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 and Drug Utilization Review

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Product Names:	Spectazole (econazole nitrate) cream, 1% Ecoza (econazole nitrate) topical foam, 1%
Pediatric Labeling Approval Date:	October 24, 2013
Application Type/Number:	NDAs: 018751, 205175 ANDAs: 076005, 076075, 076479, 076574
Applicant/Sponsor:	Veldana Medical SA, Alvogen Pine Brook LLC Various for generics
OSE RCM #:	2016-1587

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for econazole nitrate in pediatric patients.

Econazole nitrate is an azole antifungal available as a cream and topical foam in the United States (US). Econazole nitrate cream (Spectazole) was FDA approved on December 23, 1982 for the treatment of tinea pedis, tinea cruris, tinea corporis, tinea versicolor, and cutaneous candidiasis. However, this review was prompted by the FDA approval of econazole nitrate topical foam (Ecoza) on October 24, 2013 for the treatment of interdigital tinea pedis in patients 12 years of age and older.

Drug utilization for econazole products in the US outpatient retail pharmacy setting were also assessed from October 1, 2013 through June 30, 2016. More than 2 million patients received a dispensed prescription for econazole products for the review period. The pediatric population aged 0-17 years accounted for 14% of patients (approximately 282,000 patients) with a prescription for econazole cream and approximately 9% of patients (approximately 2,150 patients) with a prescription for econazole foam. Although the data showed off-label use of econazole foam in pediatric patients under 12 years of age, this use cannot be validated due to the lack of access to medical records.

The Division of Pharmacovigilance (DPV) searched the FDA Adverse Event Reporting System (FAERS) database for reports received from December 23, 1982 to June 30, 2016. DPV reviewed all US pediatric cases with a serious outcome reported with the use of econazole. Of the three pediatric cases included in the case series, there were no new safety signals identified, no apparent increased severity or frequency of any labeled adverse events, and there were no deaths reported with econazole. There is no evidence from these data that there are new pediatric safety concerns with econazole at this time. DPV will continue routine pharmacovigilance monitoring for econazole.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Product Information: Formulations, Indications, and Dosages

Econazole nitrate is an azole antifungal available as a cream and topical foam in the United States (US). Outside of the US, topical econazole (econazole nitrate, econazole base, and econazole nitrate/triamcinolone acetonide) are available in formulations such as cream, liposome jelly, lotion, ointment, paste, powder, shampoo, spray powder, and spray solution. Vaginal formulations of econazole nitrate include cream and ovules for the treatment of vulvovaginal mycoses and mycotic balanitis.[1]

In the US, econazole nitrate cream (Spectazole) was approved on December 23, 1982. Econazole nitrate topical foam (Ecoza) was approved on October 24, 2013. **Table 1.1** highlights the indications and dosages of these two products. The US label for econazole cream does not specify an age for use or provide specific instructions for use in the pediatric population.

Table 1.1 Econazole Product Information[2,3]

Formulation	Indication	Dosage
Econazole nitrate cream, 1%	Treatment of tinea pedis, tinea cruris, and tinea corporis caused by *Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans, Microsporum canis, Microsporum audouini, Microsporum gypseum,* and *Epidermophyton floccosum,* and in the treatment of tinea versicolor	Apply to cover affected areas once daily
	Treatment of cutaneous candidiasis	Apply to cover affected areas twice daily
Econazole nitrate topical foam, 1%	Treatment of interdigital tinea pedis caused by *Trichophyton rubrum, Trichophyton mentagrophytes,* and *Epidermophyton floccosum* in patients 12 years of age and older	Apply to cover affected areas once daily for 4 weeks

Pediatric Clinical Trials[3,4]

This PREA review was prompted by the initial FDA approval of econazole topical foam for use in patients 12 years of age and older. The pediatric labeling change date was October 24, 2013.

