Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	December 21, 2017
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Product Name:	Epiduo Forte (adapalene/benzoyl peroxide, 0.3%/2.5%) gel
Pediatric Labeling Approval Date:	July 15, 2015
Application Type/Number:	NDA 207917
Applicant/Sponsor:	Galderma
OSE RCM #:	2017-2380

TABLE OF CONTENTS

EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA), the Division of Pharmacovigilance (DPV) evaluated postmarketing adverse event reports for Epiduo Forte (adapalene/benzoyl peroxide 0.3%/2.5%) gel in pediatric patients.

The FDA approved Epiduo Forte (NDA 207917) on July 15, 2015, and it is indicated for the topical treatment of acne vulgaris. The efficacy of Epiduo Forte was established in one pivotal trial in subjects 12 years and older with moderate to severe acne vulgaris.

DPV did not identify new safety signals or evidence of increased severity or unexpected frequency of labeled adverse events in the pediatric population in the FDA Adverse Event Reporting System (FAERS) cases. Because of the limited number of pediatric cases with a serious outcome identified in FAERS for Epiduo Forte since approval, we evaluated all pediatric cases, including those coded with non-serious outcomes. No deaths or hospitalizations were reported. All cases were reported from the U.S., and none were reported in patients less than 12 years of age.

Two of the 26 cases reported serious outcomes, and described local skin reactions consistent with the labeling for Epiduo Forte. In the non-serious cases, dermatologic events were the most frequently reported, followed by lack of effect. The majority of events in the non-serious cases were consistent with the labeling for Epiduo Forte. None of the cases reporting events not specifically labeled, including eye irritation or emotional distress, provided information suggesting the need for regulatory action.

DPV did not identify evidence of new pediatric safety concerns with Epiduo Forte at this time, and will continue pharmacovigilance monitoring.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Epiduo Forte gel (NDA 207917) is a combination of adapalene 0.3% and benzoyl peroxide (BPO) 2.5%. Adapalene is a synthetic retinoid, and BPO is a highly lipophilic oxidizing agent. The FDA approved Epiduo Forte gel on July 15, 2015 for the topical treatment of acne vulgaris, triggering this pediatric postmarketing safety review in accordance with the Pediatric Research Equity Act (PREA). Galderma markets Epiduo Forte in pumps containing 15 to 70 grams.

Adapalene was first approved in 1996, and it is marketed in 0.1% and 0.3% concentrations, alone and in combination with BPO, for use in the topical treatment of acne vulgaris. See Table 1.1 for FDA-approved new drug applications (NDAs) for products containing adapalene. On July 8, 2016, the FDA approved the conversion of the marketing status of the 0.1% gel, marketed as Differin, to over-the-counter. BPO is marketed in a variety of formulations and concentrations, alone and in combination.

Table 1.1. FDA approved NDAs for Products Containing Adapalene

Initial FDA Approval Date	NDA Number	Adapalene Concentration and Formulation	Trade Name	Current Marketing Status*
May 31, 1996	020338	0.1% solution	Differin	Discontinued
May 31, 1996	020380	0.1% gel	Differin	Over-the-counter
May 26, 2000	020748	0.1% cream	Differin	Prescription
June 19, 2007	021753	0.3% gel	Differin	Prescription
December 8, 2008	022320	0.1%/BPO 2.5% gel	Epiduo	Prescription
March 17, 2010	022502	0.1% lotion	Differin	Prescription
July 15, 2015	207917	0.3%/BPO 2.5% gel	Epiduo Forte	Prescription

BPO = benzoyl peroxide
* As of December 21, 2017

The vehicle gel used in Epiduo Forte is the same as that used in Epiduo. One pivotal trial for Epiduo Forte was conducted in subjects 12 years and older with moderate to severe acne vulgaris. Subjects applied Epiduo Forte, Epiduo, or vehicle gel once daily for 12 weeks. Safety assessment of the NDA was based on the clinical trial and the marketing experience for other products containing adapalene and benzoyl peroxide. There were no deaths or serious adverse events that were considered related to the product in the Epiduo Forte development program, and no new safety concerns were identified. Adverse events were primarily limited to local irritation adverse reactions.[1]

