in any subject with adrenal suppression. A correlation coefficient value of 0.14 indicated no relationship between fluticasone concentrations and the serum cortisol levels obtained post stimulation.

Q. Were the active moieties in plasma appropriately identified and measured?

Yes, see Section 2.6

2.3. Intrinsic Factors

Q. How does the systemic exposure change with various intrinsic factors?

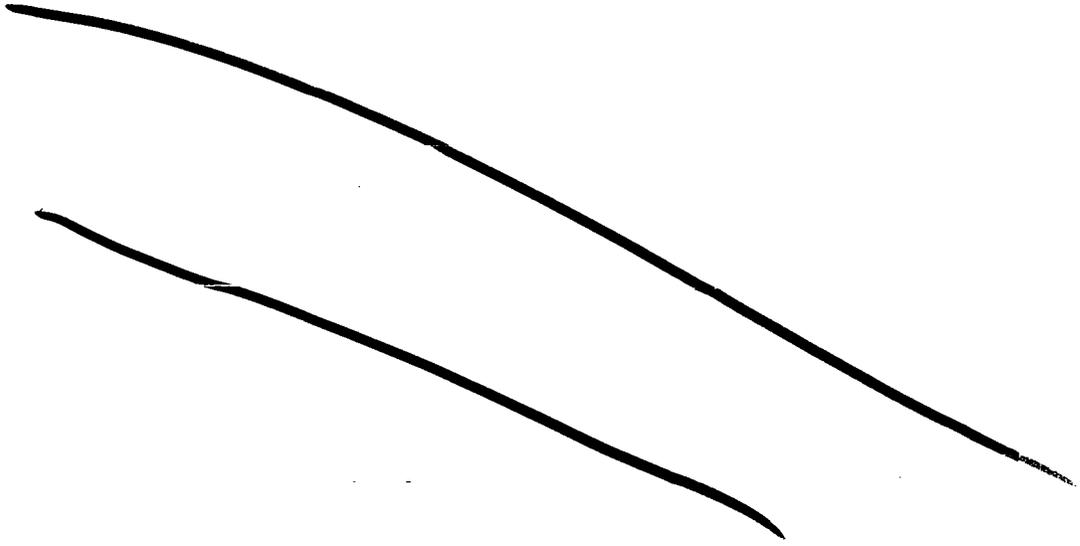
2.6. Analytical

Q. Were the analytical methods used for the determination of fluticasone propionate in biological fluids validated?

The analytical method used for the determination of fluticasone in plasma was validated and found acceptable (see table below).

Assay Method	LC/MS/MS
Accuracy <i>Inter-Day</i>	
Precision (CV %) <i>Inter-Day</i>	
<i>Intra-Day</i>	
Standard Curve range	
Recovery	
Sensitivity	

3. Labeling Recommendation:



4. Appendix

4.1. Consult Review: Medical Consult: See medical review for copy of the consult.
Pharmacometrics Consult: None required since there was no PK/PD or POPPK data submitted.



