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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	March 28, 2018
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Product Name:	Cutivate (fluticasone propionate) Lotion
Pediatric Labeling Approval Date:	January 16, 2015
Application Type/Number:	NDA 021-152
Applicant/Sponsor:	Fougera Pharmaceuticals, Inc.
OSE RCM #:	2017-2182

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports for Cutivate in pediatric patients.

Cutivate Lotion (fluticasone propionate 0.05%) is a medium potency corticosteroid approved on March 31, 2005 for the relief of the inflammatory and pruritic manifestations of atopic dermatitis in patients 1 year of age and older.

On January 16, 2015, Cutivate Lotion was approved to extend the use to patients 3 months and older. The approval was granted based on an open-labeled hypothalamic-pituitary-adrenal axis suppression study to evaluate the safety (both local and systemic) in subjects aged 3 months to <1 year. Twenty-five subjects reported 37 adverse events of which, one was determined to be a serious adverse event, but unrelated to the study medication. No deaths occurred in the study. The overall assessment of the risk-benefit analysis determined that there was sufficient data provided regarding the local and systemic safety in pediatric patients ages 3 months to 1 year of age.

The FAERS search identified a single case of pyoderma in a six-month-old female who received Cutivate Lotion. The case did not report sufficient clinical evidence to establish a causal relationship.

There is no evidence from the FAERS data that there are new pediatric safety concerns with Cutivate Lotion at this time.

DPV recommends no regulatory action and will continue to monitor adverse events associated with the use of Cutivate.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports for Cutivate (fluticasone propionate) Lotion in pediatric patients.

Cutivate Lotion (fluticasone propionate 0.05%, NDA 021-152) is a medium potency corticosteroid approved on March 31, 2005 for the relief of the inflammatory and pruritic manifestations of atopic dermatitis in patients 1 year of age and older.

Two other formulations of fluticasone propionate, Cutivate cream and ointment, are also approved for marketing in the United States. Cutivate Ointment 0.005% (NDA 19-957) was approved on December 14, 1990 and is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in adult patients, but is not recommended for use in pediatric patients because of lack of pediatric studies with this formulation.[1] Cutivate Cream 0.05% (NDA 19-958) was approved on December 18, 1990 for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 3 months of age or older.[2] Cutivate Cream's marketing status is listed as discontinued for reasons not due to safety or efficacy. All three topical formulations of Cutivate are available as generics.[3]

Safety concerns associated with topical corticosteroids include both local and systemic adverse reactions. Systemic effects are generally not commonly observed with topical corticosteroids but can include Cushing's syndrome and suppression of the hypothalamic-pituitary-adrenal (HPA) axis, hyperglycemia, osteopathy, adrenocortical suppression, decreased growth rate, edema, hypocalcemia, hypertension, posterior subcapsular cataracts, and glaucoma. Children are at higher risk than adults for HPA axis suppression due to their larger body surface area (BSA) to body mass ratio. Local adverse reactions include atrophy, striae, rosacea, perioral dermatitis, acne, purpura, hypertrichosis, pigmentary alterations, delayed wound healing, exacerbation of skin infections, and contact sensitization reactions.

The approval to extend the indication of Cutivate Lotion to patients 3 months of age was granted based on an open-labeled HPA axis suppression study to evaluate the safety (both local and systemic) in subjects age 3 months to < 1 year. Forty-nine (49) subjects with BSA of ≥ 35% were treated twice daily for three to four weeks. One subject showed laboratory evidence of adrenal suppression, which resolved within one week following discontinuation of the treatment. There were no cutaneous signs of atrophy, telangiectasia, loss of elasticity, purpura, dusky erythema, or striae seen in the study. Twenty-five (25) subjects reported 37 adverse events (AEs) of which, one was determined to be a serious adverse event (SAE), but unrelated to the study medication. One subject was hospitalized for pyrexia (SAE). This subject remained on the study medication during hospitalization and the event was determined to be unrelated to fluticasone lotion.

