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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

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Product Name:	Slynd (drospirenone)
Pediatric Labeling Approval Date:	May 23, 2019
Application Type/Number:	NDA 211367
Applicant:	Exeltis USA, Inc.
OSE RCM #:	2021-1522

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Slynd (drospirenone) in pediatric patients less than 17 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 all adverse events associated with Slynd in pediatric patients.

The FDA approved Slynd on May 23, 2019 and it is indicated for use by females of reproductive potential to prevent pregnancy. The safety and efficacy are expected to be the same for post-pubertal adolescents less than 16 years of age and users 16 years of age and older; the use of Slynd before menarche is not indicated.

We searched FAERS for all reports with Slynd in pediatric patients from May 23, 2019 through August 1, 2021 and a sole case was identified and included in our case series. Although this one case did report the occurrence of an unlabeled adverse event (i.e., hypersensitivity, and potentially anaphylaxis), the limited information precluded our ability to conduct a meaningful causality assessment. An additional cursory FAERS search completed on October 18, 2021, which included reports through October 17, 2021, utilizing the Preferred Terms (PTs) *Anaphylactic reaction*, *Anaphylactic shock*, *Anaphylactoid reaction*, *Anaphylactoid shock*, *Drug hypersensitivity*, and *Hypersensitivity* retrieved no additional relevant pediatric reports for review. Overall, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths associated with Slynd.

This review did not identify any new or unexpected pediatric safety concerns for Slynd. DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with Slynd use through routine pharmacovigilance.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Slynd (drospirenone) in pediatric patients less than 17 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 all adverse events associated with Slynd in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Slynd was FDA approved on May 23, 2019 and is an oral progestin indicated for use by females of reproductive potential to prevent pregnancy. The safety and efficacy are expected to be the same for post-pubertal adolescents less than 16 years of age and those 16 years of age and older; the use of Slynd before menarche is not indicated.[1] The FDA approval letter for Slynd noted that the Applicant had fulfilled the pediatric study requirement by assessing the product in females aged 12 years and older.[2]

Slynd consists of 24 white colored tablets each containing 4 milligrams of drospirenone and 4 green colored inert tablets. One of the white active tablets is taken daily for the first 24 days and one green inactive tablet is then taken daily for the 4 following days.[1]

The efficacy of Slynd was evaluated in Study CF111/303 (NCT02269241) and consisted of 953 females less than or equal to 35 years of age with 5,547 evaluable cycles. The demographic profile for females included a mean age of 26.4 years and a mean body mass index (BMI) of 28.5 kg/m^2, with a racial distribution of 53.3% Caucasian, 38.5% African American, 2.2% Asian, and 6% other. During these aforementioned cycles, a total of 17 females (1.8%) reported pregnancy, leading to a Pearl Index (95% confidence interval) of 4.0 (2.3, 6.4). One female who became pregnant during the study had been breastfeeding and was not included in the Pearl Index calculation. Out of the 953 females evaluated for efficacy, 332 females had a baseline BMI $\geq$ 30 (35%) and 173 females had a baseline BMI $\geq$ 35 (18%). Data were insufficient to analyze Pearl Index by BMI subgroups.[1, 3]

Vaginal bleeding patterns with Slynd were assessed using patient diaries in Study CF111/303 in adult females. The percentage of females experiencing scheduled bleeding/spotting or unscheduled bleeding/spotting decreased over time. The percentage of females with scheduled bleeding/spotting decreased from 81% in Cycle 1 to 26% in Cycle 13. Similarly, the percentage of females with unscheduled bleeding/spotting decreased from 61% in Cycle 1 to 40% in Cycle 13. The percentages of females with scheduled and unscheduled bleeding/spotting generally decreased through Cycle 10 and were maintained at a consistent amount thereafter.[1, 3]

Study CF111/304 was conducted in post-menarchal, adolescent females (12 through 17 years of age), and the vaginal bleeding data were generally consistent with those from Study CF111/303 (adult females). The percentage of adolescent females with scheduled bleeding/spotting decreased from 98.0% in Cycle 1 to 28.4% in Cycle 13. The percentage of adolescent females with scheduled bleeding/spotting generally decreased through Cycle 9 and was maintained at a consistent amount thereafter. In contrast, the percentage of adolescent females with unscheduled

bleeding/spotting was maintained at a relatively consistent amount during the study (53.0% in Cycle 1 versus 52.2% in Cycle 13).[1, 3]

Upon FDA approval of Slynd, a postmarketing requirement (PMR) was issued to assess the signal of bone loss given the anti-estrogenic effects of drospirenone (PMR 3631-1: A prospective, controlled, long-term trial to assess bone mineral density change in adults and adolescents taking Slynd compared to users of non-hormonal contraceptive methods; trial completion date of February 2023). No other safety concerns specific to the pediatric population were identified pre-approval.[2, 3]

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

1.2 RELEVANT LABELED SAFETY INFORMATION

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

---------- **CONTRAINDICATIONS** ----------

- Renal impairment (4)
- Adrenal insufficiency (4)
- Presence or history of progestin sensitive cancers (4)
- Liver tumors, benign or malignant, or hepatic impairment (4)
- Undiagnosed abnormal uterine bleeding (4)

