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 Review

Date:	March 28, 2018
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Product Name:	Natroba (spinosad topical suspension 0.9%)
Pediatric Labeling Approval Date:	December 30, 2014
Application Type/Number:	NDA 22408
Applicant/Sponsor:	ParaPRO LLC
OSE RCM #:	2018-289

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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 all postmarketing adverse event reports for Natroba (spinosad topical suspension 0.9%) in pediatric patients.

Spinosad was first approved in January 18, 2011 and is indicated for the topical treatment of head lice infestation in patients 4 years of age or older. On December 30, 2014, the approved pediatric labeling for the treatment of head lice infestation was extended to include pediatric patients aged 6 months or older.

The Division of Pharmacovigilance I (DPV-I) reviewed all serious reports in the FDA Adverse Event Reporting System (FAERS) database with spinosad topical suspension 0.9% in the pediatric population (0 - <17 years) during the period of July 1, 2012 (date of last DPV review) through January 18, 2018. We identified one case with an unlabeled event and a serious outcome, but the case lacked sufficient clinical details (e.g., concomitant medications, dechallenge/rechallenge information) which precluded a more definitive causality assessment. For completeness, we searched the FAERS database for cases of rash pruritic reported with spinosad topical suspension 0.9% use for all age groups. Our search did not identify any additional cases. Overall, there were no new safety signals identified, no increased severity or frequency of any labeled adverse event, and no reported deaths associated with spinosad topical suspension 0.9%.

There is no evidence from these data that there are new pediatric safety concerns with spinosad topical suspension 0.9% at this time. DPV will continue to monitor adverse events associated with the use of spinosad topical suspension 0.9%.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Natroba (spinosad topical suspension 0.9%) is a pediculicide approved on January 18, 2011 for the treatment of head lice infestation in patients 4 years or older. Spinosad causes neuronal excitation in insects, leading to paralysis and death. At the time of approval, the most common adverse events reported in clinical studies were application site erythema, ocular erythema, and application site irritation.[1]

On October 3, 2012, the Division of Pharmacovigilance I (DPV I) reviewed post-marketing reports of adverse events associated with the use of spinosad topical suspension 0.9% in pediatric patients (0-16 years of age) in accordance with the Pediatric Research Equity Act (PREA).[2] The FAERS database was searched for all reports of adverse events (serious and non-serious) from date of approval through June 30, 2012. The review did not identify any death cases or other serious outcomes. Overall, there were no new safety concerns.[2]

On December 30, 2014, spinosad topical suspension 0.9% was approved for use in patients 6 months and older. This approval was based on a pharmacokinetic and safety study in pediatric patients ages 6 months to 4 years of age with active head lice infestation. No new safety issues were identified and the most common adverse events reported during this study were pyrexia, application site pruritus, and erythema. However, safety in pediatric patients below the age of 6 months has not been established.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

----------WARNINGS AND PRECAUTIONS----------
Benzyl al recommended in infants below the age of 6 months; potential for increased systemic absorption. (5.1)
----------ADVERSE REACTIONS----------
Most common adverse events (>1%) were application site erythema and ocular erythema. (6.1)

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in **Table 1**. See **Appendix A** for a description of the FAERS database.

Table 1. FAERS Search Strategy	
Date of Search	January 16, 2018
Time Period of Search	July 1, 2012* - January 16, 2018
Search Type	FBIS Quick Query
Product Active Ingredient	Spinosad
Search Parameters	All ages, all outcomes, worldwide

** End date of last DPV pediatric review*

3 RESULTS

3.1 TOTAL NUMBER OF FAERS REPORTS BY AGE

Table 2. Total Adult and Pediatric FAERS reports July 1, 2012 – Jan 16, 2018 with Spinosad Topical Suspension 0.9%

	All cases (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	1 (1)	0 (0)	0 (0)
Pediatrics (0 - <17 years)	8 (8)	1 (1)	0 (0)
Age Unknown	1 (1)‡	0 (0)	0 (0)

† 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.
‡ Case described an adult patient

3.2 SELECTION OF SERIOUS PEDIATRIC CASES IN FAERS

We identified eight pediatric FAERS cases, only one of which reported a serious outcome.

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

There were no FAERS cases with an outcome of death in any age group.

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=1)

3.4.1 Unlabeled Event: Rash Pruritic (n=1)

FAERS Case# 9970475 describes a 7-year-old female patient that developed a rash from head to toe one day after applying spinosad topical solution 0.9% on her scalp. The reporter described the rash as "itchy as hives" with the patient's cheeks appearing "like they have been burnt". The patient's rash improved after treatment with diphenhydramine and steroid cream, but was not reported as resolved. Patient's medical history was significant for head lice. No concomitant medications were reported.

Reviewer comments: Time to onset suggestive of an association, but missing information (e.g. concomitant medications, dechallenge/rechallenge information) precludes a more definitive assessment. For completeness, we searched the FAERS database for cases of pruritic rash reported with spinosad use for all age groups. Our search did not identify any additional cases.

4 DISCUSSION

We reviewed all serious FAERS reports with topical suspension 0.9% in the pediatric population (0 - <17 years) during the period of July 1, 2012 (date of last DPV review) through January 18, 2018. We identified one pediatric case with an unlabeled event and a serious outcome. However, the case lacked sufficient clinical details (e.g., concomitant medications, dechallenge/rechallenge information) which precluded a more definitive

causality assessment. For completeness, we searched the FAERS database for cases of rash pruritic reported with spinosad use for all age groups. Our search did not identify any additional cases. Overall, there were no new safety signals identified, no increased severity or frequency of any labeled adverse event, and no reported deaths associated with spinosad topical suspension 0.9%.

5 CONCLUSION

There is no evidence from these data that there are any pediatric safety concerns with spinosad topical suspension 0.9% at this time.

6 RECOMMENDATIONS

DPV I recommends no regulatory action at this time, and will continue to monitor adverse events associated with the use of spinosad.

7 REFERENCES

1. Natroba (spinosad) Topical Suspension, 0.9% Prescribing Information. ParaPRO LLC. Carmel, Indiana. May 2011.
2. Weintraub J. Pediatric Postmarket Adverse Event Review. Natroba (spinosad) Topical Suspension, 0.9%. October 3, 2012.

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 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.

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