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Pediatric Postmarketing Pharmacovigilance Review

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Product Name: Aczone (dapsone) gel, 7.5%

**Pediatric Labeling
Approval Date:** February 24, 2016

Application Type/Number: NDA 207154

Applicant/Sponsor: Allergan

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Aczone (dapsone) gel, 7.5% in pediatric patients up to and including age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Aczone gel in pediatric patients.

The FDA approved Aczone gel, 7.5% on February 24, 2016 for the topical treatment of acne vulgaris in patients 12 years of age and older.

Our FAERS search retrieved two serious pediatric cases from February 24, 2016 to August 31, 2018. One case was reported with the use of Aczone gel, 5% and one case did not specify the Aczone concentration used. We reviewed both FAERS pediatric cases with a serious outcome because the safety labeling is comparable for the 5% and 7.5% concentrations, and therefore both cases could potentially be relevant to the pediatric safety profile of the 7.5% concentration.

Neither case reported death or hospitalization. One case reported a labeled event of a local skin reaction, and one case reported an unlabeled event of depression. No patterns or trends suggested a new safety signal associated with the use of Aczone gel in our pediatric cases.

DPV did not identify any pediatric safety concerns for Aczone gel, 7.5% at this time. DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of Aczone gel, 7.5%.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Aczone (dapson) gel, 7.5% in pediatric patients up to and including age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Aczone gel in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

The FDA approved Aczone (dapson) gel, 7.5% (NDA 207154) on February 24, 2016 for the topical treatment of acne vulgaris in patients 12 years of age and older. This review was prompted by the pediatric labeling at initial approval for this indication. The mechanism of action of dapson, a sulfone, in treating acne vulgaris is not known.¹ The recommended dosing interval for Aczone gel, 7.5% is once daily.

The safety and efficacy of Aczone gel, 7.5% were assessed in two 12-week multicenter, randomized, double-blind, vehicle-controlled trials (Identification Numbers NCT01974323 and NCT01974141) in 4,340 subjects 12 years of age and older.¹ Subjects were required to have a Global Acne Assessment Score (GAAS) of 3 (moderate), 20-50 inflammatory lesions (papules and pustules), and 30-100 non-inflammatory lesions (open comedones and closed comedones on the face) to enroll. Treatment response was defined as the proportion of subjects at Week 12 with at least a two-grade improvement from baseline on the GAAS, and a mean absolute change from baseline in both inflammatory and non-inflammatory lesion counts. Aczone gel, 7.5% was statistically superior to the vehicle (p -values ≤ 0.004) in all three efficacy endpoints. No serious treatment emergent adverse events were considered related to treatment with Aczone gel, 7.5% in these two trials.² Safety was evaluated in 1,066 pediatric subjects 12 to 17 years of age treated with Aczone gel, 7.5% in these trials. The safety profile in pediatric subjects was similar to the safety profile for the vehicle control group and for subjects ≥ 18 years of age.²

Allergan, the sponsor, is required to submit a postmarketing pediatric study in 100 subjects 9 years to 11 years 11 months of age to assess the safety, pharmacokinetics, and treatment effect of Aczone gel, 7.5%. The target date for final report submission is November 2019. FDA waived the pediatric study requirement for ages 0 to 8 years 11 months of age because the necessary studies are impossible or highly impractical.³

The FDA approved Aczone gel, 5% (NDA 021794) on July 7, 2005 for the topical treatment of acne vulgaris. The recommended dosing interval for Aczone gel, 5% is twice daily.⁴ The safety and efficacy of Aczone gel, 5% were assessed in 3000 subjects, including 1169 children ages 12-17 years old who were treated with Aczone gel, 5% (Identification Numbers not available). In addition, the sponsor conducted a separate double-blind, multicenter, two-period crossover study (Identification No. NCT00243542) in 64 subjects 12 years or older with glucose 6-phosphate dehydrogenase (G6PD) deficiency and acne vulgaris to evaluate the risk of hemolysis after two weeks of treatment with Aczone gel, 5%. Blood samples were drawn at baseline, Week 2, and Week 12 of vehicle and Aczone treatment periods. The proportion of subjects who experienced decreases in hemoglobin ≥ 1 g/dL was similar between Aczone gel, 5% and vehicle treatment, and there was no evidence of clinically significant hemolytic anemia.⁴

DPV has not previously completed a pediatric postmarketing pharmacovigilance review for Aczone gel, 7.5% or 5%.

On May 18, 2018, the FDA approved Prior Approval Supplements for Aczone gel, 7.5% and 5% which provided for the addition of rash (including erythematous rash and application site rash) and swelling of face (including lip swelling and eye swelling) to the *Postmarketing Experience* section of the Aczone labeling.