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

- Hyperkalemia: Check serum potassium levels during the first treatment cycle in females receiving daily, long-term treatment for chronic conditions of diseases with medications that may increase serum potassium concentrations. (5.1)
- Thromboembolic disorders: Discontinue SLYND if a thromboembolic event occurs. (5.2)
- Bone loss: It is unknown if SLYND may cause a clinically relevant loss of bone mineral density. (5.3)
- Liver Disease: Discontinue use if jaundice or acute or chronic disturbances of liver function develops. (5.5)
- Ectopic pregnancy: Be alert to the possibility of ectopic pregnancy in females who become pregnant or complain of lower abdominal pain while on SLYND. (5.6)
- Risk of Hyperglycemia in Patients with Diabetes: Patients with diabetes may be at greater risk of hyperglycemia and may require additional medication adjustments or monitoring. (5.7)
- Bleeding Irregularities and Amenorrhea: May cause irregular bleeding or amenorrhea. Evaluate for other causes, such as pregnancy, if irregular bleeding or amenorrhea persists. (5.8)

---------- **ADVERSE REACTIONS** ----------

Most common adverse reactions (>1%) are: acne, metrorrhagia, headache, breast pain, weight increased, dysmenorrhea, nausea, vaginal hemorrhage, libido decreased, breast tenderness, menstruation irregular (6)

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

- Pregnancy: Discontinue SLYND if pregnancy occurs (8.1)

8 USE IN SPECIFIC POPULATIONS

8.4 *Pediatric Use*

Safety and efficacy of SLYND have been established in females of reproductive age. Safety and efficacy are expected to be the same for post-pubertal adolescents under the age of 16 and users 16 years and older.

Study CF111/304 evaluated the bleeding associated with SLYND in females ≥12 years of age. Bleeding data were generally consistent with those from Study CF111/303 in adult females [see *Clinical Studies* (*14*)].

Use of this product 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	August 27, 2021
Time period of search	May 23, 2019† - August 1, 2021
Search type	FBIS Quick Query and Product-Manufacturer Reporting Summary
Product terms	PAI: Drospirenone
MedDRA search terms (Version 24.0)	All MedDRA Preferred Terms
* See **Appendix A** for a description of the FAERS database † U.S. approval date for Slynd **Abbreviations:** FBIS = FAERS Business Intelligence Solution, MedDRA = Medical Dictionary for Regulatory Activities, PAI = Product Active Ingredient, 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 May 23, 2019 through August 1, 2021 with Slynd.

Table 2. Total Adult and Pediatric FAERS Reports*† Received by FDA From May 23, 2019 - August 1, 2021 With Slynd			
	All reports (U.S.)	**Serious‡ (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	56 (14)	48 (6)	3 (2)
Pediatrics (0 - < 17 years)	1 (0)	1 (0)	0 (0)
* 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 events			

3.1.2 Selection of Pediatric Cases in FAERS

Our FAERS search retrieved one pediatric case from May 23, 2019 through August 1, 2021 with Slynd.

We reviewed the sole FAERS pediatric case, and this case is summarized in **Section 3.1.4** below.

3.1.3 Summary of Fatal Pediatric Cases (n=0)

We did not identify any fatal pediatric adverse event cases.

3.1.4 Summary of Non-Fatal Pediatric Cases (n=1)

FAERS Case # 19186526/Version 1; Manufacturer Control # FR-EXELTIS PHARMACEUTICAL HOLDING, S.L.-2104FR00422; Foreign (France); 2021; Expedited (15-Day) Report; Serious Outcomes - Hospitalization, Other Serious
A 15-year-old female initiated treatment with Slinda (the foreign product equivalent to Slynd) for the prevention of pregnancy. Her relevant medical history included "digestive troubles" after previous use of a combination hormonal contraceptive. No other information regarding her medical history or concomitant medication(s) was reported. Approximately 2 days after the ingestion of her first Slinda tablet, the patient presented to the emergency department (ED) with abdominal pain, hives, nausea, rash, respiratory discomfort (exact type was not specified), and vomiting. Treatment for an allergic reaction was provided in the ED; however, the type of treatment she received was not reported. Additionally, no information was reported regarding the length of time in the ED, if hospital admission (beyond her stay in the ED) was necessary/occurred, the outcome of the reaction(s), or the action taken with Slinda (i.e., if Slinda treatment was continued or discontinued).

Reviewer Comments: This case reported the occurrence of a combination of symptoms consistent with a hypersensitivity reaction, and potentially anaphylaxis (i.e., involvement of the skin-mucosal tissue, respiratory symptoms, and gastrointestinal symptoms[4, 5]), neither of which are currently labeled adverse events for Slynd. However, the lack of information regarding the time to symptom onset (as opposed to the time of presentation to the ED), the limited details regarding what type of "digestive troubles" occurred with the prior use of a hormonal contraceptive, and the absence of information related to concomitant medications limits our ability to determine the presence of a drug-event association. An additional cursory FAERS search completed on October 18, 2021 (for reports in the FAERS database with the PAI drospirenone through October 17, 2021) utilizing the Preferred Terms (PTs) Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Anaphylactoid shock, Drug hypersensitivity, and Hypersensitivity retrieved no additional relevant pediatric reports for review.

4 DISCUSSION

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths associated with Slynd in pediatric patients less than 17 years of age.

We searched FAERS for all reports with Slynd in pediatric patients less than 17 years of age from May 23, 2019 through August 1, 2021, and a sole case was identified and included in our case series. Although this one case did report the occurrence of an unlabeled adverse event (i.e., hypersensitivity, and potentially anaphylaxis), the limited information precluded our ability to conduct a meaningful causality assessment. An additional cursory FAERS search completed on October 18, 2021, which included reports through October 17, 2021, utilizing the PTs *Anaphylactic reaction*, *Anaphylactic shock*, *Anaphylactoid reaction*, *Anaphylactoid shock*, *Drug hypersensitivity*, and *Hypersensitivity* retrieved no additional relevant pediatric reports for review.

5 CONCLUSION

DPV did not identify any new or unexpected pediatric safety concerns for Slynd in this review.

6 RECOMMENDATION

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

7 REFERENCES

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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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