7 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

Withheld Track Number: Clin Pharm/Bio-1

4.3. Individual Study Reviews

Protocol Number: FPL10005

Name of Investigational Product: Cutivate	Name of Active Ingredient: Fluticasone propionate 0.05%	Indication: Treatment of pruritic manifestations of atopic dermatitis
Title of Study: An Open Label Adrenal Suppression Study of Fluticasone Propionate Lotion 0.05% used Twice Daily in Pediatric Subjects Aged 3 months to 5 years		
Principal Investigators: Multicenter with six pediatric dermatologists		
Study Centers: Multicenter with six sites in the US		
Objectives: To evaluate the safety of a 3- or 4- week course of twice-daily fluticasone propionate lotion 0.05% in pediatric subjects aged 3 months to 5 years with moderate to severe eczema or psoriasis, by monitoring the following: <ul style="list-style-type: none"> • Effect on the HPA axis as determined by response to Cosyntropin stimulation tests • Hematology and blood chemistries • Signs of skin atrophy and pigmentation changes at application site • Other adverse events • Plasma values of fluticasone (only in children ≥ 2 years of age) 		
Design of Study: Phase I, multicenter, open-label trial of a 3- or 4-week course of twice daily treatment with fluticasone propionate lotion 0.05 %. Up to 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 event assessments. Thus the maximum total time a subject could be in the study, after screening, was 6 weeks.		
Study Period: 11 November 1998-14 April 1999		
Study Population Demographics: Forty-four pediatric patients with moderate to severe eczema were enrolled and started on study treatment, and 42 (95%) completed the study. (See table at the end below for detailed demographics).		
Investigational Product: Fluticasone propionate lotion 0.05 % (60 mL bottle), Batch no. 8B310 from Glaxo Wellcome Inc.-Canada.		
Dosing Regimen, Mode of Administration and Treatment Duration: Fluticasone propionate lotion 0.05 %, applied twice daily; topically to minimum 35 % BSA for 3 or 4 weeks (21 or 28 days), depending on when the lesions cleared in an individual subject. Subjects were not to have a bath or shower within 2 hours after application of study medication. The dose of cosyntropin was 0.125 mg for subjects in the younger age group and 0.25mg for subjects in the older age group. Thirty eight of the subjects were fasted prior to the initial blood sampling and cosyntropin injection at all visits. All subjects except one consumed food and/or drink prior to the post-stimulation sampling.		

Criteria for evaluation: The primary systemic safety parameter was response to the Cosyntropin (ACTH 1-24 Cortrosyn®) stimulation test (CST) at baseline and end-treatment. Blood samples were collected prior to intravenous injection of Cortrosyn® and 30 minutes post-injection. Serum cortisol was assayed by [redacted] (LOD = [redacted]). For this study the post-stimulation cortisol level > 18 mcg/dL represents the ability of the adrenal glands to produce adequate levels of cortisol, and was selected as the pharmacological endpoint (i.e. Normal CST results). Additionally, an expert review was obtained. Plasma fluticasone values were measured in children aged 2 years of age and older at baseline and the final visit.

Plasma fluticasone values were used to assess the degree of systemic absorption 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.

Analytical Methods: Fluticasone Propionate was quantified by automated solid phase extraction (SPE) and the extracts were analyzed by HPLC with tandem mass spectrometric detection (LC-MS-MS), using a [redacted] selected reaction monitoring (SRM) using the protonated molecules. MH⁺, as the precursor ions. Linearity: [redacted] (rL), LOQ = [redacted]; Precision (% CV): Intra-assay [redacted] and Inter-assay [redacted] Recovery [redacted] (see table at end for detailed assay validation data)

Statistical methods: The study was designed to include 20-32 evaluable subjects (10-16 per age group) per agreement with FDA that adequate safety data could be obtained from this number of children. A Spearman correlation coefficient was calculated to determine the relationship between plasma fluticasone concentrations and post-stimulation cortisol levels.

Results:

Baseline mean pre-stimulation = 13.22 (6.09) mcg/dL; Mean post-stimulation = 35.30 (6.02) mcg/dL

End of treatment mean pre-stimulation = 12.35 (6.3) mcg/dL; mean post-stimulation = 33.33 (8.05) mcg/dL

All subjects had end-treatment post-stimulation cortisol levels > 18 mcg/dL. Two subjects had decreased end of treatment cortisol levels although these were still within the normal response definition. Thirteen of the 21 subjects tested had measurable levels of plasma fluticasone at end of treatment. No relationship was observed between fluticasone level and CST results (r = 0.14).

Reviewer's Comments:

Baseline

All 44 subjects enrolled had baseline pre-stimulation cortisol results and 43 subjects had baseline post-stimulation cortisol results and the 43 subjects had levels > 18 mcg/dL.

