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:	September 15, 2022
Medical Officer:	Ivone Kim, MD ovigilance-I (DPV-I)
Team Leader:	Carmen Cheng, PharmD DPV-I
Division Director:	Cindy Kortepeter, PharmD DPV-I
Product Name:	Winlevi (clascoterone)
Pediatric Labeling Approval Date:	August 26, 2020
Application Type/Number:	NDA 213433
Applicant:	Sun Pharmaceutical Industries
TTT Record ID:	2022-768

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Winlevi (clascoterone) in pediatric patients through age 18 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). This review focuses on unlabeled adverse events associated with clascoterone in pediatric patients.

Clascoterone is an androgen receptor inhibitor that received FDA approval on August 26, 2020, for the topical treatment of acne vulgaris in patients 12 years of age and older. Evidence of safety and effectiveness of clascoterone in pediatric patients relied on two identical phase 3 randomized, multicenter, double-blind, vehicle-controlled, parallel-group trials in 641 pediatric patients, aged 12 to 18 years. Safety and effectiveness for use in pediatric patients under 12 years has not been established.

This pediatric postmarketing pharmacovigilance review was prompted by the August 26, 2020, approval of clascoterone in pediatric patients aged 12 years and older. DPV has not previously presented clascoterone to the Pediatric Advisory Committee.

DPV reviewed all FAERS reports for clascoterone in the pediatric population (ages 0 through 18 years) for all dates through August 1, 2022. The FAERS search identified four reports. After hands-on review, all reports were excluded from further discussion. There were no safety signals, no increased severity or frequency of labeled adverse events, and no pediatric deaths that could be attributed to clascoterone.

DPV will continue to monitor all adverse events associated with the use of clascoterone.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Winlevi (clascoterone) in pediatric patients through age 18 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with clascoterone in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Clascoterone is an androgen receptor inhibitor that received FDA approval on August 26, 2020, for the topical treatment of acne vulgaris in patients 12 years of age and older.[1] Evidence of safety and efficacy of clascoterone in pediatric patients relied on two identical phase 3 randomized, multicenter, double-blind, vehicle-controlled, parallel-group trials in 641 pediatric patients, aged 12 to 18 years.[2,3] Safety and effectiveness for use in pediatric patients under 12 years has not been established. A summary of the study design and findings are summarized below from the Winlevi (clascoterone) Multi-Disciplinary Review and Evaluation.[4]

> "The Applicant submitted data from nonclinical studies, two pharmacokinetic (PK) maximal usage trials (MUsTs), one in pediatric subjects and one in adults, two vehicle controlled phase 3 efficacy and safety trials, and one long-term (12 months) safety trial to support the efficacy and safety of their product. Upon review of the benefits and risks, the review team recommends approval in subjects 12 years of age and older.
>
> In two multicenter, randomized, double-blind clinical trials— CB-03-01/25 and CB-03-01/26—enrolling 1,440 subjects age 9 years and older with acne vulgaris, clascoterone cream, 1%, was statistically superior to a vehicle for the treatment of acne vulgaris on all coprimary endpoints evaluating the face. Success on the Investigator Global Assessment (IGA) was evaluated for the face and defined as at least a two-grade improvement from baseline and an IGA score of clear (0) or almost clear (1). The coprimary efficacy endpoints were success on the IGA (trial CB-03-01/25: 18.8% versus 8.7% and trial CB-03-01/26: 20.9% versus 6.6%), absolute change in inflammatory lesion count (trial CB-03-01/25: -19.3 versus -15.4 and trial CB-03-01/26: -20.1 versus -12.6), and absolute change in noninflammatory lesion count (trial CB-03-01/25: -20.4 versus -13.0 and trial CB-03-01/26: -19.5 versus -10.8) at week 12.
>
> The safety profile for clascoterone cream, 1%, was adequately characterized during the drug development program. Treatment with clascoterone cream, 1%, was not associated with an increased risk of mortality or serious adverse events (SAEs). There were no deaths or drug-related serious adverse events in the phase 3 trials, trial CB-03-01/25, and trial CB-03-01/26 (referred to as study 1 and study 2 in labeling). In the pooled safety analysis set, SAEs occurred in 0% subjects in the clascoterone cream, 1% arm, and 0.3% in the vehicle arm."

This pediatric postmarketing pharmacovigilance review was prompted by the August 26, 2020, approval of clascoterone in pediatric patients aged 12 years and older. DPV has not previously presented clascoterone to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

The Winlevi (clascoterone) labeling contains the following safety information excerpted from the Highlights section of the labeling. For further clascoterone labeling information, please refer to the full prescribing information.