No deaths occurred in the study.[4] The overall assessment of the risk-benefit analysis determined that there was sufficient data provided regarding local and systemic safety in pediatric patients ages 3 months to 1 year of age. The established efficacy of the product justifies the modest risks, the most serious of which appears to be the risk of reversible HPA axis suppression.[5]

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES FOR CUTIVATE LOTION[6]

----------CONTRAINDICATIONS----------

- None

----------WARNINGS AND PRECAUTIONS----------

- Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression and Other Adverse Endocrine Effects: CUTIVATE® Lotion, can produce reversible HPA axis suppression with the potential for glucocorticoid insufficiency. Risk factors that predispose to HPA axis suppression include the use of high-potency topical corticosteroids, large treatment surface areas, prolonged use, use under occlusion, concomitant use of more than one corticosteroid-containing product, altered skin barrier, and liver failure. Pediatric patients may be at greater risk of HPA axis suppression due to their higher skin surface area to body mass ratios. Cushing's syndrome, hyperglycemia, and unmasking of latent diabetes mellitus can also result from systemic absorption of topical corticosteroids.

- Local Adverse Reactions: CUTIVATE® Lotion may cause skin atrophy and allergic contact dermatitis diagnosed by observing a failure to heal rather than clinical exacerbation. CUTIVATE® Lotion contains the excipient imidurea which releases formaldehyde as a breakdown product. Formaldehyde may cause allergic sensitization or irritation upon contact with the skin. Avoid in individuals with hypersensitivity to formaldehyde as it may prevent healing or worsen dermatitis.

- Concomitant Skin Infections: If skin infections are present or develop at the treatment site, an appropriate antimicrobial agent should be used. If a favorable response does not occur promptly, discontinue use of CUTIVATE® Lotion until the infection has been adequately controlled.

----------ADVERSE REACTIONS----------

- Controlled Clinical Trials: Local cutaneous reactions, primarily burning/stinging. Contact dermatitis, exacerbation of atopic dermatitis, folliculitis of legs, pruritus, pustules on arm, rash, skin infection, common cold, ear infection, nasal sinus infection, rhinitis, upper respiratory tract infection, normal tooth eruption, diarrhea, vomiting, cough, influenza, headache, fever, and seasonal allergy.

- Pediatric Open Label Trials: Dry skin, stinging at application site, and excoriation. (2%). There were three cases of bacterial skin infections, two cases of herpes simplex, and one case of elevations of the hepatic enzymes AST and ALT.

- Postmarketing experience: Erythema, edema/swelling, bleeding, Cushing syndrome, immunosuppression, Pneumocystis jiroveci pneumonia, leukopenia, thrombocytopenia, hyperglycemia, glycosuria, generalized body edema, blurred vision, acute urticarial reaction (edema, urticaria, pruritus, and throat swelling), acneiform eruptions, hypopigmentation, perioral dermatitis, skin atrophy, striae, hypertrichosis and miliaria.

----------USE IN SPECIAL POPULATIONS----------

- Pediatric Use: Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of systemic effects when treated with topical drugs. They are, therefore, also at greater risk of HPA axis suppression and adrenal insufficiency upon the use of topical corticosteroids. Systemic effects such as Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients, especially those with prolonged exposure to large doses of high-potency topical corticosteroids, or concomitant use of more than one corticosteroid product. Local adverse reactions including skin atrophy have also been reported with use of topical corticosteroids in pediatric patients.

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV-I searched the FAERS database with the strategy described in Table 2.1.1. See Appendix A for a description of the FAERS database.

Table 2.1.1 FAERS Search Strategy

Date of Search	January 16, 2018
Time Period of Search	December 14, 1990* - October 31, 2017
Search Type	FBIS Quick Query
Product Name	Cutivate
Product Active Ingredient	Fluticasone propionate; Fluticasone
Administration Route	Cutaneous; Topical
Search Parameters	All ages, all outcomes, worldwide

**U.S. Approval date of first Cutivate product (NDA 19-957)*

2.2 RESULTS

2.2.1 Total number of FAERS reports by Age

Using the strategy described in Table 2.1.1, the FAERS search retrieved 90 reports for fluticasone propionate products with a listed route of administration as topical or cutaneous. The majority of these reports (n=59) were of adult patients (age ≥ 17 years). There were 15 reports of pediatric patients (age 0-17 years). For those cases that did not report the patient's age (indicated as Null in Table 2.2.1), the case narratives were reviewed to determine if the patient was a pediatric patient by identifying terms such as 'child', 'boy', or 'girl'; however, none of the 16 cases contained information to indicate that the patient was pediatric.

