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Pediatric Postmarketing Pharmacovigilance Review

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Product Name	**Pediatric Labeling Approval Date**	**Application Type/Number**	**Applicant**
Altreno (tretinoin) lotion	August 23, 2018	NDA 209353	Dow Pharm
Twyneo (tretinoin/benzoyl peroxide) cream	July 26, 2021	NDA 214902	Galderma Labs LP

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Altreno (tretinoin) lotion or Twyneo (tretinoin/benzoyl peroxide) cream in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA) for Altreno and Twyneo. This review focuses on unlabeled adverse events associated with Altreno or Twyneo in pediatric patients.

Altreno (NDA 209353) is a retinoid lotion approved by FDA on August 23, 2018, for the topical treatment of acne vulgaris in patients 9 years of age and older. Twyneo (NDA 214902) is a combination of tretinoin and benzoyl peroxide approved by FDA on July 26, 2021, for the treatment of acne vulgaris in adults and pediatric patients 9 years of age and older. This pediatric postmarketing pharmacovigilance review was prompted by the approval of Altreno on August 23, 2018, and Tywneo on July 26, 2021.

DPV reviewed all FAERS reports for Altreno or Twyneo in the pediatric population (ages 0 to <17 years) from August 23, 2018, through September 27, 2022. The FAERS search identified no pediatric reports.

DPV will continue to monitor all adverse events associated with the use of Altreno and Twyneo.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Altreno (tretinoin) lotion or Twyneo (tretinoin/benzoyl peroxide) cream in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA) for Altreno and Twyneo. This review focuses on unlabeled adverse events associated with Altreno or Twyneo in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Altreno (NDA 209353) is a retinoid lotion approved by FDA on August 23, 2018, for the topical treatment of acne vulgaris in patients 9 years of age and older. The safety and effectiveness of Altreno in pediatric patients below 9 years of age have not been established. A summary of the study design and findings are summarized below from the Altreno Clinical Review.[1]

> "In two, multicenter, randomized, double-blind clinical trials enrolling 1640 subjects age 9 years and older with acne vulgaris, tretinoin lotion was statistically superior to vehicle for the treatment of acne vulgaris. The co-primary efficacy endpoints were success on the Evaluator's Global Severity Score (EGSS), absolute change in noninflammatory lesion count, and absolute change in inflammatory lesion count at Week 12. Success on the EGSS was defined as at least a 2-grade improvement from Baseline and an EGSS score of clear (0) or almost clear (1).
>
> The safety profile for tretinoin lotion was adequately characterized during the drug development program. Treatment with tretinoin lotion was not associated with an increased risk of mortality or serious adverse events. There were no deaths or drug-related, serious adverse events (SAEs) in the Phase 3 trials, Study V01-121A-301 and Study V01-121A-302 (referred to as Study 301 and Study 302). In the pooled safety analysis set, SAEs occurred in 0.9% subjects in the tretinoin lotion group and 0.5% subjects in the vehicle group. Review of the data supports including the potential for skin irritation and effects of ultraviolet light and environmental exposure in Section 5 WARNINGS AND PRECAUTIONS of labeling. Active assessment of local tolerability indicated that the percentage of subjects who reported signs and symptoms (erythema, scaling, hypopigmentation, itching, burning, and stinging) at a post Baseline visits was greater in the tretinoin lotion group than the vehicle group. The most common adverse reactions occurred at the application site: dryness (4%), pain (3%), erythema (2%), irritation (1%), and exfoliation (1%).
>
> In summary, acne vulgaris is a chronic disease which may be associated with substantial impairment of quality of life. Tretinoin lotion provides an additional treatment option. The available evidence of safety and efficacy supports the approval of ALTRENO (tretinoin) Lotion, 0.05% for the topical treatment of acne vulgaris in the population 9 years of age and older. In view of a favorable overall benefit/risk assessment, the review team recommends approval of this product."