INDICATIONS AND USAGE

WINLEVI® (clascoterone) cream is an androgen receptor inhibitor indicated for the topical treatment of acne vulgaris in patients 12 years of age and older. (1)

DOSAGE AND ADMINISTRATION

- Apply a thin layer (approximately 1 gram) to affected area twice daily (morning and evening). Avoid contact with eyes, mouth, and mucous membranes. (2)
- Not for ophthalmic, oral, or vaginal use. (2)

DOSAGE FORM AND STRENGTHS

Cream 1%. (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Local Irritation: Pruritus, burning, skin redness or peeling may be experienced with WINLEVI cream. If these effects occur, discontinue or reduce the frequency of application of WINLEVI cream. (5.1)
- Hypothalamic-pituitary-adrenal (HPA) axis suppression may occur during or after treatment with clascoterone. (5.2)
- Attempt to withdraw use if HPA axis suppression develops. (5.2)
- Pediatric patients may be more susceptible to systemic toxicity. (5.2, 8.4)
- Hyperkalemia: Elevated potassium levels were observed in some subjects during the clinical trials. (12.2)

ADVERSE REACTIONS

Most common adverse reactions occurring in 7 to 12% of patients are erythema/reddening, pruritus and scaling/dryness. Additionally, edema, stinging, and burning occurred in >3% of patients and were reported in a similar percentage of subjects treated with vehicle. (6.1)

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	August 2, 2022
Time period of search	All reports through August 1, 2022
Search type	RxLogix PV Signal Quick Query
Product terms	PAI: Clascoterone
MedDRA search terms (Version 25)	All PT terms

Table 1. FAERS Search Strategy*
* See Appendix A for a description of the FAERS database. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PAI=Product Active Ingredient, 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 through August 1, 2022, with clascoterone.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA Through August 1, 2022, With Clascoterone

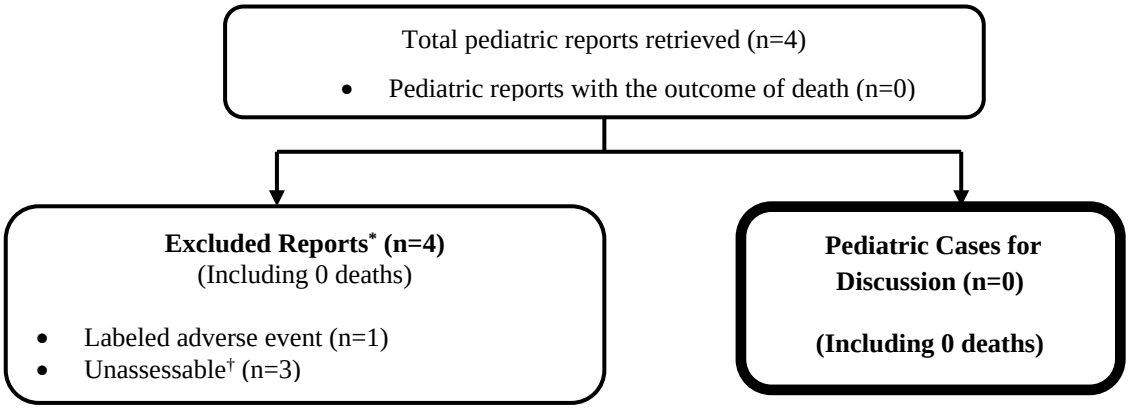
	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 19 years)	5 (5)	1 (1)	0 (0)
Pediatrics (0 - <19 years)	4 (4)	1 (1)	0 (0)

* 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 Pediatric Cases in FAERS

The FAERS search retrieved four pediatric reports with clascoterone through August 1, 2022. DPV reviewed the four FAERS reports and excluded all reports from further discussion due to the reports describing a labeled adverse event (n=1) or being unassessable (n=3). **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of Pediatric Cases with Clascoterone



* DPV reviewed these reports, but they were excluded from further discussion for the reasons listed above.
† Unassessable: Report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information is contradictory, or information provided in the report cannot be supplemented or verified.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for further discussion.

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

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

4 DISCUSSION

DPV reviewed all FAERS reports for clascoterone in the pediatric population (ages 0 through 18 years) for all dates through August 1, 2022. The FAERS search identified four reports. After hands-on review, all reports were excluded from further discussion. There were no safety signals, no increased severity or frequency of labeled adverse events, and no pediatric deaths that could be attributed to clascoterone.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for clascoterone at this time.

6 RECOMMENDATION

DPV will continue to monitor all adverse events associated with the use of clascoterone.

7 REFERENCES

1. Winlevi cream (clascoterone) [package insert]. Milan, Italy: Cassiopea SpA. August 2020.
2. A Study to Evaluate the Safety and Efficacy of CB-03-01 Cream, 1% in Subjects With Facial Acne Vulgaris (25). (2020). Retrieved from https://clinicaltrials.gov/ct2/show/NCT02608450?term=clascoterone&draw=2&rank=4. (Identification no. NCT02608450).
3. A Study to Evaluate the Safety and Efficacy of CB-03-01 Cream, 1% in Subjects With Facial Acne Vulgaris. (2020). Retrieved from https://clinicaltrials.gov/ct2/show/NCT02608476?term=clascoterone&draw=2&rank=3. (Identification no. NCT02608476).
4. Williams D. Winlevi cream (clascoterone) Multi-Disciplinary Review and Evaluation. August 26, 2020. Available at: https://www.fda.gov/media/142578/download. Accessed August 2, 2022.

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.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

IVONE E KIM
09/15/2022 03:05:56 PM

CARMEN CHENG
09/15/2022 03:11:22 PM

CINDY M KORTEPETER
09/15/2022 04:04:49 PM