CLINICAL PHARMACOLOGY REVIEW

NDA	21152 (S-004)	**Submission Letter Date(s)**	July 18, 2014
Product Name		Cutivate (fluticasone propionate) lotion, 0.05%	
Primary Reviewer		Chinmay Shukla, Ph.D.	
Team Leader		Doanh Tran, Ph.D.	
OCP Division		Division of Clinical Pharmacology 3	
OND Division		Division of Dermatology and Dental Products	
Sponsor		Fougera Pharmaceuticals Inc.	
Submission Type		Complete response to a CR letter and Physician Labeling Rule (PLR) Conversion	
Approved Indication		Relief of the inflammatory and pruritic manifestations of atopic dermatitis in patients 1 year of age or older	

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1. Executive Summary:

Cutivate (fluticasone propionate) lotion, 0.05% was approved on 03/31/2005 for the relief of the inflammatory and pruritic manifestations of atopic dermatitis in patients 1 year of age or older. This NDA was approved with a post marketing requirement (PMR) to conduct the deferred pediatric studies including evaluating safety and systemic exposure of the product for the treatment of atopic dermatitis in pediatric subjects ages 3 months to 1 year.

The original supplement (submitted on 04/22/2010) provided the final study report for a PREA post-marketing requirement. The applicant requested to expand the indication to include patients 3 months to 11 months of age.

With regard to assessment of systemic exposure, Clinical Pharmacology considered this requirement fulfilled as per Clinical Pharmacology review by Dr. Abimbola Adebowale (see review dated 09/28/2010 in DARRTS). The medical officer Dr. Amy Woitach also recommended an approval action to modify the indicated age range from 1 year and older to 3 months and older and had considered the PMR fulfilled (see review dated 10/26/2010 in DARRTS). However, Dr. Woitach has indicated in her review that the approval recommendation is contingent upon resolution of outstanding issues which included the fact that Cutivate Lotion was manufactured at a non-FDA approved facility.

Hence, the original supplement NDA application received a complete response on 07/18/2012 (see communication in DARRTS) and the action letter stated that the deficiency precluding approval was that the applicant did not have an approved manufacturing site. The applicant subsequently submitted Supplement S-006 for approval of (b) (4) as the manufacturing site. (b) (4)

Hence, the current submission is a complete response to a FDA CR letter dated 07/18/2012. This resubmission of the supplement also contains a PLR formatted package insert.

Since the data to support indication down to 3 months was found adequate and the PMR was considered fulfilled from a scientific standpoint, the focus of this review will be only on the PLR labeling.

1.1 Recommendations:

On review of the Sponsor's proposed changes to the format and the text of the PLR formatted label, the Office of Clinical Pharmacology has made recommended changes as specified in Section 3 of this review.

1.2 Phase IV Commitments:

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings:

None

2. Question Based Review:

Not Applicable

3. Detailed Labeling Recommendations:

This section captures recommended revisions to the Sponsor proposed label submitted on 08/06/2014 where Clinical Pharmacology provided input and recommendations. Deletions are indicated as "~~strikethroughs~~" and additions are indicated as "**bold underlined**". It is noted that the Clinical team will revise section 5.1 to be consistent with current labeling practice for topical corticosteroids and therefore will not be fully addressed in this review.

5 WARNINGS AND PRECAUTIONS

5.1 Hypothalamic-pituitary-adrenal (HPA) Axis Suppression

The effects of CUTIVATE Lotion on HPA axis function in pediatric patients were investigated in two **trials** (b) (4) Among a total of (b) (4) **89** evaluable subjects from the two **trials** (b) (4) who were treated with CUTIVATE Lotion twice daily for 3 to 4 weeks, a single subject with > 90% body surface area treated showed laboratory evidence of transient suppression immediately post-treatment. The **post cosyntropin stimulation testing serum cortisol** (b) (4) returned to a normal level (22.1μg/dL) within one week of the final treatment visit [*see Use In Specific Populations (8.4)* ***and Clinical Pharmacology (12.2)***].

Reviewer comments: *Edits to the standard language for HPA axis suppression in section 5.1 will be proposed by Clinical.*

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

CUTIVATE Lotion may be used in pediatric patients as young as 3 months of age. The safety and (b) (4) **effectiveness** of CUTIVATE Lotion in pediatric patients below 3 months of age have not been established.