Twyneo (NDA 214902) is a combination of tretinoin and benzoyl peroxide approved by FDA on July 26, 2021, for the treatment of acne vulgaris in adults and pediatric patients 9 years of age and older. The safety and effectiveness of Twyneo in pediatric patients below 9 years of age have not been established. A summary of the study design and findings are summarized below from the Twyneo Summary Review for Regulatory Action.[2]

> "In two, multicenter, randomized, double-blind, vehicle-controlled clinical trials enrolling 858 subjects age 9 years and older with acne vulgaris, benzoyl peroxide and tretinoin, 3%/0.1%, cream was statistically superior to vehicle for the treatment of acne vulgaris. The co-primary efficacy endpoints were the absolute change from baseline in non-inflammatory lesion count, absolute change from baseline in inflammatory lesion count, and the proportion of subjects with treatment success, defined as an IGA score of 0 ("clear") or 1 ("almost clear"), and at least a two-grade improvement (decrease) from baseline at Week 12.
>
> The safety profile for tretinoin/benzoyl peroxide cream, 0.1%/3%, was adequately characterized during the drug development program. There were no deaths or drug-related serious adverse events (SAEs) in the phase 3 trials SGT-65-04 and SGT-65-05. In the phase 3 trials pooled safety analysis set, SAEs occurred in 0.2% of subjects in the tretinoin/benzoyl peroxide cream, 0.1%/3%, group and in 0.4% of subjects in the vehicle group. Adverse reactions (ARs) occurred at a higher frequency in the tretinoin/benzoyl peroxide cream group compared to the vehicle cream group (29% vs. 0.2%). Active assessment of cutaneous safety and tolerability assessment (erythema, scaling, pigmentation, itching, burning and stinging) indicated that the percentage of subjects who reported signs and symptoms at any post-baseline visit was greater in the tretinoin/benzoyl peroxide cream group than the vehicle cream group. The most common ARs occurred at the application site and included the following ARs in the tretinoin/benzoyl peroxide cream group, compared to the vehicle cream group: pain (10.6% vs. 0.4%), dryness (4.9% vs. 0.4%), exfoliation (4.1% vs. 0), erythema (4% vs. 0), dermatitis (1.3% vs. 0.4%), pruritis (1.3% vs. 0), and irritation (1.1% vs. 0.4%). Although there were no severe hypersensitivity reactions during the development program for Twyneo cream, literature suggests that rare but severe hypersensitivity reactions may occur following the use of benzoyl peroxide-containing products. Therefore, labeling pertaining to hypersensitivity reactions should be included in Section 4 CONTRAINDICATIONS. Review of the data supports including the potential for skin irritation and increased sun sensitivity in Section 5 WARNINGS AND PRECAUTIONS of labeling.
>
> Tretinoin/benzoyl peroxide cream, 0.1%/3%, provides an additional treatment option for acne vulgaris. The available evidence of safety and efficacy supports the approval of Twyneo (tretinoin/benzoyl peroxide) Cream, 0.1%/3%, for the topical treatment of acne vulgaris in the population 9 years of age and older. In view of a favorable overall benefit/risk assessment, the review team recommends approval of this product."

This pediatric postmarketing pharmacovigilance review was prompted by the approval of Altreno on August 23, 2018, and Tywneo on July 26, 2021. DPV has not previously presented Altreno or Twyneo to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

1.2.1 Altreno

The Altreno labeling contains the following safety information excerpted from the Highlights section of the labeling as well as the Pediatric Use subsection.[3] For further labeling information, please refer to the full prescribing information.

---------- **CONTRAINDICATIONS** ----------

None. (4)

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

- Skin Irritation: Dryness, pain, erythema, irritation and exfoliation may occur with use of ALTRENO. (5.1)
- Ultraviolet Light and Environmental Exposure: Minimize exposure to sunlight and sunlamps. Use sunscreen and protective clothing when sun exposure cannot be avoided. (5.2)
- Fish Allergies: Use ALTRENO with caution if allergic to fish due to potential for allergenicity to fish protein. Advise patients to contact their healthcare provider if they develop pruritus or urticaria. (5.3)

---------- **ADVERSE REACTIONS** ----------

- The most common adverse reactions occurring in ≥1% of subjects and greater than vehicle were dryness, pain, erythema, irritation and exfoliation (all at the application site). (6.1)

8.4 Pediatric Use

Safety and effectiveness of ALTRENO for the topical treatment of acne vulgaris have been established in pediatric patients age 9 years to less than 17 years based on evidence from two multicenter, randomized, double-blind, parallel-group, vehicle-controlled, 12-week trials and an open-label pharmacokinetic study. A total of 318 pediatric subjects aged 9 to less than 17 years received ALTRENO in the clinical studies *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

The safety and effectiveness of ALTRENO in pediatric patients below the age of 9 years have not been established.