End of Treatment

All 42 subjects who completed the study had end of treatment post-stimulation cortisol values > 18 mcg/dL indicative of a normal adrenal response. Two subjects had decreased end of treatment cortisol levels although still > than 18 mcg/dL, these two subjects showed a decrease in end of treatment plasma cortisol levels, both pre- and post- CST stimulation. According to applicant's endocrinologist these patients had mild partial suppression. However, if one goes by the endocrinologist's evaluation more than two subjects would be mildly suppressed as shown in the table below:

Subject		Pre-stimulation (mcg/dL)	Post-stimulation (mcg/dL)
Applicant's Evaluations			
5008	Baseline	23.1	32.9
	End-Treatment	8.9	21.1
6029	Baseline	9.1	29.1
	End-Treatment	4.5	22.5
Other Possible Subjects			
5020	Baseline	22.8	34.9
	End-Treatment	14.5	27.0
5032	Baseline	16.3	40.2
	End-Treatment	8.30	26.5
6017	Baseline	14.2	33.8
	End-Treatment	8.4	27.3
5009	Baseline	30.4	51.8
	End-Treatment	2.9	27.7

Consultant Medical Reviewer in HFD-510/Division of Metabolic and Endocrine Drug Products agreed with applicant's conclusions that these findings for the two patients were not clinically relevant.

Sources of variability:

Some patients had low pre-stimulation serum cortisol levels < 5 mcg/dL. Applicant stated that this could be due to late

sampling time (samples were collected between 8:51 AM and 12:35 PM)
 Time between cosyntropin injection and post-stimulation sample collection was somewhat variable (26-55 minutes at baseline and 26-45 minutes at end of treatment). This could have contributed to variability in data. Serum cortisol levels usually peak about 45 to 60 minutes after injection of Cortrosyn, so data was collected within peak times.

Fluticasone Concentrations

Summary of fluticasone plasma concentrations are inserted in the table below. Two of the subjects [Subject 6001=446.28 pg/mL and Subject 6029 = 48.23 pg/mL] had measurable fluticasone values at baseline. Applicant stated that neither of these subjects' parents had reported recent use of fluticasone. Sample contamination was considered the most likely explanation, occurring during the blood drawing procedure.

Safety: Six (14 %) subjects had six drug-related AE's, all local dermatologic reactions. Dry skin occurred in three subjects (7%), stinging in two subjects (5%) and excoriation (abrasion) in one subject (2 %).

Table 30
 Summary of Plasma Fluticasone Assay Results (in pg/mL)

		Age 3 mos. - 2 yrs. (N=26)	Age 3- 5 yrs. (N=18)	Total (N=44)
Baseline:	Number tested	3	18	21
	n*	0	2	2
	Mean		247.255	247.255
	SD		281.464	281.464
	Median		247.255	247.255
	Minimum		48.23	48.23
	Maximum		446.28	446.28
	Number of Results BCL	3	15	18
	Number of Results NR	0	1	1
End of Treatment:	Number tested	3	18	21
	n*	2	11	13
	Mean	47.685	175.458	155.801
	SD	31.742	243.561	227.643
	Median	47.685	59.680	59.680
	Minimum	25.24	20.46	20.46
	Maximum	70.13	819.81	819.81
	Number of Results BCL	1	5	6
	Number of Results NR	0	2	2

Demographics:

	4 months to <3 years	3 years to < 6 years	Total
Number of Patients	26	18	44
Age (range)	4 months to 2 years 7 months	3 years 3 months to 5 years 11 months	4 months to 5 years 11 months
Sex	14 F and 12 M	8 F and 10 M	22 F and 22 M

Race	14 Caucasian 7 Black 2 Asian 3 American Hispanic	4 Caucasian 8 Black 2 Asian 4 American-Hispanic	18 Caucasian 15 Black 4 Asian 7 American,- Hispanic
Height (cm)	25-92	93-120	25-120
Weight (kg)	6.6 to 13.6	14.5 to 31.3	6.6 to 31.3
Body Surface Area (m²)	0.21 to 0.59	0.63 to 1.01	0.21 to 1.01
BSA/Weight (m²/kg)	0.03 to 0.05	0.03 to 0.05	0.03 to 0.05
% BSA Covered by Disease	40-94	35-90	35-94
% BSA treated	38-92 [Mean = 65.5 ± 14.6]	35-85 [Mean = 63.2 ± 16.5]	35-92 [Mean = 64.6 ± 15.3]
Duration of treatment (days)	19-33	22-36	19-36
13-19 days	1	0	1
20-26 days	4	5	9
> 26 days	20	13	33
Mean Amount of Drug Used	196 ± 118.9g	199 ± 109.5g	197 ± 114.5g [range 34-462g]
Status of Disease			
Worsening	22	15	37
Stable	4	3	7

