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

Pediatric Postmarketing Pharmacovigilance

Date:	June 10, 2020
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Product Name:	Luzu (luliconazole) cream, 1%
Pediatric Labeling Approval Date:	February 20, 2018
Application Type/Number:	NDA 204153/S4, S5
Applicant:	Medicis/ Valeant Pharmaceuticals
OSE RCM #:	2020-521

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Luzu (luliconazole) cream, 1% in pediatric patients through age 17 years old. 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 Luzu cream, 1% in pediatric patients.

The FDA approved Luzu cream, 1% on November 14, 2013 and it is indicated for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Trichophyton rubrum* and *Epidermophyton floccosum*. Fulfillment of postmarketing requirements and commitments supported the approved pediatric labeling of Luzu cream, 1% on February 20, 2018 for patients:

- 2 years of age and older with tinea corporis
- 12 years and older with tinea cruris and tinea pedis.

Our FAERS search retrieved five pediatric cases through March 2, 2020. All were non-serious, and four did not report an adverse event; thus, one case was included in our review. The case reported an unlabeled event of acne. The single case reporting an adverse event described a common comorbidity in the teenage age group and had limited information which precluded a meaningful causality assessment. No patterns or trends suggested a new safety signal associated with the use of Luzu cream, 1% in our pediatric cases.

DPV did not identify any pediatric safety concerns for Luzu cream, 1%. DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of Luzu cream, 1%.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Luzu cream, 1% in pediatric patients through age 17 years old. 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 Luzu (luliconazole) cream, 1% in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY[1, 2, 3, 4, 5]

The FDA approved Luzu (luliconazole) cream, 1% (NDA 204153) on November 14, 2013 for topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Trichophyton rubrum* and *Epidermophyton floccosum*, in patients 18 years of age and older. The exact mechanism of action of luliconazole, an azole antifungal, against dermatophytes is unknown, but luliconazole appears to inhibit ergosterol synthesis by inhibiting the enzyme lanosterol demethylase. Inhibition of this enzyme's activity by azoles results in decreased amounts of ergosterol, a constituent of fungal cell membranes, and a corresponding accumulation of lanosterol. The recommended dosing interval for Luzu cream, 1% is once daily for:

- 2 weeks for interdigital tinea pedis
- 1 week for tinea cruris or tinea corporis

Under PREA, the following pediatric assessments were waived:

- Ages 0 to 1 year 11 months for tinea corporis
- Ages 0 to 11 years 11 months for interdigital tinea pedis and tinea cruris

Under PREA, the following pediatric assessments were deferred:

- Ages 2 to 17 years 11 months for tinea corporis
  - PMR 2101-1 Conduct a multi-center, randomized, blinded, vehicle-controlled study, including pharmacokinetic assessments, with luliconazole cream 1% for the treatment of tinea corporis in pediatric patients 2 years of age and older.
- Ages 12 to 17 years 11 months for interdigital pedis and tinea cruris
  - PMR 2101-2 Conduct a maximum use pharmacokinetic safety study in pediatric patients 12 years to 17 years 11 months of age with interdigital tinea pedis and tinea cruris.

The initial safety and efficacy of Luzu cream, 1% was assessed in three studies:

- **Interdigital tinea pedis**: Two randomized, double-blind, vehicle-controlled, multi-center clinical trials in 423 subjects with a clinical and culture-confirmed diagnosis of interdigital tinea pedis were conducted. Subjects were randomized to receive Luzu cream, 1% or vehicle. Subjects applied either Luzu cream, 1% or vehicle cream to the entire area of the forefeet including all interdigital web spaces and approximately 2.5 cm (1 in) of the surrounding area of the foot once daily for 14 days. Signs and symptoms of tinea pedis (erythema, scaling, and pruritus), KOH exam and dermatophyte culture were assessed at baseline, end-of-treatment (Day 14), and 2- and 4-weeks post-treatment. Overall treatment success was defined as complete clearance (clinical cure and

mycological cure) at 4 weeks post-treatment. Luzu cream, 1% demonstrated complete clearance in subjects with interdigital tinea pedis.

- **Tinea cruris**: One randomized, double-blind, vehicle-controlled, multi-center clinical trial in 256 subjects with a clinical and culture-confirmed diagnosis of tinea cruris was conducted. Subjects were randomized to receive Luzu cream, 1% or vehicle. Subjects applied either Luzu cream, 1% or vehicle cream to the affected area and approximately 2.5 cm (1 in) of the surrounding area once daily for 7 days. Signs and symptoms of tinea cruris (erythema, scaling, and pruritus), positive KOH exam and dermatophyte culture were assessed at baseline, end-of-treatment (Day 7), and 2- and 3-weeks post-treatment. Overall treatment success was defined as complete clearance (clinical cure and mycological cure) at 3 weeks post-treatment. Luzu cream, 1% demonstrated complete clearance in subjects with tinea cruris.

