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:	Aklief (trifarotene) cream
Pediatric Labeling Approval Date:	October 4, 2019
Application Type/Number:	NDA 211527
Applicant:	Galderma Laboratories, L.P.
TTT Record ID:	2023-5802

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Aklief (trifarotene) cream 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 trifarotene in pediatric patients.

Aklief (trifarotene) cream is a retinoid that was initially approved in the U.S. on October 4, 2019. Aklief is currently indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

This pediatric postmarketing safety review was prompted by pediatric labeling at FDA approval on October 4, 2019, that included pediatric patients aged 9 – 17 years old. A pediatric safety review for trifarotene has not been previously presented to the Pediatric Advisory Committee.

DPV reviewed all serious FAERS reports with trifarotene in pediatric patients less than 18 years of age from October 4, 2019 – July 24, 2023, and identified one report. However, the report was 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 trifarotene in pediatric patients less than 18 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Aklief (trifarotene) cream 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 trifarotene in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY[1]

Aklief (trifarotene) cream is a retinoid that was initially approved in the U.S. on October 4, 2019. Aklief is currently indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

This pediatric postmarketing safety review was prompted by the pediatric labeling at FDA approval on October 4, 2019, that included pediatric patients aged 9 – 17 years old. Safety and effectiveness of Aklief cream for use in pediatric patients aged 9 – 17 years was based on evidence from well-controlled clinical trials (n=897 pediatric subjects aged 9 – 17 years), a long-term safety trial, and a pharmacokinetic trial. A pediatric safety review for trifarotene has not been previously presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

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

---------- CONTRAINDICATIONS ----------
None (4)

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

- Skin irritation: Erythema, scaling, dryness, and stinging/burning may be experienced with use of AKLIEF Cream. Use a moisturizer from the initiation of treatment, and, if appropriate, reduce the frequency of application of AKLIEF Cream, suspend or discontinue use. (5.1)
- Ultraviolet Light and Environmental Exposure: Minimize exposure to sunlight and sunlamps. Use sunscreen and protective clothing over treated areas when exposure cannot be avoided. (5.2)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence ≥ 1%) in patients treated with AKLIEF Cream were application site irritation, application site pruritus, and sunburn (6).

8.4 Pediatric Use
Safety and effectiveness of AKLIEF Cream for the topical treatment of acne vulgaris have been established in pediatric patients aged 9 years to 17 years based on evidence from well-controlled clinical trials, a long-term safety trial, and a pharmacokinetic trial. A total of 897 pediatric subjects aged 9 to 17 years received AKLIEF Cream in the clinical trials *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

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	October 4, 2019† - July 24, 2023
Search type	RxLogix Post-Market Cases
Product terms	Product Active Ingredient: Trifarotene
MedDRA search terms (Version 26.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database † Aklief U.S. approval date 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 October 4, 2019 – July 24, 2023, with trifarotene.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From October 4, 2019 – July 24, 2023, With Trifarotene			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	12 (11)	3 (3)	0 (0)
Pediatrics (0 - < 18 years)	6 (6)	1 (1)	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 one serious pediatric report from October 4, 2019 – July 24, 2023. We reviewed all FAERS pediatric reports with a serious outcome. We excluded the singular report from the case series as the adverse event was more likely due to a concomitant medication.

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 trifarotene in pediatric patients less than 18 years of age from October 4, 2019 – July 24, 2023, and identified one report. However, the report was 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 trifarotene in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Aklief (trifarotene) cream, for topical use [Prescribing information]. Fort Worth, TX; Galderma Laboratories, L.P.: January, 2022.

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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