Analytical Method Validation:

Assay Method	LC/MS/MS after solid phase extraction (SPE)
Analytical Site	
Compound	Fluticasone
Accuracy	
Inter-Day	
Precision (CV %)	
Inter-Day	
Intra-Day	
Standard curve range	
Recovery	
Sensitivity (LOQ)	(However, LOQ was higher (up to) for a few subjects due to insufficient sample volume. Dilution of these samples to achieve the required sample volume raised the LOQ proportionally to the amount of dilution necessary.)
QC Samples	
Selectivity	
Stability	
Reviewer's Comments	Method acceptable

Protocol Number FPLA1001:

Name of Investigational Product: Cutivate I	Name of Active Ingredient: Fluticasone propionate 0.05%	Indication: Treatment of inflammatory and pruritic manifestations of atopic dermatitis
Title of Study: A randomized, double-blind, single-center evaluation of the vasoconstrictive properties of two fluticasone propionate lotion formulations (0.05 %) in normal healthy volunteers		
Principal Investigator (s): _____		
Study Centers: _____		
Objectives: The primary objective of this study was to evaluate the relative potency (skin-blanching) of two fluticasone lotion formulations (0.05 %), using the vasoconstrictor assay, in comparison with their corresponding vehicles, fluticasone (Cutivate [®]) cream 0.05 %, clobetasol (Temovate [®]) cream 0.05 %, mometasone (Elocon [®]) lotion, 0.1 %, and hydrocortisone (Hytone [®]) lotion 2.5 %. [Applicant stated that the lotion having a potency ranking that is at least equal to the fluticasone cream will be selected for further clinical development]		
Design of Study: Randomized, Double-Blind, Single-Center, Phase I study.		
Study Period: 02 Feb 1998 – 13 Feb 1998		
Study Population Demographics: Thirty three healthy volunteers		
Age range: 20-66 years; Race: Caucasian; Gender: 6 Male, 27 Female; Weight: 55-159 Kg; Height: 157 – 191 cm		
Investigational Products:		
Test Products: Fluticasone propionate lotion # 1 (0.05 %), [Lot # 415]; Lotion #1 vehicle, [Lot # 409]; Fluticasone propionate lotion # 2 (0.05 %) and lotion # 2 vehicle, [Lot # 413] Lotion # 1 was prepared by sequential dilution of the marketed fluticasone cream (0.05 %) and Lotion # 2 was prepared by adding fluticasone (0.05 %) to the diluted Temovate cream vehicle.		
Reference Products: Fluticasone (Cutivate [®]) cream 0.05 % [lot # 7ZP0976]; clobetasol (Temovate [®]) cream 0.05 %, [Lot # 7ZP0508]; mometasone (Elocon [®]) lotion, 0.1 %, [Lot #7-FJF-100] and hydrocortisone (Hytone [®]) lotion 2.5 %, [Lot # MN02222].		
Dosing Regimen, Mode of Administration and Treatment Duration: Treatment period was for 3 days. On Day 1, a single application of approximately 0.1 mL each of eight study drugs was made to one of eight 2 cm ² sites on the volar surface of each volunteer's forearm (4 sites/arm) by a third party in accordance with a computer-generated randomization code. After application, the sites were secured in a non-occlusive manner and the subjects were scheduled to return the following day after being instructed to keep the sites dry. On Day 2, after ~ 16 hours of contact between the study drugs and the skin, the protective guards were removed by the clinic staff and the test sites gently washed with water and patted dry. Patch applications were worn for a duration of 16-18 hours.		
Pharmacodynamic(s): Visual assessment of skin blanching that results from the localized vasoconstrictor response to the topical application of corticosteroids was used as an indication of the potency of the study drugs. The degree of skin-blanching at all eight study drug application sites was assessed at 2, 3, 6, 8 and 24 hours after the removal of the study drug using a 4-point scale (0=no blanching, 1 = mild blanching, 2 = moderate blanching, 3= marked blanching). The same evaluator was responsible for performing all of the skin-blanching evaluations for the study.		
Analytical Methods: Does the visual reading method have to be validated?		
Statistical methods: Three primary efficacy endpoints were analyzed: 1) mean 2-hour blanching scores, 2) mean skin-blanching scores averaged for all five assessment timepoints, and 3) the AUC, or area-under-the-skin blanching score-curve. For each of the efficacy endpoints, the following six statistical comparisons were performed using the Kruskal-Wallis test: Lotion 1 versus its vehicle, Lotion 2 versus its vehicle, Lotion 1 versus Lotion 2, Lotion 1 versus Cutivate, Lotion 2 versus Cutivate cream. This analyses was also repeated on a subset of subjects (N = 17) derived by excluding those subjects who showed no response to either Lotion 1, Lotion 2, or Cutivate cream. This sub-population was deemed appropriate to better characterize the relative ranking of the three fluticasone products to each other.		
Results: The potency rankings obtained across all three efficacy endpoints were as follows: Temovate and Elocon were the most potent, Lotion 1, 2 and Cutivate cream were the next most potent (or mid-potency) and Vehicles 1 and 2 and Hytone were the least potent. Therefore both lotions investigated in this trial were ranked close in potency to each other and to the currently marketed Cutivate cream, a mid-potency topical corticosteroid. The applicant decided that either lotion was a viable candidate for further development as a mid-potency topical corticosteroid.		
Safety: Two AE's were reported (pain from root canal and friction/pressure blisters at guard site). Neither was judged to be related to the study drug. Applicant concluded that no safety concerns emerged from this trial that would preclude further development of either of the two fluticasone lotions.		