The efficacy and safety of econazole topical foam were studied in two phase 3 multi-center, randomized, double-blind, vehicle-controlled trials in patients with interdigital tinea pedis. Of the 505 subjects who enrolled in the two trials, a total of 339 subjects who had a positive fungal culture were evaluated for efficacy. There were 173 subjects treated with econazole topical foam, but only two subjects were between 12 and 17 years of age. The efficacy for the use of

econazole topical foam in adolescents was extrapolated from the adult population. The safety findings were similar between the adolescent and adult populations. A phase 2 pediatric pharmacokinetic trial conducted in subjects 12 to 17 years of age with interdigital tinea pedis provided additional safety data and no safety concerns were identified. Econazole topical foam contains the following text in Section 8.4 Pediatric Use of the label:

> Of the 173 subjects treated with Ecoza topical foam, 1% in the clinical trials, 2 subjects were 12-17 years old. In a pediatric maximal use trial, Ecoza topical foam, 1% was applied once daily to eighteen subjects aged 12 to 17 years with interdigital tinea pedis for 28 days [see Clinical Pharmacology (12.3)]. The safety findings for subjects 12 to 17 years were similar to those in adult population.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

The FDA-approved label for econazole cream, 1%, includes the following information:2 above[2]

CONTRAINDICATIONS
- SPECTAZOLE Cream is contraindicated in individuals who have shown hypersensitivity to any of its ingredients.

WARNINGS
- SPECTAZOLE is not for ophthalmic use.

PRECAUTIONS
- General: If a reaction suggesting sensitivity or chemical irritation should occur, use of the medication should be discontinued.
- For external use only. Avoid introduction of SPECTAZOLE Cream into the eyes.
- Nursing Mothers: It is not known whether econazole nitrate is excreted in human milk. Caution should be exercised when econazole nitrate is administered to a nursing woman.

ADVERSE REACTIONS
- During clinical trials, approximately 3% of patients treated with econazole nitrate 1% cream reported side effects thought possibly to be due to the drug, consisting mainly of burning, itching, stinging, and erythema. One case of pruritic rash has also been reported.

The FDA-approved label for econazole topical foam, 1%, includes the following information:[3]

CONTRAINDICATIONS
- None.

WARNINGS AND PRECAUTIONS
- Contents are flammable. Instruct the patient to avoid heat, flame, and/or smoking during and immediately following application.

ADVERSE REACTIONS
- During clinical trials with Ecoza topical foam, the most common adverse reactions were application site reactions which occurred in less than 1% of subjects in both the Ecoza and vehicle arms.

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

Proprietary databases available to the Agency were used to conduct the drug utilization analyses in this review (see **Appendix A** for full database descriptions and limitations).

2.1.1 Determining Settings of Care

IMS Health, IMS National Sales Perspectives™ was used to determine the various retail and non-retail channels of distribution for econazole. Sales data for the period of October 2013 through June 2016 indicated that approximately 86% of packages for econazole were distributed to US outpatient retail pharmacies; 10% were to non-retail settings; and 4% were to mail-order/specialty pharmacies.[5] As a result, only US outpatient retail pharmacy utilization patterns were examined. Data from mail-order/specialty and non-retail settings were not included in this analysis.

2.1.2 Data Sources Used

The IMS Health, Vector One®: Total Patient Tracker (TPT) database was used to provide national estimates of patients who received an econazole prescription dispensed from U.S. outpatient retail pharmacies from October 1, 2013 through June 30, 2016, cumulative.

