Department of Health and Human Services
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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:	June 5, 2023
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Product Name:	Annovera (segesterone acetate and ethinyl estradiol)
Pediatric Labeling Approval Date:	August 10, 2018
Application Type/Number:	NDA 209627
Applicant:	Mayne Pharma LLC
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TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Annovera (segesterone acetate and ethinyl estradiol) in pediatric patients less than 18 years of age. 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 United States (U.S.) serious unlabeled adverse events associated with Annovera in pediatric patients.

The FDA approved Annovera on August 10, 2018, and it is indicated for the prevention of pregnancy in females of reproductive potential. The safety and efficacy of Annovera have been established in females of reproductive potential and are expected to be the same for post-menarchal females less than 18 years of age as for users 18 years of age and older. Annovera use before menarche is not indicated.

DPV searched FAERS for all reports with Annovera in pediatric patients less than 18 years of age from August 10, 2018 - January 31, 2023, and three reports were identified; however, all three were excluded from further discussion. There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths that could be attributed to Annovera in pediatric patients less than 18 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Annovera (segesterone acetate and ethinyl estradiol) in pediatric patients less than 18 years of age. 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 United States (U.S.) serious unlabeled adverse events associated with Annovera in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Annovera was FDA approved on August 10, 2018, and is a silicone elastomer vaginal system containing 103 mg of segesterone acetate and 17.4 mg of ethinyl estradiol, which releases on average 0.15 mg/day of segesterone acetate and 0.013 mg/day of ethinyl estradiol. It is indicated for the prevention of pregnancy in females of reproductive potential. Annovera is administered via intravaginal insertion and must remain in place continuously for 3-weeks (21-days), followed by a 1-week (7-day) Annovera-free interval. The removed Annovera should be cleaned with mild soap and warm water, patted dry with a clean cloth towel or paper towel, and placed in its case during the 1-week (7-day) Annovera-free interval. At the end of the 1-week (7-day) Annovera-free interval, the vaginal system should be cleaned prior to being placed back in the vagina for another 3-week (21-day) cycle. One single Annovera vaginal system provides contraception for 13-cycles.[1]

The safety and efficacy of Annovera have been established in females of reproductive potential and are expected to be the same for post-menarchal females less than 18 years of age as for users 18 years of age and older. Annovera use before menarche is not indicated.[1, 2]

The efficacy of Annovera was evaluated in two 1-year multi-center trials that enrolled 2,265 sexually active females from 18 to 40 years of age with regular menstrual cycles. The trials were conducted internationally, and included the U.S., Australia, Brazil, Chile, Dominican Republic, Finland, Hungary, and Sweden. The mean age was 26.7 years, and the mean body mass index (BMI) was 24.1 kg/m^2 (range: 16.0, 41.5). Of note, at approximately 50% total enrollment, women with a BMI > 29.0 kg/m^2 were no longer enrolled in the two trials and all women with a BMI > 29.0 kg/m^2 were discontinued from the trials. Based on pooled data from the two trials, 2,111 females ≤ 35 years of age completed 17,427 evaluable 28-day cycles (i.e., cycles in which no back-up contraception was used). The pooled pregnancy rate, as evaluated by the Pearl Index, was 2.98 (95% Confidence Interval: 2.13, 4.06) per 100 woman-years of Annovera use.[1]

The pediatric study requirement for pre-menarchal females from birth to 11 years of age and all males was waived by FDA because necessary studies were determined to be highly impractical or impossible.[2, 3] Additionally, no other safety concerns specific to the pediatric patient population were identified pre-approval.[2] Therefore, the extrapolation of the adult safety and efficacy data was determined to be acceptable for the adolescent post-menarchal female population.[1, 2, 3]

Of note, this is the first pediatric postmarketing review for the Pediatric Advisory Committee being completed by DPV for Annovera.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Annovera labeling provides the following relevant safety information (excerpted from the pertinent sections). For additional Annovera labeling information, please refer to the full prescribing information.[1]

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

- A high risk of arterial or venous thrombotic diseases (4)
- Breast cancer (4)
- Liver tumors, acute hepatitis, or severe (decompensated) cirrhosis (4)
- Undiagnosed abnormal uterine bleeding (4)
- Hypersensitivity to any of the components of ANNOVERA (4)
- Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (4)

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

- Thrombotic Disorders and Other Vascular Problems: Stop Annovera if a thrombotic or thromboembolic event occurs. Stop Annovera at least 4 weeks before and through 2 weeks after major surgery. Start Annovera no earlier than 4 weeks after delivery, in females who are not breastfeeding. Consider cardiovascular risk factors before initiating in all females, particularly those over 35 years. (5.1, 5.5)
- Liver Disease: Discontinue if jaundice occurs. (5.2)
- Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment: Stop Annovera prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir. Annovera can be restarted 2 weeks following completion of this regimen. (5.3)
- Hypertension: Do not prescribe Annovera for females with uncontrolled hypertension or hypertension with vascular disease. If used in females with well-controlled hypertension, monitor blood pressure and stop use if blood pressure rises significantly. (5.4)
- Carbohydrate and lipid metabolic effects: Monitor glucose in prediabetic and diabetic females taking Annovera. Consider an alternate contraceptive method for females with uncontrolled dyslipidemias. (5.7)
- Headache: Evaluate significant change in headaches and discontinue Annovera if indicated. (5.8)
- Bleeding Irregularities and Amenorrhea: May cause irregular bleeding or amenorrhea. Evaluate for other causes if irregular bleeding or amenorrhea persists. (5.9)

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

The most common adverse reactions (> 5%) are headache/migraine, nausea/vomiting, vulvovaginal mycotic infection/candidiasis, abdominal pain lower/upper, dysmenorrhea, vaginal discharge, urinary tract infection, breast tenderness/pain/discomfort, bleeding irregularities including metrorrhagia, diarrhea, genital pruritus. (6)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Safety and efficacy of Annovera have been established in women of reproductive age. Efficacy is expected to be the same for postpubertal adolescents under the age of 18 as for users 18 years and older. Use of Annovera before menarche is not indicated.