Table 2.2.1 Total adult and pediatric FAERS reports* from December 14, 1990 through October 31, 2017 with Cutivate (n=90)

	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	59 (33)	38 (12)	7 (0)
Pediatrics (0 - < 17 years)	15 (9)	10 (4)	0 (0)
Null	16 (15)	2 (1)	0 (0)

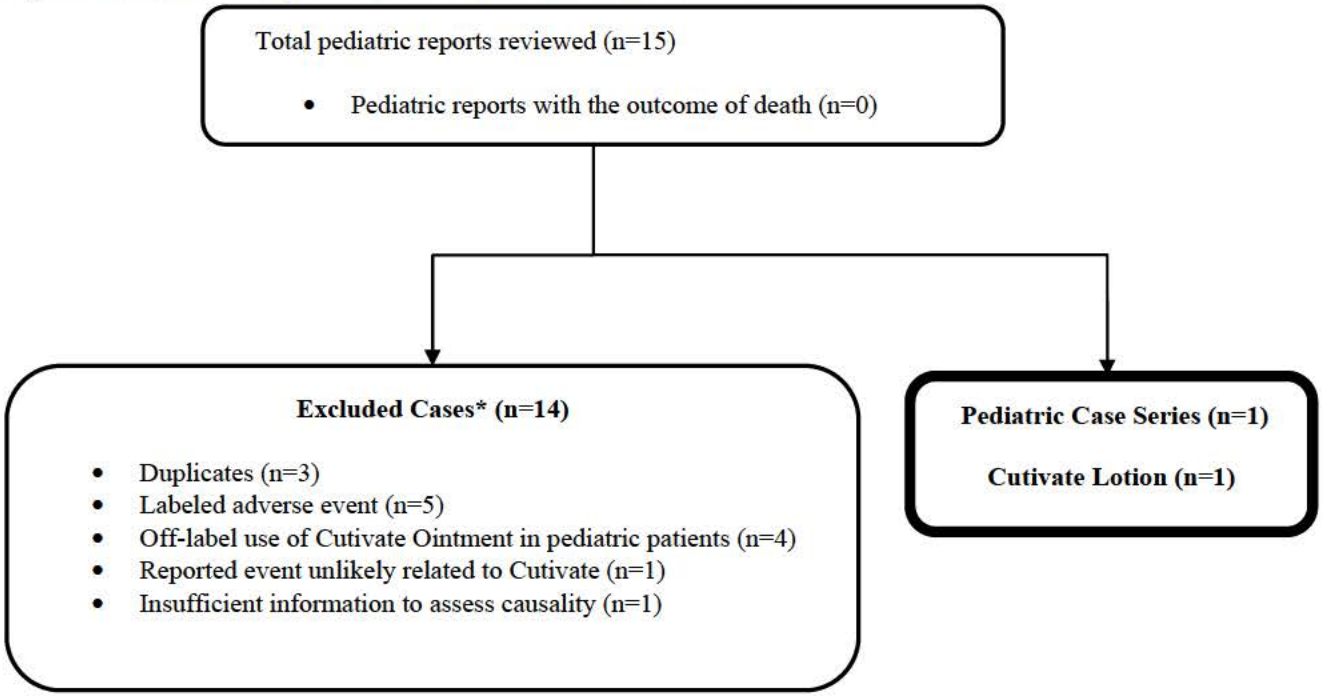
* Includes duplicates and have not been assessed for causality

† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

2.2.2 Selection of Pediatric Cases in FAERS

Using the strategy described in Table 2.1.1, the FAERS search retrieved 15 pediatric reports. Fourteen reports were excluded for the reasons described in Figure 1 below.

Figure 1. Selection of Pediatric Cases with Cutivate Lotion



* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above

A broad search of the FAERS database was conducted to review as many pediatric reports for fluticasone propionate topical products as possible and retrieved cases submitted to the FDA from December 14, 1990 through October 31, 2017. This approach yielded 15 pediatric reports. Three reports were excluded because they were duplicates. The excluded non-duplicate reports included cases for Cutivate Cream (n=6), Cutivate Ointment (n=4), and one case where the specific formulation was not specified.