Tables of the summary of primary analysis of blanching score results for all subjects are inserted below:

Characteristic	Lotion 1	Vehicle1	Lotion 2	Vehicle2	Cutivate	Temovate	Elocon L	Hytone L
2 Hours After Removal of Product								
N	33	33	33	33	33	33	33	33
Mean	1.5	0.6	1.2	0.6	1.1	2.2	2.1	0.8
SD	1.2	0.8	1.1	0.8	1.1	1.1	1.0	0.8
Min	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
25%	0.0	0.0	0.0	0.0	0.0	2.0	2.0	0.0
Median	2.0	0.0	1.0	0.0	1.0	3.0	2.0	0.0
75%	2.0	1.0	2.0	1.0	2.0	3.0	3.0	1.0
Max	3.0	3.0	3.0	2.0	3.0	3.0	3.0	2.0

Characteristic	Lotion 1	Vehicle1	Lotion 2	Vehicle2	Cutivate	Temovate	Elocon L	Hytone L
Area Under the Curve								
N	33	33	33	33	33	33	33	33
Mean	18.2	7.3	14.5	7.4	13.6	30.5	29.5	7.0
SD	16.8	10.7	17.2	9.9	14.4	15.0	15.8	9.8
Min	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
25%	0.0	0.0	0.0	0.0	0.0	21.0	17.0	0.0
Median	12.0	2.0	3.5	2.5	9.0	33.5	30.0	2.0
75%	34.5	11.0	30.0	16.0	24.0	43.0	42.0	9.5
Max	45.0	40.0	50.5	30.0	45.0	53.0	61.0	36.5

Characteristic	Lotion 1	Vehicle1	Lotion 2	Vehicle2	Cutivate	Temovate	Elocon L	Hytone L
Mean Blanching Score								
N	33	33	33	33	33	33	33	33
Mean	1.0	0.4	0.8	0.4	0.8	1.7	1.6	0.4
SD	0.9	0.6	0.9	0.5	0.7	0.7	0.7	0.5
Min	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
25%	0.0	0.0	0.0	0.0	0.0	1.4	1.0	0.0
Median	0.8	0.2	0.4	0.2	0.8	1.8	1.6	0.2
75%	1.8	0.8	1.6	0.8	1.2	2.2	2.2	0.8
Max	2.4	1.8	2.4	1.6	2.4	2.8	2.8	1.8

