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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

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Seysara (sarecycline) in pediatric patients through age 16 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 U.S. serious unlabeled adverse events associated with sarecycline in pediatric patients.

Seysara is a tetracycline drug approved in the U.S. on October 1, 2018, for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older.

This pediatric postmarketing pharmacovigilance review was prompted by the approval of sarecycline on October 1, 2018.

DPV reviewed all U.S. serious FAERS reports with sarecycline in the pediatric population (ages 0 – 16 years) from October 1, 2018, through September 15, 2022. We identified a singular case reporting an unlabeled event of an anaphylactic reaction. The additional evaluation of the FAERS database and medical literature did not identify sufficient evidence to support a signal of anaphylactic reactions with sarecycline at this time. We identified no new safety signals and no deaths directly associated with sarecycline.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Seysara (sarecycline) in pediatric patients through age 16 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 U.S. serious unlabeled adverse events associated with sarecycline in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Seysara is a tetracycline drug approved in the U.S. on October 1, 2018, for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older. Evidence of efficacy for use in patients 9 years and older came from clinical studies whose study design and findings are summarized below from the sarecycline Multidisciplinary Review.[1]

> "Sarecycline was evaluated in 14 phase 1 clinical studies (in healthy subjects and in patients with impaired hepatic or renal function), as well as a phase 2 dose ranging study, 2 pivotal phase 3 clinical trials, and a long-term extension safety study in patients with moderate to severe acne vulgaris. Two multicenter, randomized, double-blind, placebo-controlled, pivotal phase 3 clinical trials compared sarecycline tablets (60 mg, 100 mg, and 150 mg) and placebo tablets administered orally once daily for 12 weeks in a total of 2002 patients (intent-to-treat population) 9 to 45 years of age with moderate to severe acne vulgaris (Studies SC1401 and SC1402). The pivotal clinical trials enrolled subjects with moderate to severe acne vulgaris (Investigator Global Assessment (IGA) score ≥3 [moderate], 20-50 inflammatory lesions, ≤100 noninflammatory lesions) with a co-primary efficacy endpoint of absolute change from baseline in inflammatory lesions counts and the proportion of subjects with an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-point decrease from baseline at Week 12.
>
> The results for the co-primary efficacy endpoints showed sarecycline was statistically superior to vehicle for both co-primary efficacy endpoints at Week 12.
>
> Pooled safety data included all subjects receiving sarecycline; N=2133 total (sarecycline N=1064 and N=1069 for placebo). 295 of 1064 patients (27.7%) receiving sarecycline and 312 of 1069 patients (29.2%) receiving placebo reported at least 1 treatment emergent adverse event (TEAE). The most common TEAEs were headache (3.1% in sarecycline versus 4.3% in placebo), nasopharyngitis (2.8% versus 2.6%), nausea (3.1% versus 2.0%), upper respiratory tract infection (1.6% versus 1.5%), blood creatine phosphokinase (CPK) increased (1.2% versus 1.3%), diarrhea (1.0% versus 1.3%), vomiting (1.3% versus 0.9%), oropharyngeal pain (1.0% versus 0.9%), urinary tract infection, dizziness, and cough (each 0.5% versus 1.0%). Vulvovaginal mycotic infections and vulvovaginal candidiasis were ≤1% and more frequent in sarecycline-treated females (0.8% [5 of 618]) than in placebo (0 of 610). Vestibular TEAEs (dizziness, vertigo, tinnitus, nausea, and vomiting) occurred more frequently in the sarecycline group [4.5% (48 patients)] compared with placebo [3.5% (37 patients)]. Tinnitus did not occur in either treatment group. [sic] The incidences of treatment-emergent serious adverse events (SAEs) were similar in the sarecycline and

placebo groups (0.7% versus 0.6% respectively). Similarly, the incidence of TEAEs that led to patient discontinuation was the same in both treatment groups (1.3%). The open-label long-term extension study provided supportive safety data. Sarecycline, as a tetracycline class antibiotic, should not be used in children ≤8 years of age due to risk of permanent discoloration of teeth and interference with bone growth/formation. Sarecycline should not be taken during pregnancy or breastfeeding."

This pediatric postmarketing pharmacovigilance review was prompted by the approval of sarecycline on October 1, 2018. DPV has not previously presented sarecycline to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The sarecycline labeling contains the following safety information excerpted from the Highlights section of the labeling as well as the Pediatric Use subsection.[2] For further labeling information, please refer to the full prescribing information.