At approval, the FDA waived the pediatric study requirement for ages less than 12 years old, because the product did not represent a meaningful therapeutic benefit over existing therapies and was not likely to be used in a substantial number of pediatric patients in this age group.[2]

There have been no labeling updates for Epiduo Forte since approval. Although a postmarketing pediatric review for Epiduo Forte has not been previously presented to the Pediatric Advisory Committee (PAC), pediatric postmarketing reviews for Epiduo (adapalene/benzoyl peroxide,

0.1%/2.5%) gel were presented to the PAC in December 2010 and September 2015.[3,4] The 2010 review included recommendations for labeling updates, and subsequently Galderma submitted a labeling supplement to add irritant and allergic contact dermatitis to the WARNINGS AND PRECAUTIONS section of the Epiduo labeling, and to add a *Postmarketing Experience* subsection to ADVERSE REACTIONS, including events such as facial edema, pruritus, and rash. The recommendation in the 2015 review was to continue pharmacovigilance monitoring.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

Highlights of labeled safety issues include the following:[5]

> CONTRAINDICATIONS
> None.
>
> WARNINGS AND PRECAUTIONS
> *Ultraviolet Light and Environmental Exposure*
> Exposure to sunlight, including sunlamps, should be minimized during the use of EPIDUO FORTE gel. Patients with high levels of sun exposure and those with inherent sensitivity to sun should exercise particular caution. Use of sunscreen products and protective apparel (e.g., hat) are recommended when exposure cannot be avoided. Weather extremes, such as wind or cold, may be irritating to patients under treatment with EPIDUO FORTE gel.
>
> *Local Cutaneous Reactions*
> Erythema, scaling, dryness, and stinging/burning may be experienced with use of EPIDUO FORTE gel. These are most likely to occur during the first four weeks of treatment, are mostly mild to moderate in intensity, and usually lessen with continued use of the medication. Irritant and allergic contact dermatitis may occur. Depending upon the severity of these adverse reactions, patients should be instructed to use a moisturizer, reduce the frequency of the application of EPIDUO FORTE gel, or discontinue use. The product should not be applied to cuts, abrasions, eczematous or sunburned skin. As with other retinoids, use of "waxing" as a depilatory method should be avoided on skin treated with EPIDUO FORTE gel.
>
> Avoid concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have strong skin-drying effect and products with high concentrations of alcohol, astringents, spices, or limes).
>
> USE IN SPECIFIC POPULATIONS
> *Pediatric Use*
> Safety and effectiveness of EPIDUO FORTE gel in pediatric patients under the age of 12 have not been established.

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

The Division of Pharmacovigilance (DPV) 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	November 15, 2017
Time Period of Search	July 15, 2015* - November 15, 2017
Search Type	FBIS Quick Query
Product Terms	Product Name: Epiduo Forte NDA #: 207917
Search Parameters	All ages, all outcomes, worldwide

* FDA approval date
FBIS = FAERS Business Intelligence Solutions

2.2 RESULTS

2.2.1 Total number of FAERS reports by Age

Table 2.2.1. Total Adult and Pediatric FAERS Reports* July 15, 2015 to November 15, 2017 with Epiduo Forte (adapalene/benzoyl peroxide 0.3%/2.5%) Gel

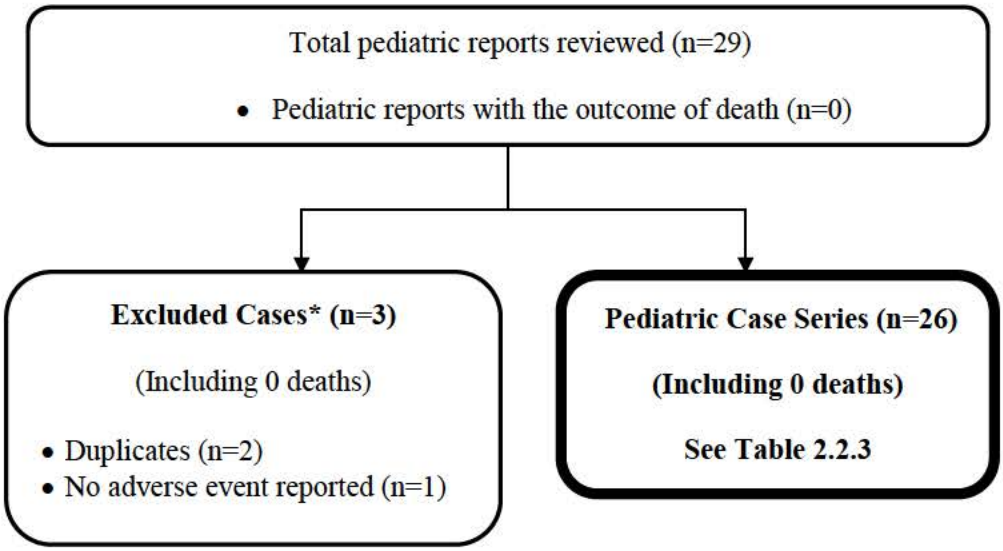
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥17 years)	31 (31)	2 (2)	0 (0)
Pediatrics (0 - <17 years)	29 (29)‡	**2 (2)**	0 (0)

