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:	May 22, 2024
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Product Name:	Natroba (spinosad) topical suspension
Pediatric Labeling Approval Date:	April 28, 2021
Application Type/Number:	NDA 022408/0010
Applicant:	ParaPRO, LLC
TTT Record ID:	2024-9177

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Natroba (spinosad) topical suspension in pediatric patients less than 18 years of age. 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 spinosad in pediatric patients.

Natroba (spinosad) topical suspension was initially approved as a pediculicide in the U.S. on January 18, 2011, for the topical treatment of head lice infestations in patients aged 4 years and older. On December 30, 2014, FDA approved the use of spinosad for the topical treatment of head lice infestations in patients aged 6 months and older. On April 28, 2021, FDA approved the expansion of the spinosad indication for use as a scabicide for the treatment of scabies infestations in adult and pediatric patients aged 4 years and older.

This pediatric postmarketing safety review was stimulated by pediatric labeling on April 28, 2021. DPV previously performed two pediatric postmarketing pharmacovigilance reviews for spinosad. The reviews were presented before the Pediatric Advisory Committee on March 14, 2013, as a live presentation, and on June 18, 2018, via webposting. Neither review identified new safety concerns with spinosad in pediatric patients, and DPV recommended continued routine pharmacovigilance with spinosad.

DPV reviewed all serious FAERS reports with spinosad in pediatric patients less than 18 years of age from January 16, 2018 through April 22, 2024, and identified no pediatric reports.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with spinosad in pediatric patients less than 18 years of age.

DPV did not identify any new pediatric safety concerns for spinosad at this time and will continue routine pharmacovigilance monitoring for spinosad.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Natroba (spinosad) topical suspension in pediatric patients less than 18 years of age. 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 spinosad in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Natroba (spinosad) topical suspension was initially approved as a pediculicide in the U.S. on January 18, 2011, for the topical treatment of head lice infestations in patients aged 4 years and older.[1] On December 30, 2014, FDA approved the use of spinosad for the topical treatment of head lice infestations in patients aged 6 months and older. On April 28, 2021, FDA approved the expansion of the spinosad indication for use as a scabicide for the treatment of scabies infestations in adult and pediatric patients aged 4 years and older.[2]

This pediatric postmarketing safety review was stimulated by pediatric labeling on April 28, 2021. DPV previously performed two pediatric postmarketing pharmacovigilance reviews for spinosad. The reviews were presented before the Pediatric Advisory Committee on March 14, 2013, as a live presentation,[3] and on June 18, 2018, via webposting.[4] Neither review identified new safety concerns with spinosad in pediatric patients, and DPV recommended continued routine pharmacovigilance with spinosad.

1.2 RELEVANT LABELED SAFETY INFORMATION

The spinosad labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional spinosad labeling information, please refer to the full prescribing information.[2]

> ----------CONTRAINDICATIONS----------
> None. (4)
>
> ----------WARNINGS AND PRECAUTIONS----------
> Benzyl Alcohol Toxicity: Not recommended in infants below the age of 6 months; potential for increased systemic absorption. (5.1)
>
> ----------ADVERSE REACTIONS----------
> Most common adverse events for lice treatment (>1%) were application site erythema and ocular erythema. (6.1)
> Most common adverse reactions for scabies treatment (>1%) were application site irritation (pain and burning) and dry skin. (6.1)
>
> 8.4 Pediatric Use
>
> Head Lice Infestation
>
> The safety and effectiveness of NATROBA for the topical treatment of head lice infestation have been established in pediatric patients 6 months of age and older [see Clinical Pharmacology (12.3) and Clinical Studies (14)].

NATROBA is not recommended in pediatric patients below the age of 6 months because of the potential for increased systemic absorption due to a high ratio of skin surface area to body mass and the potential for an immature skin barrier.

NATROBA contains benzyl alcohol. Intravenous administration of benzyl alcohol has been associated with serious adverse reactions and death in neonates and low birth-weight infants. The "gasping syndrome" (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birthweight infants when administered intravenously. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse.

The minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birthweight infants, as well as patients receiving high dosages of benzyl alcohol, may be more likely to develop toxicity [see Warning and Precautions (5.1)].

Scabies Infestation

The safety and effectiveness of NATROBA for the topical treatment of scabies infestation have been established in pediatric patients 4 years of age and older. Use of NATROBA in this age group is supported by Trial 1 and Trial 2 which included 165 pediatric subjects ages 4 to 17 years old with scabies infestation. The safety and efficacy were generally consistent between pediatric and adult patients. [see Clinical Pharmacology (12.3) and Clinical Studies (14)].

The safety and effectiveness of NATROBA have not been established in pediatric patients less than 4 years of age with scabies infestation.

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	April 23, 2024
Time period of search	January 16, 2018[†] through April 22, 2024
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product active ingredient: spinosad
MedDRA search terms (Version 26.1)	All Preferred Terms

* See **Appendix A** for a description of the FAERS database.
[†] Since data lock date of the FAERS search period for the most recently completed DPV pediatric postmarketing pharmacovigilance review for spinosad.
Abbreviations: 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 April 22, 2024, with spinosad.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From January 16, 2018 Through April 22, 2024, With Spinosad			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	2 (2)	1 (1)	0 (0)
Pediatrics (0 - < 18 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 U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved no pediatric reports from January 16, 2018 through April 22, 2024.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

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

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

4 DISCUSSION

DPV reviewed all serious FAERS reports with spinosad in pediatric patients less than 18 years of age from January 16, 2018 through April 22, 2024, and identified no pediatric reports.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with spinosad in pediatric patients less than 18 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for spinosad at this time and will continue routine pharmacovigilance monitoring for spinosad.

6 REFERENCES

1. Natroba (spinosad) topical suspension, 0.9% for topical use. [Prescribing information]. Carmel, IN; ParaPRO, LLC: December 2014.
2. Natroba (spinosad) topical suspension. [Prescribing information]. Carmel, IN; ParaPRO, LLC: April 2021.
3. Pediatric Advisory Committee. Meeting Minutes. March 14, 2013. Available at: https://wayback.archive-it.org/7993/20170406202258/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM351116.pdf
4. Mohamoud, M. NDA 22408. Pediatric Postmarketing Pharmacovigilance Review. March 28, 2018. Available at: https://www.fda.gov/media/114093/download

7 APPENDICES

7.1 APPENDIX A. 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 terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

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 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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