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

Pediatric Postmarketing Pharmacovigilance Review

Date:	October 24, 2023
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Product Name:	Aczone (dapsone) gel, 7.5%
Pediatric Labeling Approval Date:	September 10, 2019
Application Type/Number:	NDA 207154
Applicant:	Almirall, LLC
TTT Record ID:	2023-5786

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Aczone (dapsone) gel in pediatric patients less than 18 years of age. 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 dapsone in pediatric patients.

Aczone (dapsone) gel, 7.5% is a sulfone that was initially approved in the United States on February 24, 2016. Aczone gel, 7.5% is currently indicated for the topical treatment of acne vulgaris in patients 9 years of age and older. Another dapsone formulation, Aczone gel, 5% was first approved on July 7, 2005, and it is currently indicated for the topical treatment of acne vulgaris in patients aged 12 years and older.

This pediatric postmarketing safety review was prompted by the pediatric labeling on September 10, 2019, that expanded the indication to include patients aged 9 – 12 years old. Safety and effectiveness have not been established in patients younger than 9 years old. On November 20, 2018, the Office of Surveillance and Epidemiology (OSE) completed a review of postmarketing adverse event reports with a serious outcome for Aczone in pediatric patients. OSE's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with Aczone.

DPV reviewed all serious FAERS reports with dapsone in pediatric patients less than 18 years of age from September 1, 2018 – July 24, 2023, and eight reports were identified; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with dapsone in pediatric patients less than 18 years of age.

DPV did not identify any new pediatric safety concerns for dapsone at this time and will continue routine pharmacovigilance monitoring for dapsone.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Aczone (dapsone) gel in pediatric patients less than 18 years of age. 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 dapsone in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Aczone (dapsone) gel, 7.5% is a sulfone that was initially approved in the United States on February 24, 2016. Aczone gel, 7.5% is currently indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.[1] Another dapsone formulation, Aczone gel, 5% was first approved on July 7, 2005, and it is currently indicated for the topical treatment of acne vulgaris in patients aged 12 years and older.[2]

This pediatric postmarketing safety review was stimulated by pediatric labeling on September 10, 2019, that expanded the indication of Aczone gel, 7.5% to include patients aged 9 – 12 years old.[1]

On November 20, 2018, the Office of Surveillance and Epidemiology (OSE) completed a review of postmarketing adverse event reports with a serious outcome for Aczone in pediatric patients. OSE's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with Aczone.[3]

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

The Aczone gel 7.5% labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Aczone labeling information, please refer to the full prescribing information.

> _____CONTRAINDICATIONS_____
> None (4).
>
> _____WARNINGS AND PRECAUTIONS_____
> - Methemoglobinemia: Cases of methemoglobinemia have been reported. Discontinue ACZONE Gel if signs of methemoglobinemia occur (5.1).
> - Hemolysis: Some patients with Glucose-6-phosphate Dehydrogenase (G6PD) deficiency using topical dapsone developed laboratory changes suggestive of hemolysis (5.1)(8.6).
>
> _____ADVERSE REACTIONS_____
> Most common (incidence ≥ 0.9%) adverse reactions are application site dryness and pruritus (6.1).
>
> **8.4 Pediatric Use**
> The safety and effectiveness of ACZONE Gel, 7.5% for the topical treatment of acne vulgaris have been established in patients 9 years of age and older. Use of ACZONE Gel, 7.5% in patients 9 to 11 years of age for this indication is supported by evidence from adequate and well-controlled clinical trials in 1066 subjects 12 years of age and older and with additional pharmacokinetic and safety data in pediatric subjects 9 to 11 years of age from an open label study of 100 subjects with acne [see Adverse Reactions (6.1), and Clinical Pharmacology (12.3)].
>
> The safety profile for ACZONE Gel, 7.5% in clinical trials 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 9 years.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*	
Date of search	July 25, 2023
Time period of search	September 1, 2018† - July 24, 2023
Search type	RxLogix Post-Market Cases
Product terms	Product active ingredient: Dapsone
MedDRA search terms (Version 26.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database † Data lock date from OSE's last pediatric postmarketing pharmacovigilance review for Aczone Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