2.2 RESULTS

2.2.1 Number of Patients

Table 2.2.1

Nationally estimated number of patients who received a dispensed prescription for econazole from U.S. outpatient retail pharmacies, stratified by formulation & patient age (0-11, 12-17, 18+ yrs)

	October 2013 - June 2016	
	Patient Count (N)	***Share (%)***
econazole total patients	**2,041,243**	***100.0%***
econazole cream	**2,017,485**	***98.8%***
Age 0-17 yrs	**281,813**	***14.0%***
Age 0-11 yrs	**180,728**	***64.1%***
Age 12-17 yrs	**101,975**	***36.2%***
Age 18+ yrs	**1,733,946**	***85.9%***
Unknown Age	**9,212**	***0.5%***
econazole foam	**25,299**	***1.2%***
Age 0-17 yrs	**2,153**	***8.5%***
Age 0-11 yrs	**540**	***25.1%***
Age 12-17 yrs	**1,623**	***75.4%***
Age 18+ yrs	**23,131**	***91.4%***
Unknown Age	**52**	***0.2%***

Source: IMS, Vector One®: Total Patient Tracker. Oct 2013 - Jun 2016. Extracted September 2016. File:TPT 2016-1587 Econazole by age 9-27-16.xls

**Patient age groups are inclusive of all patients up to the day before their next birthday. For example patients aged 0-17 years include patients less than 18 years of age (17 years and 11 months).*

**Unique patient counts may be added due to the possibility of double counting those patients aging during the review period, and may be counted more than once in the individual age categories.*

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in **Table 3.1.1**. See **Appendix B** for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy

Date of Search	July 8, 2016
Time Period of Search	December 23, 1982* - June 30, 2016
Search Type	FBIS Quick Query
Product Names	Product Active Ingredient: Econazole, Econazole nitrate
Search Parameters	All ages, all outcomes, worldwide

** US approval date of Spectazole, the first econazole product approved in the US*

Reference ID: 4015167

3.2 RESULTS

3.2.1 Total Number of FAERS reports by Age

Table 3.2.1 Total adult and pediatric FAERS reports* from December 23, 1982 to June 30, 2016 with econazole

	All reports (US)	Serious[†] (US)	Death (US)
Adults (≥ 17 years)	278 (112)	237 (72)	5 (0)
Pediatrics (0 - <17 years)	31 (14)	**25 (8)**[‡]	**3 (1)**[§]

** 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, and other serious important medical events.*

[‡] *See Section 3.2.2*

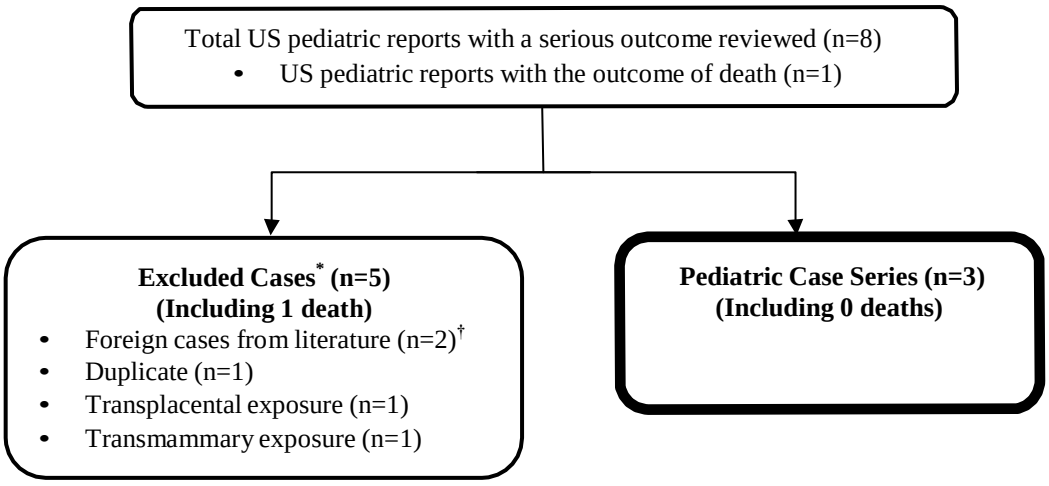
[§] *One additional report of pediatric death was identified among those not reporting an age.*

3.2.2 *Selection of Serious Pediatric Cases in FAERS*

The FAERS search retrieved 25 serious pediatric reports, including 17 foreign reports. Of the 17 foreign reports, there were five duplicate cases. Eight foreign cases reported the use of an econazole formulation not available in the US (e.g., vaginal, powder, topical solution), and two cases reported the use of an unspecified econazole formulation. One case reported a medication error where the patient did not receive the prescribed econazole product. The remaining case reported dermatitis, a labeled event, with the use of econazole cream. Overall, we did not identify any adverse events of interest from the foreign pediatric cases with a serious outcome reported with econazole.