Dapsone gel, 5% is also marketed by Taro Pharmaceuticals under Abbreviated New Drug Application (ANDA) number 209506. The FDA approved this ANDA on October 16, 2017.

Dapsone is marketed for oral use under various ANDAs for the treatment of dermatitis herpetiformis and leprosy.

1.2 RELEVANT LABELED SAFETY INFORMATION

The following safety information is an excerpt from the Aczone gel, 7.5% labeling:¹

5 WARNINGS AND PRECAUTIONS

5.1 Hematological Effects

Methemoglobinemia

Cases of methemoglobinemia, with resultant hospitalization, have been reported postmarketing in association with twice daily dapsone gel, 5%, treatment. Patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methemoglobinemia are more susceptible to drug-induced methemoglobinemia. Avoid use of ACZONE Gel, 7.5% in those patients with congenital or idiopathic methemoglobinemia.

Hemolysis

Oral dapsone treatment has produced dose-related hemolysis and hemolytic anemia. Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more prone to hemolysis with the use of certain drugs.

In clinical trials, there was no evidence of clinically relevant hemolysis or hemolytic anemia in subjects treated with topical dapsone. Some subjects with G6PD deficiency using dapsone gel, 5%, twice daily developed laboratory changes suggestive of hemolysis.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Adverse drug reactions that were reported in at least 0.9% of subjects treated with ACZONE Gel, 7.5% appear in Table 1 below.

Table 1. Adverse Reactions Occurring in a Least 0.9% of Subjects with Acne Vulgaris in 12-week Controlled Clinical Trials		
	ACZONE Gel, 7.5% (N=2161)	Vehicle (N=2175)
Application Site Dryness	24 (1.1%)	21 (1.0%)
Application Site Pruritus	20 (0.9%)	11 (0.5%)

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of topical dapsone: methemoglobinemia, rash (including erythematous rash, application site rash) and swelling of face (including lip swelling, eye swelling).

7 DRUG INTERACTIONS

7.2 Topical Benzoyl Peroxide

Topical application of dapsone gel followed by benzoyl peroxide in patients with acne vulgaris may result in a temporary local yellow or orange discoloration of the skin and facial hair.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Safety and efficacy was evaluated in 1066 subjects aged 12-17 years old treated with ACZONE Gel, 7.5% in the clinical trials. The safety profile for ACZONE Gel, 7.5%, was similar to the vehicle control group. Safety and effectiveness of ACZONE Gel, 7.5%, have not been established in pediatric patients below the age of 12 years.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 2.

Table 2. FAERS Search Strategy*	
Date of Search	September 5, 2018
Time Period of Search	February 24, 2016 [†] - August 31, 2018
Search Type	FDA Business Intelligence Solution Quick Query
Product Terms	Product name: Aczone [‡] NDA #: 207154
MedDRA Search Terms (Version 21.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database. [†] U.S. approval date for Aczone gel, 7.5% [‡] Includes 7.5%, 5%, and concentration not specified Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 3 presents the number of adult and pediatric FAERS reports from February 24, 2016 to August 31, 2018 with Aczone gel, 7.5%, 5%, and concentration not specified.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA from February 24, 2016 to August 31, 2018 with Aczone Gel[†]			
	All reports (U.S.)	Serious[‡] (U.S.)	Death (U.S.)
Adults (≥18 years)	51 (51)	7 (7)	0 (0)
Pediatrics (0 - <18 years)	10 (10)	2[§] (2)	0 (0)
<p>* May include duplicates and transplacental exposures, and have not been assessed for causality [†] Includes 7.5%, 5%, and concentration not specified. [‡] 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 Section 3.1.2.</p>			

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved two serious pediatric cases from February 24, 2016 to August 31, 2018. One case was reported with the use of Aczone gel, 5% and one case did not specify the Aczone concentration used. We reviewed both FAERS pediatric cases with a serious outcome because the safety labeling is comparable for the 5% and 7.5% concentrations, and therefore both cases could potentially be relevant to the pediatric safety profile of the 7.5% concentration. See Appendix B for a line listing of the serious pediatric cases.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event cases.

3.1.4 Summary of All Pediatric Serious Cases (N=2)

We identified two FAERS cases with Aczone gel in the pediatric population reporting a non-fatal serious outcome. Both cases were reported from the United States and are summarized below. One case reported events consistent with the known adverse reactions described in the labeling for the two suspect products used by the patient, and the other case reported depression, an unlabeled adverse event. We did not identify patterns or trends suggestive of new safety signals in our pediatric cases.