* May include duplicates and transplacental exposures, 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.
‡ See Figure 2.2.2.

2.2.2 Selection of Pediatric Cases in FAERS

We identified 29 pediatric reports, including two reports coded with a serious outcome (see Table 2.2.1). See **Figure 2.2.2** for the specific selection of cases to be summarized in **Sections 2.3 and 2.4.**

Figure 2.2.2. Selection of Pediatric Cases with Epiduo Forte (adapalene/benzoyl peroxide 0.3%/2.5%) Gel



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

2.2.3 Characteristics of Pediatric Case Series

Appendix B lists the FAERS case numbers, FAERS version numbers, and Manufacturer Control Numbers for the pediatric case series. Table 2.2.3 provides the case characteristics for the case series.

Table 2.2.3. Characteristics of Pediatric Case Series with Epiduo Forte (N=26)

Age	12- < 17 years	26
Sex	Female	13
	Male	11
	Unknown	2
Country	United States	26
Reported Reason for Use	Acne	19
	Unknown	7
Serious Outcome*	Other serious	2

* 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.

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

There were no cases reporting deaths in the pediatric case series.

2.4 SUMMARY OF NON-FATAL PEDIATRIC ADVERSE EVENT CASES (N=26)

2.4.1 Cases reporting serious outcomes (n=2)

There were two cases for which the case or its duplicate was coded with a serious outcome. Neither reported hospitalization. The cases are summarized below:

FAERS Case #12360724 Version 1, 2016, Non-serious
(Duplicate to FAERS Case #12262711 Version 1, 2016, Other serious)
A 14-year-old female experienced erythema and irritation, described as "extreme," after using Epiduo Forte (dosing interval not specified) and going out in the sun approximately three months after starting Epiduo Forte. Medical history included acne and "extremely sensitive skin," and she had no known allergies. Concomitant medication included clindamycin (route not specified). She discontinued Epiduo Forte for at least two weeks. After restarting Epiduo Forte, using it once weekly to once every other week, irritation and erythema recurred without sun exposure. In addition, her acne symptoms persisted. Concomitant medication at this time included topical dapsone (Aczone; concentration not specified) daily. Aquaphor helped alleviate the irritation. At the time of reporting, the patient continued to use Epiduo Forte.

FAERS Case #12388641 Version 1, 2016, Other serious
A 15-year-old male experienced "all related side effects that are listed in the insert" and small blisters after using Epiduo Forte for two nights. The patient reported no relevant medical history, used no concomitant medications, and had no allergies. He treated the symptoms with an unspecified medication, and discontinued Epiduo Forte. Symptoms were ongoing at the time of reporting.

Reviewer's comment: Based on the information provided in these cases, the events appear to be consistent with those labeled for Epiduo Forte, including the risk of sun exposure and local skin reactions. Concomitant medication use may have contributed in the first case.

2.4.2 Cases reporting non-serious outcomes (n=24)

The remaining 24 cases reported one or more of the following: dermatologic events (20), lack of effect or loss of effect over time (7), ophthalmic events (2), and emotional distress (1).

2.4.2.1 Dermatologic Events

Twenty cases coded with non-serious outcomes reported dermatologic events. Local dryness, burning, and redness were the most frequently reported. Other events reported in more than one case included skin irritation, peeling, pain, itching, rash, swelling, and skin discoloration. Worsening of acne was reported in one case; this case is described in Section 2.4.2.4.