(b) (4)

In an HPA axis suppression trial, none of the 40 evaluable pediatric subjects, 4 months old to < 6 years old, with moderate to severe atopic dermatitis covering ≥ 35% Body Surface Area (BSA) who were treated with an exaggerated dosing regimen (twice daily) of CUTIVATE Lotion experienced adrenal suppression (defined as a 30-minute post-stimulation cortisol level ≤18 micrograms/dL). *[See Warnings and Precautions (5.1) and Clinical Pharmacology (12.2)]*.

In another HPA axis suppression trial, one of 49 (2%) evaluable pediatric subjects, 3 months to 11 months old, with moderate to severe atopic dermatitis covering ≥ 35% Body Surface Area (BSA) who applied an exaggerated dosing regimen (twice daily) of CUTIVATE Lotion experienced reversible adrenal suppression (defined as a 30-minute post-stimulation cortisol level ≤18 micrograms/dL) following 4 weeks of therapy. *[See Warnings and Precautions (5.1) and Clinical Pharmacology (12.2)]*.

(b) (4)

Reviewer comments: *Additional edits in section 8.4 will be proposed by Clinical.*

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Corticosteroids play a role in cellular signaling, immune function, inflammation, and protein regulation; however, the precise mechanism of action of CUTIVATE Lotion in corticosteroid responsive dermatoses is unknown.

12.2 Pharmacodynamics

Vasoconstrictor Assay

Trials performed with CUTIVATE Lotion indicate that it is in the medium range of potency as demonstrated in vasoconstrictor trials in healthy subjects when compared with other topical corticosteroids. However, similar blanching scores do not necessarily imply therapeutic equivalence.

Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression

In an open label HPA axis suppression trial (Trial A), 42 pediatric subjects (ages 4 months to <6 years) with moderate to severe atopic dermatitis covering ≥ 35% Body Surface Area (BSA) were treated with an exaggerated dosing regimen of CUTIVATE Lotion twice daily (rather than the indicated dosing regimen of once daily) for at least 3-4 weeks were assessed for HPA axis suppression. The mean BSA treated was 65%. None of the 40 evaluable subjects were suppressed. The criterion for HPA axis suppression was a serum cortisol level of less than or equal to 18 micrograms per deciliter at 30-minutes after cosyntropin stimulation.

Another open label HPA axis suppression trial (Trial B) enrolled 56 pediatric subjects (ages 3 months to 11 months) with moderate to severe atopic dermatitis covering ≥ 35% BSA. Subjects were treated with an exaggerated dosing regimen of CUTIVATE Lotion twice daily over a period of 3 or 4 weeks. The mean BSA treated was 54%. Out of 56 subjects, 49 were considered evaluable with respect to their adrenal axis function post-treatment. One of 49 subjects showed laboratory evidence of suppression immediately post treatment. The criterion for HPA axis suppression was a serum cortisol level of less than or equal to 18 micrograms per deciliter at 30-minutes after cosyntropin stimulation (b) (4) **This 4-month old subject had a baseline treatment BSA of 94% and was reported to have received 100% of the twice-daily applications of CUTIVATE Lotion over the 27 day treatment period.**

12.3 Pharmacokinetics

Absorption

The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusive dressing enhances penetration. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption.

Plasma fluticasone levels were measured in a subset of subjects 2 years - 5 years and 11 months of age in HPA axis suppression trial (Trial A)described above A total of 13 (62%) of 21 subjects tested had measurable fluticasone at the end of 3 - 4 weeks of treatment. The mean ± SD fluticasone plasma concentration was 0.16 ± 0.23 ng/mL. Three subjects aged 3, 4 and 4 years had fluticasone concentrations over 0.30 ng/mL, with one of these having a concentration of 0.82 ng/mL. No data was obtained for patients < 2 years of age.

Distribution

(b) (4) The percentage of fluticasone propionate bound to human plasma proteins averaged 91%. Fluticasone propionate is

weakly and reversibly bound to erythrocytes. Fluticasone propionate is not significantly bound to human transcortin.

Metabolism

No metabolites of fluticasone propionate were detected in an in vitro study of radiolabeled fluticasone propionate incubated in a human skin homogenate. (b) (4)

(b) (4)

luticasone propionate is metabolized in the liver by cytochrome P450 3A4-mediated hydrolysis of the 5-fluoromethyl carbothiolate grouping. This transformation occurs in 1 metabolic step to produce the inactive 17β-carboxylic acid metabolite, the only known metabolite detected in man. This metabolite has approximately 2000 times less affinity than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

(b) (4)

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/s/

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11/06/2014

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11/06/2014