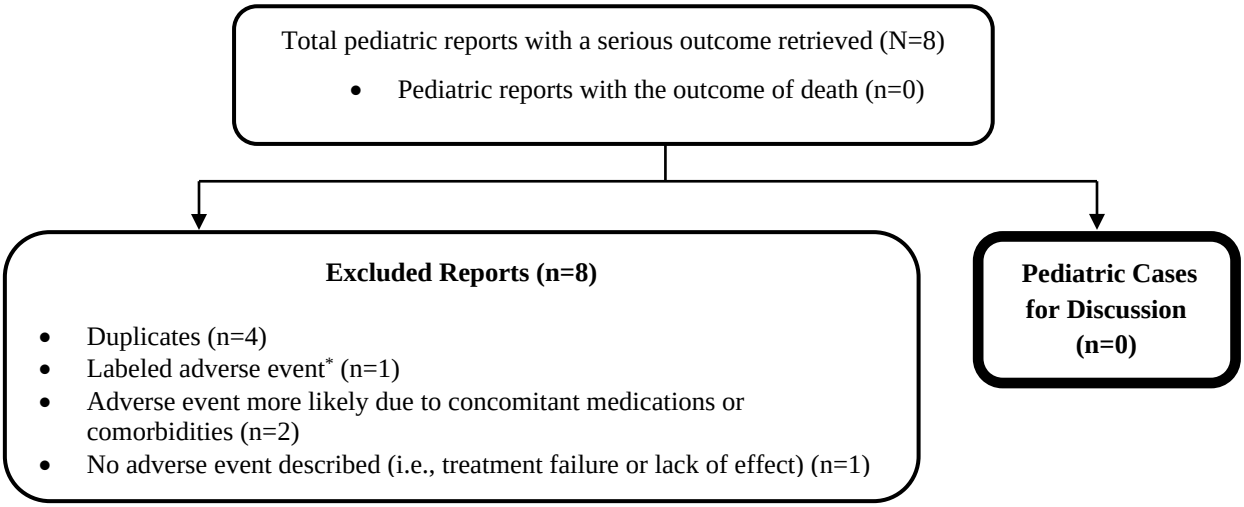
Table 2 presents the number of adult and pediatric FAERS reports from September 1, 2018 – July 24, 2023, with dapsone.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From September 1, 2018 – July 24, 2023, With Dapsone			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	30 (15)	18 (3)	0 (0)
Pediatrics (0 - < 18 years)	13 (11)	8 (6)	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, or other serious important medical events.			

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved eight serious pediatric reports from September 1, 2018 – July 24, 2023, with dapsone. We reviewed all FAERS pediatric reports with a serious outcome. We excluded all eight reports from the case series for the reasons listed in **Figure 1**. **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious Pediatric Cases With Dapsone



* Labeled adverse event does not represent increased severity or frequency.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.4 Summary of Serious Non-Fatal Pediatric Cases (N=0)

There are no non-fatal pediatric adverse event cases for discussion.

4 DISCUSSION

DPV reviewed all serious FAERS reports with dapsone in pediatric patients less than 18 years of age from September 1, 2018 – July 24, 2023, and eight reports were identified; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled
adverse events, and no deaths directly associated with dapsone in pediatric patients less than 18 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for dapsone at this time and will continue routine pharmacovigilance monitoring for dapsone.

6 REFERENCES

1. Aczone (dapsone) gel, 7.5%, for topical use. [Prescribing information]. Exton, PA; Almirall, LLC: September, 2019.

2. Aczone (dapsone) gel, 5%, for topical use. [Prescribing information]. Madison, NJ; Allergan USA, Inc.: May, 2018.

3. Weintraub J. Pediatric Postmarketing Pharmacovigilance Review. November 20, 2018. Available at: https://www.fda.gov/media/123624/download

7 APPENDICES

7.1 APPENDIX A. 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 FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

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 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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