In three cases, the events were reported as possibly related to allergic reactions. One reported that after an unknown duration of using Epiduo Forte, the patient experienced swelling around the eyes, facial redness, and flaking skin. No medical history or concomitant medications were provided. The patient discontinued Epiduo Forte, and the events were reported as ongoing. The second reported that the patient experienced tiny, white, itchy bumps on the neck, jaw, and eyebrows after the first use of Epiduo Forte. The patient had no known allergies, and used no concomitant medications. Symptoms improved with discontinuation of Epiduo Forte. The third case reported hives, redness, and itching in an unspecified area an unspecified time after starting Epiduo Forte. The patient previously used an unspecified retinoid, but medical history and concomitant medications were not provided. The patient's physician recommended

diphenhydramine, but no follow-up was provided. There were no cases reporting angioedema, anaphylaxis, or other events suggestive of severe hypersensitivity reactions.

Reviewer's comment: The cases describe events consistent with the labeling for Epiduo Forte. Worsening of acne, urticaria, and hypersensitivity are not specifically labeled, but allergic contact dermatitis is labeled in the WARNINGS AND PRECAUTIONS section. The cases do not suggest the need for regulatory action.

2.4.2.2 Lack of Effect or Loss of Effect (n=7)

Six cases coded with non-serious outcomes reported lack of effect, and one reported that Epiduo Forte was effective initially, but acne recurred with continued use.

Five of the seven cases did not provide sufficient information to determine how long after starting Epiduo Forte it was determined to be ineffective. One case reported use for three months without resolution of acne, and Epiduo Forte was discontinued. Another case reported skin peeling and acne two days after starting Epiduo Forte, and changed the dosing interval from once daily to once every other day. There was no improvement in the peeling or acne, and Epiduo Forte was discontinued after 11 days. Symptoms were ongoing at the time of reporting.

Reviewer's comment: In the pivotal trial for Epiduo Forte, clinical efficacy was evaluated at 12 weeks. Approximately 35% of subjects reported a two-grade improvement and a rating of "clear" or "almost clear" on the Investigator's Global Assessment at Week 12, compared to 11% of vehicle-treated subjects.[5] *The persistence of acne symptoms in some cases is consistent with the findings of the pivotal trial, and insufficient information was provided in some cases to determine the duration of Epiduo Forte use.*

2.4.2.3 Ophthalmic Events (n=2)

Two cases coded with non-serious outcomes reported ophthalmic events.

A 14-year-old male experienced accidental eye exposure to Epiduo Forte. His medical history included acne and pollen allergy. Concomitant medication included ketotifen (Zaditor) ophthalmic solution. After the exposure to Epiduo Forte, he rinsed the eye for an unspecified time, but the next day his eye was irritated. He used the ketotifen drops, and no additional follow-up was provided.

A 15-year-old female with acne and "very sensitive skin" experienced "a very bad reaction," skin irritation, burning, crying, and eye tearing after each use within one month of starting Epiduo Forte. She did not report accidental eye exposure. Concomitant medications and allergies were not provided. In addition, her acne symptoms persisted. She changed the dosing interval from daily to every other day, and treated the skin symptoms with various cleansers, witch hazel, and an unspecified product. The sensitivity improved, but the acne was ongoing, and she discontinued Epiduo Forte. No follow-up on the crying and eye tearing was provided.

Reviewer's comment: The Epiduo Forte labeling includes instructions to avoid eye exposure in the DOSAGE AND ADMINISTRATION, PATIENT COUNSELING INFORMATION, and

PATIENT PACKAGE INSERT sections. In the second case, it was difficult to determine if crying and tearing were related to a local skin reaction or eye exposure.

2.4.2.4 Emotional Distress (n=1)

A 16-year-old Caucasian female experienced worsening of acne and emotional distress three days after starting to apply Epiduo Forte to a quarter-sized area of the forehead. Her medical history included mild acne and keloids. She alternated between two cleansing products to wash her face for the previous year. Within three days of starting Epiduo Forte, her pimples became enlarged, and one ruptured. Her acne progressed from mild to "horrible." The patient was "upset, felt terrible, embarrassed," and was concerned about the potential for scarring and keloids. She had some sun exposure, but had not been at the beach or pool. The patient's physician recommended an unspecified antibiotic and discontinuing Epiduo Forte. The patient received unknown treatments from an aesthetician for the skin symptoms, and the events were reported as ongoing.