FAERS Case # 12891340, Version 1, 2016, United States, Direct, Other serious

A 17-year-old female started Epiduo Forte (adapalene 0.3%/benzoyl peroxide 2.5%) gel twice daily for the treatment of acne and experienced a slight burning sensation. Three days later, she started Aczone gel, 5% once daily, as prescribed by her physician. After one or two applications of Aczone gel, she experienced a severe burning sensation, which worsened with continued use of both products. She experienced pain and inflammation of the face, especially around the eyes and on the chin, and had difficulty eating and talking. She applied Cetaphil after washing her face with water several times, but the Cetaphil also caused burning. She had no other medical history or allergies. Concomitant medication included an oral contraceptive. Both the Epiduo and Aczone were discontinued, and the events were ongoing at the time of reporting. No additional follow-up was provided.

FAERS Case # 12936277, Version 1, 2016, United States, Direct, Other serious

A 16-year-old female experienced three episodes of depression during the month that she used an unspecified concentration of Aczone gel for the treatment of acne. The depression “hits out of

nowhere and leaves her scared and exhausted.” Medical history and concomitant medication use were not provided. The case does not report medical or psychiatric evaluation of the events. Aczone gel was discontinued, and the depression was ongoing at the time of reporting.

4 DISCUSSION

We did not identify patterns or trends suggesting a new safety signal in the two FAERS cases with Aczone gel in the U.S. pediatric population reporting a serious outcome. Both cases were direct reports from consumers who selected the outcome of “Other serious.” Neither case reported death or hospitalization. One case reported a labeled event of a local skin reaction, and one case reported an unlabeled event of depression.

In the case reporting a local skin reaction in a patient using a combination of adapalene and benzoyl peroxide gel (Epiduo Forte) and Aczone gel, 5%, symptoms started after initiation of Epiduo Forte and worsened with the addition of Aczone gel. Both Aczone products are labeled for local skin reactions including application site rash, pruritus, and dryness, and the Aczone gel, 5% labeling includes application site burning. The Aczone labeling also recommends that concomitant benzoyl peroxide use be avoided because of the potential for temporary skin and facial hair discoloration.^{1,4} The Epiduo Forte labeling includes a variety of local skin reactions, including stinging and burning, and describes the potential for possible cumulative irritancy with other concomitant topical acne therapy.⁵ The labeling for local skin reactions for Aczone appears adequate at this time.

The second case reports symptoms of depression, but provides limited information for case assessment, such as medical history, social history, or concomitant medication use. At the time of reporting, symptoms were ongoing an unspecified time after stopping Aczone. Depression is listed in the labeling for oral dapsone as a clinical feature of erythema nodosum leprosum, a complication of leprosy.⁶ Depression is also listed in the oral dapsone labeling along with convulsions and severe cyanosis as a feature of methemoglobinemia, although it is unclear if this refers to central nervous system or respiratory depression. Depressive disorders in adolescents are common, especially in females, and acne has been associated with psychiatric morbidity, including depression.^{7,8} Based on these factors, the limited information provided in the case, and the lack of other pediatric cases reporting similar symptoms, there does not appear to be a safety signal for Aczone gel and depression.

5 CONCLUSION

DPV did not identify any pediatric safety concerns for Aczone gel, 7.5% at this time.

6 RECOMMENDATION

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of Aczone gel, 7.5%.

7 REFERENCES

- 1 Aczone (dapson) Gel, 7.5% Prescribing Information. Allergan. Madison, NJ. May 2018.
- 2 Brown P. Clinical Review NDA 207154: Aczone gel, 7.5%. January 21, 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/207154Orig1s000MedR.pdf
- 3 Marcus K. Approval Letter NDA 207154: Aczone gel, 7.5%. February 24, 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2016/207154Orig1s000ltr.pdf
- 4 Aczone (dapson) Gel, 5% Prescribing Information. Allergan. Madison, NJ. May 2018.
- 5 Epiduo Forte (adapalene 0.3%/benzoyl peroxide 2.5%) Gel Prescribing Information. Galderma Laboratories, L.P. Fort Worth, TX. June 2018.
- 6 Dapsone Tablet Prescribing Information. Jacobus Pharmaceutical Company, Inc. Princeton, NJ. June 2015.
- 7 Bonin L. Pediatric unipolar depression: epidemiology, clinical features, assessment, and diagnosis. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed October 5, 2018.
- 8 Vallerand IA, Lewinson RT, Parsons LM, et al. Risk of depression among patients with acne in the U.K.: a population-based cohort study. *Br J Dermatol*. 2018 Mar;178(3): e194-e195.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

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.

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=2)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	October 26, 2016	12891340	1	Not applicable	Direct	17	Female	USA	Other serious
2	November 12, 2016	12936277	1	Not applicable	Direct	16	Female	USA	Other serious

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. A case may have more than one serious outcome.

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