Therefore, this review focuses on the eight US reports with a serious outcome associated with the use of FDA approved econazole products. After further excluding five cases for the reasons shown in **Figure 3.2.2**, we included three cases in our case series.

Figure 3.2.2 Selection of Serious Pediatric Cases with Econazole



** DPV reviewed these cases, but they were excluded from the case series for the reasons listed above.*
† Two foreign literature case reports of an unspecified topical econazole formulation, including one fatal case where the cause of death was not directly associated with econazole.

Appendix C lists the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASE (N=0)

There were no pediatric deaths in this case series.

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=3)

Three non-fatal pediatric serious cases reported the PTs *Dermatitis* or *Dermatitis contact* following the use of econazole cream. The patients' ages ranged from an "infant" (exact age unknown) up to 10 years old. The reported adverse events in these three cases were: (1) "irritant dermatitis" after two days (2) "redness, burning and irritation" after an unspecified time of use, or (3) "rash" and "burning after the second application." These events are consistent with the known risks labeled in the Adverse Reactions section of econazole cream, such as "burning, itching, stinging, and erythema." The econazole cream was discontinued in all three cases, with reported improvement of the adverse event in two cases. In the third case, treatment with another topical antifungal was initiated, but the clinical outcome of the adverse event was not reported.

4 DISCUSSION

Of the three US pediatric (0-17 years old) FAERS cases coded with a serious outcome included in the case series, there were no new safety signals identified, no apparent increased severity or frequency of any labeled adverse events, and there were no deaths reported.

Reference ID: 4015167

Additionally, drug utilization for econazole products in the US outpatient retail pharmacy setting were assessed. The pediatric population aged 0-17 years accounted for 14% of patients who received an outpatient retail prescription for econazole cream and approximately 9% of patients for econazole foam, from October 2013 through June 2016. Although the data showed off-label use of econazole foam in pediatric patients under 12 years of age, this use cannot be validated due to the lack of access to medical records.

5 CONCLUSION

There is no evidence from these data that there are new pediatric safety concerns with econazole at this time.

6 RECOMMENDATIONS

DPV will continue routine pharmacovigilance monitoring for econazole.

7 REFERENCES

1. Econazole Nitrate and Econazole Nitrate/Triamcinolone Acetonide - Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report for the period 16 November 2012 to 15 November 2013. January 9, 2014. (\\cdsesub1\evsprod\nda018751\0011\m5\53-clin-stud-rep\536-postmark-exp\econazole-nitrate-psur-20121116-to-20131.pdf)

2. Spectazole® (econazole nitrate 1%) Cream [Prescribing Information]. Greensboro, NC:Merz Pharmaceuticals, LLC. February 2014.

3. Ecoza® (econazole nitrate) topical foam 1% [Prescribing Information]. Jamison, PA: Quinnova Pharmaceuticals, LLC, Inc. October 2013.

4. Woitach AS. Clinical review for Ecoza (NDA 205175). FDA Medical Review. September 20, 2013. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM376095.pdf

5. IMS Health, IMS National Sales Perspectives™. October 2013-June 2016. Extracted September 2016. NSP 2016-1587 Econazole channels 9-27-16.xlsx.

8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS, Total Patient Tracker (TPT)

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

8.2 APPENDIX B. 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 the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference 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.

8.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH ECONAZOLE (N=3)

FAERS Case #	Version Number	Manufacturer Control #
4463996	1	SPEC43
4526826	1	SPEC51
5640428	1	(blank)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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