Treatments (N = 33)	2-Hr Mean Blanching Score (mean (SD))	AUC (mean (SD))	Mean Blanching (5 Timepoints) (mean (SD))
Temovate 0.05 %	2.2 (1.1)	30.5 (15.0)	1.7 (0.7)
Elocon 0.1 %	2.1 (1.0)	29.5 (15.8)	1.6 (0.7)
Lotion 1 0.05 %	1.5 (1.2)	18.2 (16.8)	1.0 (0.9)
Lotion 2 0.05 %	1.2 (1.1)	14.5 (17.2)	0.8 (0.9)
Cutivate Cream 0.05 %	1.1 (1.1)	13.6 (14.4)	0.8 (0.7)
Vehicle 1	0.6 (0.8)	7.3 (10.7)	0.4 (0.6)
Vehicle 2	0.6 (0.8)	7.4 (9.9)	0.4 (0.5)
Hytone 2.5 %	0.6 (0.8)	7.0 (9.8)	0.4 (0.5)

Lotion 1-fluticasone 0.05 % in diluted Cutivate cream vehicle

Lotion 2-fluticasone 0.05 % in diluted Temovate cream vehicle

As shown in the table above, the ranking of the potency of the eight study drugs using the 2-hour mean blanching score (as per FDA guidance), the derived mean AUC and the mean blanching scores showed three groupings as follows:

1. Temovate and Elocon
2. Lotion 1, lotion 2 and Cutivate cream
3. Vehicle 1, Vehicle 2 and Hytone

The analysis for the subset did not affect the ranking of the potency because the same potency rankings were observed for the subset analysis except that the mean scores were generally higher.

Statistical analysis

The overall Kruskal-Wallis test for differences between all eight treatments was statistically significant ($p < 0.001$) for the three endpoints. Comparisons of the two lotions against each other or against Cutivate were not statistically significant ($p > 0.05$) for all endpoints. Comparison of lotion # 1 against its vehicle was statistically significant ($p < 0.009$) for all endpoints. Comparison of lotion 2 against its vehicle was only statistically significant ($p = 0.003$) for the mean 2-hr blanching score. It was not statistically significant ($p > 0.05$) for the other 2 endpoints. (For subset analysis this was the only difference in that this comparison was statistically significant for all three endpoints).

Protocol FPL10002: A two part (Pilot and Pivotal), Randomized, Controlled, Single Center Bioequivalence Comparison of Fluticasone Propionate Lotion (0.05%) to Fluticasone Propionate Cream (0.05%) in normal healthy volunteers.

The bioequivalence study (FPL 10002) designed to compare the lotion to the cream was not completed. The applicant only submitted the data obtained from the pilot dose-duration study. The applicant stated that no acceptable dose-response model was obtainable from either the chromometer or visual readings in the Pilot dose-duration phase of the study. Large variability was observed in the chromometer results which were likely due to fluctuations of skin tone in the absence of significant vasoconstrictor response (poor signal to noise ratio). The applicant stated that the extremely low visual response and small AUC are consistent with the low vasoconstrictor effect elicited by the durations of exposure used in the study (15-300 minutes as per guidance). The Sponsor decided not to proceed with the definitive phase (BE) of the study. Therefore, no valid conclusions could be drawn regarding the comparison of the cream and the lotion with regards to bioequivalence. Since the data from the pilot study would not add any information to this application on its own it was not reviewed.

4.4. OCPB Filing form

Office of Clinical Pharmacology and Biopharmaceutics			
New Drug Application Filing and Review Form			
General Information about the Submission			
	Information		Information
NDA Number	21-152	Brand Name	Cutivate
OCPB Division (I, II, III)	DPEIII	Generic Name	Fluticasone Propionate 0.05% w/w
Medical Division	HFD-540	Drug Class	Corticosteroid
OCPB Reviewer	Abi Adebowale	Indication(s)	Corticosteroid-Responsive Dermatoses in adult and pediatric patients ≥ 3 months of age
OCPB Team Leader	Dennis Bashaw	Dosage Form	Emulsion
		Dosing Regimen	Apply a thin film of _____ to the affected skin areas once daily. Rub in gently.
Date of Submission, Filing Date	March 11 th , 2004 May 10 th , 2004	Route of Administration	Topical
Estimated Due Date of OCPB Review	November 11 th , 2004	Sponsor	GlaxoSmithKline Consumer Healthcare, L.P.
PDUFA Due Date	January 11 th , 2005	Priority Classification	3S
Division Due Date	December 11 th , 2004	IND Number	54,894