The Applicant submitted efficacy supplements (S4 and S5), which included:

- S4: the study report for safety, efficacy, and pharmacokinetic data for pediatric tinea corporis addressing the PREA postmarketing requirement (PMR) for luliconazole cream, 1% in the treatment of tinea corporis in pediatric patients $\geq$ 2 years of age (PMR 2101-1)
- S5: the study report for a single PK study that evaluated the safety of luliconazole cream, 1% in the treatment of tinea pedis and tinea cruris in pediatric subjects 12 to 17 years of age (PMR 2101-2)

Both efficacy supplements were approved on February 20, 2018.

The safety and efficacy of Luzu cream, 1% in the treatment of tinea corporis in patients aged 2 to < 18 years old was assessed in a post-approval clinical trial:

- One randomized, double-blind, vehicle-controlled, multi-center clinical trial in 75 subjects age 2 to <18 years old with a clinical and culture-confirmed diagnosis of tinea corporis was conducted. Subjects were randomized to receive Luzu cream, 1% or vehicle cream. Subjects applied either Luzu cream, 1% or vehicle cream to the affected area and approximately 2.5 cm (1 in) of the surrounding skin once daily for 7 days. Signs and symptoms of tinea cruris (erythema, scaling, and pruritus), positive KOH exam and dermatophyte culture were assessed at baseline, end-of-treatment (Day 7), and 2- and 3-weeks post-treatment.
- The adverse reactions in the Luzu cream, 1% treated population were similar to the vehicle treated population.

The safety of Luzu cream[4], 1% in the treatment of tinea pedis and tinea cruris in patients 12 to < 18 years of age was assessed in an open-label pharmacokinetic study in 30 adolescent subjects with moderate to severe interdigital tinea pedis (N=15) or moderate to severe tinea cruris (N=15). There were no serious adverse events reported.

DPV has not previously completed a pediatric postmarketing pharmacovigilance review for Luzu cream, 1%.

1.2 RELEVANT LABELED SAFETY INFORMATION

The following safety information is an excerpt from the Luzu cream, 1% labeling:[5]

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In three Phase 3 clinical trials, 616 subjects were exposed to LUZU Cream, 1%: 305 with interdigital tinea pedis and 311 subjects with tinea cruris. Subjects with interdigital tinea pedis or tinea cruris applied LUZU Cream, 1% or vehicle cream once daily for 14 days or 7 days, respectively, to affected and adjacent areas. During clinical trials with LUZU Cream, 1%, the most common adverse reactions were application site reactions which occurred in less than 1% of subjects in both the LUZU and vehicle arms. Most adverse reactions were mild in severity.

A post-approval clinical trial was conducted in 75 subjects age 2 to <18 years old with tinea corporis. The adverse reactions in the LUZU Cream, 1% treated population were similar to the vehicle treated population.

6. 2 Postmarketing Experience
The following adverse reactions have been identified during postmarketing use of luliconazole cream, 1%: contact dermatitis and cellulitis. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use
The safety and effectiveness of LUZU Cream, 1% in pediatric patients 12 to <18 years of age with tinea pedis and tinea cruris have been established by evidence from well-controlled trials in adult and pediatric subjects and a pharmacokinetic (PK) study in pediatric subjects *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

The safety and effectiveness of LUZU Cream, 1% in pediatric patients 2 to <18 years of age with tinea corporis have been established by evidence from a well-controlled trial in pediatric subjects *[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	March 3, 2020
Time period of search	All through March 2, 2020
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Product terms	Luliconazole
MedDRA search terms (Version 22.1)	All Preferred Terms
* See Appendix A for a description of the FAERS database. Abbreviation: 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 through March 2, 2020 with Luzu cream, 1%.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA Through March 2, 2020 with Luzu (Luliconazole) Cream, 1%

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	15 (10)	4 (0)	0 (0)
Pediatrics (0 - <18 years)	5 (5)	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.