Reviewer's comment: Emotional distress is not labeled for Epiduo Forte, and appears to be related to worsening acne symptoms. The role of Epiduo Forte in the worsening of the patient's acne is difficult to assess, given the limited area of application and duration of use.

3 DISCUSSION

DPV did not identify new safety signals or evidence of increased severity or unexpected frequency of labeled adverse events in the pediatric population in the FAERS cases. Because of the limited number of pediatric cases with a serious outcome identified in FAERS for Epiduo Forte since approval, we evaluated all pediatric cases, including those coded with non-serious outcomes. No deaths or hospitalizations were reported. All cases in the case series were reported from the U.S., and none were reported in patients less than 12 years of age.

Two of the 26 cases reported serious outcomes, and described local skin reactions consistent with the labeling for Epiduo Forte.

In the 24 non-serious cases, dermatologic events were the most frequently reported, followed by lack of effect. The majority of events in the non-serious cases were consistent with the labeling for Epiduo Forte. None of the cases reporting events not specifically labeled, including eye irritation or emotional distress, provided information suggesting the need for regulatory action.

4 CONCLUSION

DPV did not identify evidence of new pediatric safety concerns with Epiduo Forte at this time.

5 RECOMMENDATIONS

DPV will continue pharmacovigilance monitoring for Epiduo Forte.

6 REFERENCES

1 Liedtka JE. NDA 207917 Clinical Review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207917Orig1s000MedR.pdf. Accessed November 15, 2017.

2 Lindstrom J. NDA 207917 Approval Letter. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/207917Orig1s000ltr.pdf. Accessed November 15, 2017.

3 Salaam T. NDA 022320 Pediatric Postmarketing Adverse Event Review: Epiduo (adapalene and benzoyl peroxide gel 0.1%/2.5%). RCM# 2010-1457. August 30, 2010.

4 Weintraub J, Lee J. NDA 022320 Pediatric Postmarketing Adverse Event Review: Epiduo (adapalene and benzoyl peroxide gel 0.1%/2.5%). RCM #2015-333. August 3, 2015.

5 Epiduo Forte Gel Prescribing Information. Galderma Laboratories, L.P. Fort Worth, TX. September 16, 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 actually 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.

7.2 APPENDIX B. FAERS CASE NUMBERS, FAERS VERSION NUMBERS, AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH EPIDUO FORTE (N=26)

FAERS Case Number* [Duplicate]	FAERS Version Number [Duplicate]	Manufacturer Control Number [Duplicate]
11723277	1	US-GALDERMA-US15007041
11990252	1	US-GALDERMA-US15008065
12360700 [11929541]	1 [1]	US-GALDERMA-US16000313 [Not applicable]
12360722	1	US-GALDERMA-US16002185
12360724 [12262711]	1 [1]	US-GALDERMA-US16002269 [Not applicable]
12388641	1	
12651797	1	US-GALDERMA-US16002822
12911619	1	US-GALDERMA-US16006133
12911621	1	US-GALDERMA-US16005140
12911629	1	US-GALDERMA-US16005976
13213830	1	US-GALDERMA-US17000273
13213832	2	US-GALDERMA-US17000368
13536385	1	US-GALDERMA-US17002091
13536386	1	US-GALDERMA-US17000398
13536387	1	US-GALDERMA-US17001180
13536391	1	US-GALDERMA-US17001611
13536404	1	US-GALDERMA-US17000771
13536406	1	US-GALDERMA-US17001489
13536409	1	US-GALDERMA-US17001980
13842845	2	US-GALDERMA-US17004001
13842847	2	US-GALDERMA-US17003946
13842873	1	US-GALDERMA-US17004444
13842886	1	US-GALDERMA-US17004194
13910622	1	
14128132	1	US-GALDERMA-US17007616
14128136	1	US-GALDERMA-US17007149
* FAERS Case #13536393 Version 2, Manufacturer Control Number US-GALDERMA-US17002323 was excluded because no adverse event was reported.		

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/s/

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