Clin. Pharm. and Biopharm. Information

Background and Introduction: Fluticasone propionate is a synthetic fluorinated 17- carbothioate corticosteroid with high specificity for the glucocorticoid receptor. Topical corticosteroids are believed to be effective primarily through their antipruritic, anti-inflammatory and vasoconstriction properties. Cutivate (fluticasone propionate) is currently available in the market as Cutivate® 0.005% ointment (NDA 19-957, approved Dec. 14th, 1990) and, Cutivate® 0.05 % cream (NDA-19-958, approved Dec.18th, 1990). Both the cream and ointment are currently indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. The ointment is labeled to be applied twice daily. The cream is labeled to be applied once or twice daily for atopic dermatitis and twice daily for other corticosteroid-responsive dermatoses. The label for the cream indicates that it can be used with caution in pediatric patients 3 months of age or older. The applicant stated that fluticasone propionate _____ formulation is not yet commercially available in any country. One of the potential benefits of the _____ formulation stated by the applicant was that the once daily regimen is more convenient than a twice-daily regimen, requires less drug and may improve user compliance. Fluticasone cream and ointment are rated to be mid-potency corticosteroids based on their activity in the vasoconstrictor assay. The applicant included two adequate and well-controlled pivotal Phase 3 studies and three studies characterizing the PK and BA of fluticasone propionate _____ 0.05 % in this application.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Numbers if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	1		For Protocol # FPL10005 HPA axis suppression study. Plasma fluticasone concentrations measured only in children > 2 years old.
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD (HEALTHY OR PATIENTS):				

Phase 1 or 2:	X	2		FPLA 1001, vasoconstrictor assay to evaluate relative potency and FPL10005, HPA axis suppression study in pediatric subjects > 3months to 5 years with moderate to severe eczema or psoriasis.
Phase 3:				
PK/PD (HEALTHY OR PATIENTS):				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X			FPL10002, In vivo BE using PD (skin blanching) response.
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Other (in vitro percutaneous absorption study)				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		3		
Fileability and QBR comments				
	"X" if yes X	Comments		
Application fileable?	X	Reasons if the application is not fileable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm?	NA	Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	<p>What is the maximal systemic exposure or bioavailability of fluticasone following application as an  to healthy volunteers or patients? How were the dose and dosing regimen selected?</p> <p>What is the safety of fluticasone propionate 0.05% as an  in patients with corticosteroid-responsive dermatoses based on the HPA axis suppression evaluation?</p> <p>For the vasoconstriction study FPLA1001, only the 2-hr assessment was kept as a separate end point, although protocol specified 2, 3, 6, 8 and 24 hours would be considered endpoints. Do we need the Applicant to analyze the other endpoints?</p> <p>Do we need a PM consult? NO</p> <p>Following discussions with Dennis, the answer is NO. For an NDA the 2-hr assessment is the standard and since the Applicant was able to bracket the relative potency of the drug product using this time point this is Okay for the objectives of the study.</p> <p>Do we need a BSI consult on the bioequivalence study especially since the applicant terminated the second phase of the study?</p> <p>As per discussions with Dennis, the answer is NO.</p>			

Other comments or information not included above	Notified DSI Bioequivalence on 04/29/04
Primary reviewer Signature and Date	Abi Adebawale 11/16/04
Secondary reviewer Signature and Date	

CC: NDA 21-152, HFD-850 (P.Lee), HFD-540 (M.Wright), HFD-880 (R. Baweja, A. Selen)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Abi Adebawale
11/19/04 11:38:30 AM
BIOPHARMACEUTICS

Raman Baweja
11/19/04 04:00:29 PM
BIOPHARMACEUTICS