1.2.2 Twyneo

The Twyneo labeling contains the following safety information excerpted from the Highlights section of the labeling as well as the Pediatric Use subsection.[4] For further labeling information, please refer to the full prescribing information.

----------**CONTRAINDICATIONS**----------

History of serious hypersensitivity reaction to benzoyl peroxide or any component of TWYNEO. (4)

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

- *Hypersensitivity*: Severe hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with use of benzoyl peroxide products. (4, 5.1)
- *Skin Irritation*: Pain, dryness, exfoliation, erythema, and irritation may occur with use of TWYNEO. Avoid application of TWYNEO to cuts, abrasions, eczematous or sunburned skin. (5.2)
- *Photosensitivity*: Minimize unprotected exposure to sunlight and sunlamps. Use sunscreen and protective clothing when sun exposure cannot be avoided. (5.3)

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

The most common adverse reactions (incidence ≥ 1%) are pain, dryness, exfoliation, erythema, dermatitis, pruritus and irritation (all at the application site). (6.1)

8.4 Pediatric Use

The safety and effectiveness of TWYNEO for the topical treatment of acne vulgaris have been established in pediatric patients 9 years of age and older based on evidence from two multicenter, randomized, double-blind, parallel-group, vehicle-controlled, 12-week clinical trials and an open-label pharmacokinetic study. A total of 283 pediatric subjects 9 years of age and older received TWYNEO in the clinical studies *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

The safety and effectiveness of TWYNEO in pediatric patients below 9 years of age have not been established.

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	September 28, 2022
Time period of search	August 23, 2018† - September 27, 2022
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Product terms	Product Name: Altreno, Twyneo NDA #: 209353, 214902
MedDRA search terms (Version 25.0)	All PT terms
* See Appendix A for a description of the FAERS database. † U.S. Approval Date for Altreno Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, NDA=new drug application, PT=Preferred Term	

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 August 23, 2018, through September 27, 2022, with Altreno or Twyneo.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From August 23, 2018 through September 27, 2022 With Altreno or Twyneo

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	11 (10)	2 (1)	0 (0)
Pediatrics (0 - <17 years)	0 (0)	0 (0)	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 Pediatric Cases in FAERS

Our FAERS search retrieved no pediatric reports from August 23, 2018, through September 27, 2022.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for further discussion with Altreno or Twyneo.

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

We did not identify any unlabeled non-fatal adverse event cases associated with Altreno or Twyneo in the pediatric population.

4 DISCUSSION

DPV reviewed all FAERS reports for Altreno or Twyneo in the pediatric population (ages 0 to <17 years) from August 23, 2018, through September 27, 2022. No pediatric reports were identified in FAERS.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for Altreno or Twyneo at this time.

6 RECOMMENDATION

DPV will continue to monitor all adverse events associated with the use of Altreno or Twyeno.

7 REFERENCES

1. McCord M. NDA/BLA Mulit-disciplinary Review of Altreno (tretinoin) Lotion, 0.05% July 2018. https://www.fda.gov/media/116197/download.
2. Schreiber S. NDA/BLA Multi-Disciplinary Review and Evaluation of Twyneo (tretinoin and benzoyl peroxide) cream, 0.1/3%. June 2021. https://www.fda.gov/media/151645/download.
3. Altreno®(tretinoin) lotion, for topical use [Prescribing Information]. Bridgewater, NJ Dow Pharmaceutical Sciences; August 2018.
4. Twyneo®(tretinoin and benzoyl peroxide) cream, for topical use [Prescribing Information]. Whippany, NJ: Sol-Gel Technologies Inc.; July 2021.

8 APPENDICES

8.1 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 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 (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.

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