----------CONTRAINDICATIONS----------

SEYSARA is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines. (*4*)

----------WARNINGS AND PRECAUTIONS----------

- The use of SEYSARA during tooth development (second and third trimesters of pregnancy, infancy, and childhood up to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). (*5.1*)
- If Clostridium difficile Associated Diarrhea (antibiotic associated colitis) occurs, discontinue SEYSARA. (*5.2*)
- Central nervous system side effects, including light-headedness, dizziness or vertigo, have been reported with tetracycline use. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery. These symptoms may disappear during therapy and may disappear when the drug is discontinued. (*5.3*)
- SEYSARA may cause intracranial hypertension. Discontinue SEYSARA if symptoms occur. (*5.4*)
- Photosensitivity can occur with SEYSARA. Patients should minimize or avoid exposure to natural or artificial sunlight. (*5.5*)

----------ADVERSE REACTIONS----------

Most common adverse reaction (incidence ≥ 1%) is nausea. (*6.1*)

----------USE IN SPECIFIC POPULATIONS----------

- Sarecycline, like other tetracycline-class drugs, can cause fetal harm when administered to a pregnant woman. (*5.1*, *8.1*)
- The use of drugs of the tetracycline class during tooth development may cause permanent discoloration of teeth. (*5.1*, *8.4*)
- Lactation: Breastfeeding is not recommended. (*8.2*)

8.4 Pediatric Use

The safety and effectiveness of SEYSARA have been established in pediatric patients 9 years of age and older for the treatment of moderate to severe inflammatory lesions of non-nodular acne vulgaris *[see Pharmacokinetics (12.3) and Clinical Studies (14)]*.

Safety and effectiveness of SEYSARA in pediatric patients below the age of 9 years has not been established. Use of tetracycline-class antibiotics below the age of 8 is not recommended due to the potential for tooth discoloration *[see Warnings and Precautions (5.1)]*.

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	September 16, 2022
Time period of search	October 1, 2018† - September 15, 2022
Search type	RxLogix PV Signal Quick Query
Product terms	Product Active Ingredient: sarecycline; sarecycline hydrochloride
MedDRA search terms (Version 25.0)	All PT terms
* See Appendix A for a description of the FAERS database. † U.S. Approval Date Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, 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 from October 1, 2018, through September 15, 2022, with sarecycline.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From October 1, 2018, through September 15, 2022 with Sarecycline			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	8 (7)	7 (7)	0 (0)
Pediatrics (0 - <17 years)	3 (3)	2 (2)	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 two U.S. serious pediatric reports from October 1, 2018, through September 15, 2022. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded one report because no adverse event was described, and we included the remaining case for discussion. Appendix B contains a line listing of this case.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event cases with sarecycline.

3.1.4 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=1)

We identified one serious FAERS case with sarecycline in the U.S. pediatric population reporting a non-fatal outcome. The case is summarized below.

FAERS #19806099 involves a 13-year-old-female on sarecycline 100 mg for an unknown indication. The patient experienced an "anaphylactic reaction" 20 minutes after taking her first tablet of sarecycline and was taken to the hospital for treatment. Of note, the patient had taken minocycline and doxycycline in the past with no issues.

Reviewer's comment: Anaphylactic reactions are serious clinical conditions that may be caused by any medication, with a higher prevalence seen with antibiotics[3] Although the narrative describes a temporal relationship between sarecycline exposure and anaphylaxis, there is missing information regarding other exposures, past medical history, and information about other known allergens. The case also did not provide the clinical signs and symptoms associated with anaphylaxis, nor the treatment and outcome. A search of the FAERS database performed on September 16, 2022, for reports with the MedDRA PT "Anaphylactic reaction" and Higher Level Group Term "Allergic conditions" with sarecycline in patients of all ages did not identify any additional cases describing anaphylactic reactions with sarecycline. Additionally, we performed a search of the medical literature for sarecycline and anaphylactic reaction that also did not result in any cases. Because this is a singular case with missing clinical details, we do not have sufficient evidence to support a signal of anaphylactic reactions with sarecycline at this time.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with sarecycline in the pediatric population (ages 0 – 16 years) from October 1, 2018, through September 15, 2022. We identified a singular case reporting an unlabeled event of an anaphylactic reaction. An additional evaluation of the FAERS database and medical literature did not identify sufficient evidence to support a signal of

anaphylactic reactions with sarecycline at this time. We identified no new safety signals and no deaths directly associated with sarecycline.

5 CONCLUSION

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

6 RECOMMENDATION

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

7 REFERENCES

1. Chiang G. NDA/BLA Multi-Disciplinary Review and Evaluation of Seysara (sarecycline) tablets. September 2018. https://www.fda.gov/media/124116/download.
2. Seysara® (sarecycline) tablets for oral use. [Prescribing Information]. Exton, PA: Almirall, LLC; June 2020.
3. Regateiro FS, Marques ML, Gomes ER. Drug-Induced Anaphylaxis: An Update on Epidemiology and Risk Factors. Int Arch Allergy Imm. 2020;181(7):481-7.

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	09/08/2021	19806099	1	US-ALMIRALL, LLC-2021AQU000394	15-Day	13	Female	USA	HO

*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.
Abbreviations: HO=hospitalization, USA= United States of America

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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/

OMAYMA A KISHK
11/04/2022 10:45:45 AM

IVONE E KIM
11/04/2022 11:07:30 AM

CARMEN CHENG
11/04/2022 11:10:05 AM

CINDY M KORTEPETER
11/04/2022 12:19:26 PM