Comprehensive review of the eleven excluded pediatric FAERS cases did not identify any adverse events not already included in the current product labeling for Cutivate Lotion or any occurring with increased severity. The eleven excluded non-duplicate reports included five cases coded for non-serious AE, and six cases for SAE, including two patients that were hospitalized; a 5-month-old that developed idiopathic intracranial hypertension and a 3-year-old that developed pneumocystis jiroveci pneumonia that the reporter determined was not likely related to Cutivate. The four remaining SAE reported were reports of a worsening rash, lymphocytic leukemia, unlikely related to Cutivate use based on the reported information, an unspecified skin cancer which lacked sufficient detail to assess causality, and a report that described intentional drug misuse of three different topical corticosteroid ointments used concurrently. Four cases reporting three AE and one SAE, for Cutivate Ointment were excluded because this product is not recommended for use in pediatric patients[2] and the product was used in patients ranging from 3 to 16 years of age.

Furthermore, none of the excluded reports specified Cutivate Lotion.

2.2.3 Pediatric Cases in FAERS

We identified one pediatric report for Cutivate Lotion with an unlabeled adverse event, pyoderma, using the search strategy defined in Section 2.1.1.

2.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=0)

There were no pediatric deaths reported with the use of Cutivate Lotion.

2.4 SUMMARY OF PEDIATRIC ADVERSE EVENT CASE (N=1)

FAERS Case# 12207367 v.2 (Ecuador, Initial FDA Received Date 2016): A physician reported that a 6-month-old female patient experienced pyoderma at an unreported time after starting treatment with Cutivate Lotion (dose not reported) for atopic dermatitis.
On an unreported date, Cutivate Lotion was discontinued and pyoderma resolved after an unspecified duration. No additional information was provided.
(Manufacturer Control# EC-GLAXOSMITHKLINE-EC2016GSK039749)

Reviewer's Comments: This foreign report from Ecuador describes the occurrence of pyoderma after starting treatment with Cutivate Lotion. The report does not provide histological or laboratory findings, or describe clinical features to support a diagnosis of pyoderma, time-to-onset, concomitant medications, or medical history. The information provided in this single report is insufficient to determine that pyoderma is a new safety signal for Cutivate Lotion.

3 DISCUSSION

There were no new safety signals identified, including no increased severity or frequency of any labeled adverse events, and there were no deaths reported with Cutivate Lotion use in pediatric patients.

A broad search of the FAERS database was conducted to review as many pediatric reports for fluticasone propionate topical products as possible. This approach yielded 15 pediatric reports. However, fourteen were excluded because they reported a labeled event, an event unlikely to be caused by application of a topical corticosteroid, reported off-label use, or were duplicates.

A single case of pyoderma in a 6-month-old female patient who received Cutivate Lotion did not report sufficient clinical evidence to establish a causal relationship. Furthermore, our review of the excluded pediatric FAERS cases did not identify any adverse events not already included in the current product labeling or any occurring with increased severity.

4 CONCLUSION

The Division of Pharmacovigilance analyzed the pediatric postmarketing adverse event reports for Cutivate products received in FAERS from December 14, 1990 through October 31, 2017. We did not identify any new pediatric safety concerns for Cutivate Lotion at this time.

5 RECOMMENDATIONS

DPV recommends no regulatory action at this time, and will continue to monitor adverse events associated with the use of Cutivate Lotion.

6 REFERENCES

1. Cutivate Ointment Product Label. Fougera Pharmaceuticals Inc. Revised February 2015.
2. Cutivate Cream Product Label. Fougera Pharmaceuticals Inc. Revised September 2010.
3. Drugs@FDA: Approved Drug Products. Search fluticasone propionate. Accessed February 4, 2018.
4. Woitach AS. Medical Officer Consult Review, Division of Metabolism and Endocrinology Products. DARRTS Reference ID: 2854427. 25Oct10.
5. Lindstrom J. Summary Review for Regulatory Action. DARRTS Reference ID: 3688714. 16Jan15.
6. Cutivate Lotion Product Label. Fougera Pharmaceuticals Inc. Revised January 2015.

7 APPENDICES

7.1 APPENDIX A FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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/s/

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