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	February 1, 2023
Time period of search	August 10, 2018† - January 31, 2023
Search types	RxLogix PV Reports Profile Report and RxLogix PV Reports Quick Query
Product term	PAI: Ethinyl estradiol\segesterone acetate
MedDRA search terms (Version 25.1)	All MedDRA PTs
* See **Appendix A** for a description of the FAERS database † U.S. approval date for Annovera **Abbreviations:** MedDRA = Medical Dictionary for Regulatory Activities, PAI = Product Active Ingredient, PT = Preferred Term, U.S. = United States	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

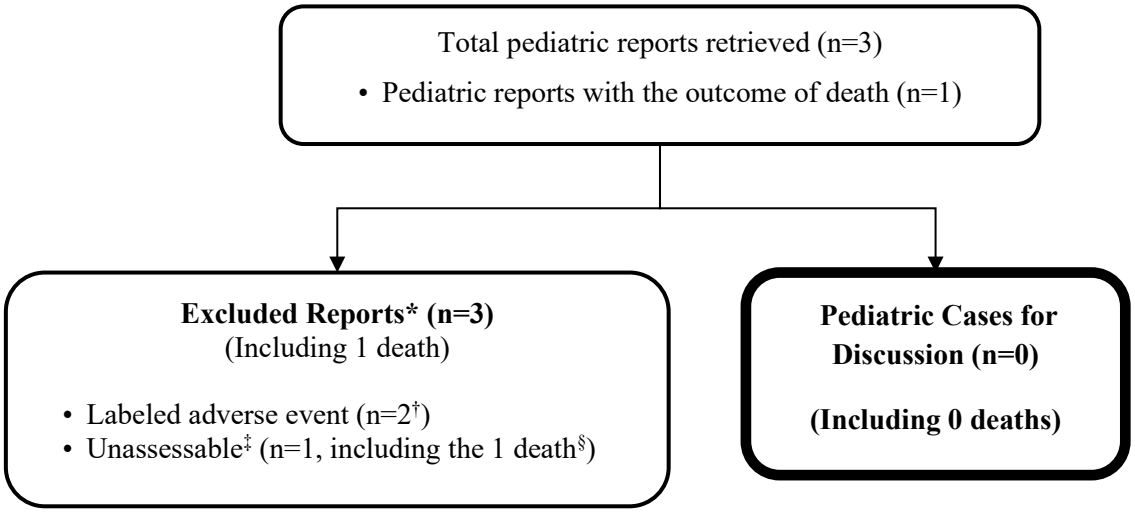
Table 2 presents the number of adult and pediatric FAERS reports from August 10, 2018 - January 31, 2023, with Annovera.

Table 2. Total Adult and Pediatric FAERS Reports*† Received by FDA From August 10, 2018 - January 31, 2023, With Annovera			
	All reports (U.S.)	**Serious‡ (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	70 (70)	20 (20)	0 (0)
Pediatrics (0 - < 18 years)	3 (3)	1 (1)	1 (1)
* May include duplicates and have not been assessed for causality † No transplacental exposure reports were identified ‡ 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 event			

3.1.2 Selection of Pediatric Cases in FAERS

Our FAERS search retrieved three pediatric reports from August 10, 2018 - January 31, 2023, with Annovera. We reviewed these three FAERS reports and excluded all three from further discussion because they either described labeled adverse events (n=2) or because the report was unassessable (n=1). **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of Pediatric Cases with Annovera



* DPV reviewed these reports, but they were excluded from further discussion for the reasons listed in **Figure 1** above.
† The labeled adverse events included dysmenorrhea (report 1) and both vomiting and Annovera expulsion (report 2).
‡ Unassessable: The report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome) or the information is contradictory or information provided in the report cannot be supplemented or verified.
§ The sole report with an outcome of death in a 16-year-old female provided limited information (e.g., cause of death was not reported, concomitant medications were not reported, date of Annovera initiation/use was not reported) precluding our assessment of the report.

3.1.3 Summary of Fatal Pediatric Cases (n=0)

There are no fatal pediatric adverse event cases for further discussion.

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

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

4 DISCUSSION

DPV searched FAERS for all reports with Annovera in pediatric patients less than 18 years of age from August 10, 2018 - January 31, 2023, and three reports were identified; however, all three were excluded from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths that could be attributed to Annovera in pediatric patients less than 18 years of age.

5 CONCLUSION

DPV did not identify any new or unexpected pediatric safety concerns for Annovera at this time.

6 RECOMMENDATION

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

7 REFERENCES

[1] Annovera (segesterone acetate and ethinyl estradiol) vaginal system [package insert]. Boca Raton, FL: TherapeuticsMD, Inc.; April 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209627s003lbl.pdf
[2] U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Multi-Discipline Review and Evaluation of NDA 209627, Annovera (segesterone acetate and ethinyl estradiol) vaginal system. August 8, 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/209627Orig1s000MultidisciplineR.pdf
[3] U.S. Food and Drug Administration. NDA Approval Letter for NDA 209627, Annovera (segesterone acetate and ethinyl estradiol) vaginal system. August 10, 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/209627Orig1s000ltr.pdf

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.

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