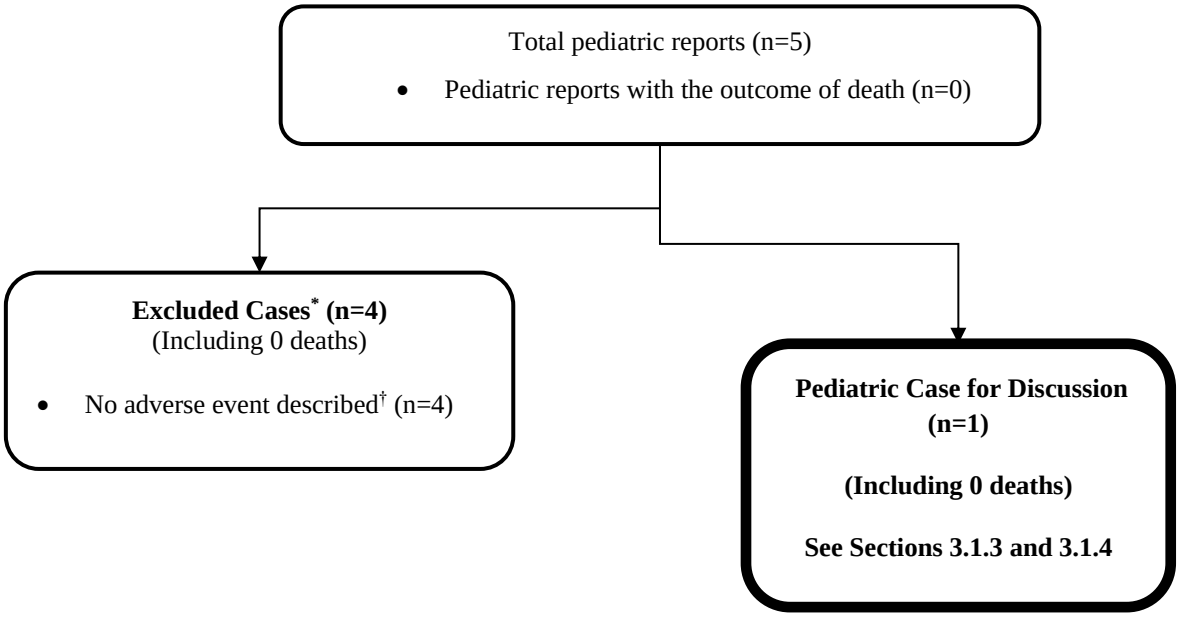
3.1.2 Selection of Pediatric Cases in FAERS

Our FAERS search retrieved five pediatric reports through March 2, 2020.

Given the small number of cases, we did not limit our search to pediatric cases reported after approval of pediatric labeling. We excluded reports from the case series if they did not report an adverse event.

Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of Pediatric Cases with Luzu (luliconazole) cream, 1%



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above.
† Cases reported no adverse event/drug prescribing error (n=1; age 13), no adverse event/drug use in unapproved age group (n=1; age 16), or use in unapproved age population (n=2; age 6 and <18). Of note, all pediatric cases were reported prior to the inclusion of pediatric labeling.

Appendix B contains a line listing of the included pediatric case.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event reports.

3.1.4 Summary of ALL Pediatric Cases (N=1)

We identified one FAERS case with Luzu cream, 1% in the pediatric population. The case was reported from the U.S. and did not report a serious outcome. The single report is summarized below. We did not identify patterns or trends suggestive of new safety signals in our pediatric cases.

FAERS Case # 11427171, Version 1, 2015, United States, non-serious outcome
A 16-year-old male patient started treatment with Luzu cream, 1% twice daily for ringworm on an unspecified location. The following day, he developed an acne breakout on his face. No additional information was included in the report.

4 DISCUSSION

We reviewed all FAERS reports with Luzu cream, 1% in the pediatric population (ages 0 - < 18 years) through March 2, 2020. Our FAERS search retrieved five pediatric cases. Of note, all pediatric cases were reported prior to the inclusion of pediatric labeling. All were non-serious, and four did not report an adverse event; thus, one case was included in our review. The case reported an unlabeled event of acne. The single case reporting an adverse event described a common comorbidity in the teenage age group and had limited information which precluded a meaningful causality assessment. In reviewing all pediatric FAERS reports, no new safety signals, no increased severity or frequency of any labeled adverse events, and no deaths were directly associated with Luzu cream, 1%.

5 CONCLUSION

DPV did not identify any pediatric safety concerns for Luzu cream, 1%.

6 RECOMMENDATION

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of Luzu cream, 1%.

7 REFERENCES

[1] Luzu (luliconazole) Cream, 1% Approval Letter, NDA 204153, November 14, 2013.
[2] Luzu (luliconazole) Cream, 1% Clinical Review, NDA 204153, supplement 4 and 5, January 25, 2018.
[3] Luzu (luliconazole Cream, 1% Cross Disciplinary Team Leader review, NDA 204153, September 17, 2013.
[4] Luzu (luliconazole Cream, 1% Cross Disciplinary Team Leader review, NDA 204153, supplement 4 and 5, November 14, 2013.
[5] Luzu (luliconazole) Cream, 1% Prescribing Information. Valeant. Bridgewater, NJ. February 2017.

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.

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=1)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	08/27/2015	11427171	1	US-BAUSCH-BL-2015-019483	NON-EXPEDITED	16	Male	United States	None

*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, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.

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/

MELISSA A REYES
06/10/2020 11:26:34 AM

IVONE E KIM
06/10/2020 11:29:35 AM

CARMEN CHENG
06/10/2020 11:34:04 AM

CINDY M KORTEPETER
06/10/2020 11:38:21 AM