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 29, 2026
Reviewers:	Faye Rozwadowski, MD, Medical Officer Miriam Chehab, PharmD, BCPPS, Safety Evaluator Division of Pharmacovigilance II Ivone Kim, MD, Medical Officer Division of Pharmacovigilance I
Team Leader:	Lynda McCulley, PharmD, BCPS Division of Pharmacovigilance II
Deputy Division Director:	Sara Camilli, PharmD, BCPS Division of Pharmacovigilance II
Product Name:	Nextstellis (drospirenone/estetrol)
Pediatric Labeling Approval Date:	April 15, 2021
Application Type/Number:	NDA 214154
Applicant:	Mayne Pharma LLC
TTT Record ID:	2026-20025

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Nextstellis (drospirenone/estetrol) 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 United States (U.S.) serious unlabeled adverse events associated with drospirenone/estetrol in pediatric patients.

Nextstellis (drospirenone/estetrol) is a combination hormonal contraceptive, initially FDA approved on April 15, 2021. Drospirenone/estetrol is currently indicated for use by females of reproductive potential to prevent pregnancy.

This pediatric postmarketing safety review was prompted by the pediatric labeling on April 15, 2021, which was part of the original approval for drospirenone/estetrol.

DPV reviewed all U.S. serious FAERS reports with drospirenone/estetrol in pediatric patients less than 18 years of age from April 15, 2021, through March 26, 2026, and identified one report; however, this report was excluded from further discussion because it described a labeled adverse event that did not represent increased severity.

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

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Nextstellis (drospirenone/estetrol) 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 United States (U.S.) serious unlabeled adverse events associated with drospirenone/estetrol in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Nextstellis (drospirenone/estetrol) is a combination hormonal contraceptive and was initially FDA approved on April 15, 2021. Drospirenone/estetrol is currently indicated for use by females of reproductive potential to prevent pregnancy.[1]

This pediatric postmarketing safety review was prompted by the pediatric labeling on April 15, 2021, which was part of the original approval for drospirenone/estetrol.

A pediatric safety review for drospirenone/estetrol has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The drospirenone/estetrol labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional drospirenone/estetrol labeling information, please refer to the full prescribing information.[1]

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning.

- **Females over 35 years old who smoke should not use NEXTSTELLIS (4)**
- **Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. (4)**

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

- A high risk of arterial or venous thrombotic diseases (4)
- Breast cancer or history of breast cancer (4)
- Hepatic adenoma, hepatocellular carcinoma, acute hepatitis or decompensated cirrhosis (4)
- Co-administration with hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (4, 7.1)
- Abnormal uterine bleeding that has an undiagnosed etiology (4)
- Renal impairment (4)
- Adrenal insufficiency (4)

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

- Thromboembolic Disorders and Other Vascular Problems: Stop NEXTSTELLIS if a thrombotic or thromboembolic event occurs. Start no earlier than 4 weeks after delivery. Consider all cardiovascular risk factors before initiating in any female, particularly in the presence of multiple risk factors. (5.1)
- Hyperkalemia: Check serum potassium concentration during the first NEXTSTELLIS treatment cycle in females on long-term treatment with medications that may increase serum potassium concentration. (5.2, 7.2)
- Hypertension: Monitor blood pressure periodically and stop use if blood pressure rises significantly. (5.3)
- Migraine: Discontinue if new, recurrent, persistent, or severe migraines occur. (5.4)
- Hormonally-Sensitive Malignancy: Discontinue NEXTSTELLIS if a hormonally-sensitive malignancy is diagnosed. (5.5)
- Liver Disease: Withhold or permanently discontinue for persistent or significant elevation of liver enzymes. (5.6)
- Glucose Tolerance and Hypertriglyceridemia: Monitor glucose in females with prediabetes or diabetes. Consider an alternate contraceptive method for females with hypertriglyceridemia. (5.8)
- Gallbladder Disease and Cholestasis: Consider discontinuing NEXTSTELLIS in females with symptomatic gallbladder or cholestatic disease. (5.9)
- Bleeding Irregularities and Amenorrhea: May cause irregular bleeding or amenorrhea. Evaluate for other causes if symptoms persist. (5.11)

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

Most common adverse reactions (≥2%): bleeding irregularities, mood disturbance, headache, breast symptoms, dysmenorrhea, acne, weight increased, and libido decreased (6)

8.4 Pediatric Use

Safety and efficacy of NEXTSTELLIS have been established in females of reproductive potential. The study population of C302 [see Clinical Studies (14)] was in females of reproduction age 16-50 years of age. Use of NEXTSTELLIS before menarche is not indicated.

2 METHODS AND MATERIALS

DPV searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*

Date of search	March 27, 2026
Time period of search	April 15, 2021† – March 26, 2026
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product term	PAI: Drospirenone\estetrol monohydrate
MedDRA search terms (Version 28.1)	All Preferred Terms

* See **Appendix A** for a description of the FAERS database.

† U.S. approval date.

Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities, PAI = Product Active Ingredient

3 RESULTS

3.1 SELECTION OF U.S. SERIOUS PEDIATRIC CASES IN FAERS

Our FAERS search retrieved one U.S. serious[a] pediatric report for patients less than 18 years old from April 15, 2021, through March 26, 2026. There were zero reports with the outcome of death. We excluded the one report from the case series for the reason described below:

- Labeled adverse event not representing increased severity (n=1)

After excluding the report as described above, no cases remained for discussion.

3.2 SUMMARY OF U.S. FATAL PEDIATRIC CASES (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.3 SUMMARY OF U.S. SERIOUS NON-FATAL PEDIATRIC CASES (N=0)

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

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with drospirenone/estetrol in pediatric patients less than 18 years of age from April 15, 2021, through March 26, 2026, and identified one report; however, this report was excluded from further discussion.

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

5 CONCLUSION

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

[a] 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.

6 REFERENCES

1. Nextstellis (drospirenone/estetrol) [package insert]. Greenville, NC: Mayne Pharma LLC; April 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214154s002lbl.pdf

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 is consistent with international safety reporting guidance issued by the International Council on Harmonisation and adheres to FDA guidance on adverse event reporting. 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.