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Pediatric Postmarketing Pharmacovigilance Review

Date:	February 24, 2025
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Product Name:	Liletta (levonorgestrel-releasing intrauterine system)
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Applicant:	Medicines360
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EXECUTIVE SUMMARY

Liletta (levonorgestrel-releasing intrauterine system) is a progestin-containing intrauterine system initially approved in the U.S. on February 26, 2015, for the prevention of pregnancy in women of reproductive age.

Since initial approval, Liletta underwent five labeling changes that reflect the expansion of its indication. Liletta is currently approved for 1) prevention of pregnancy for up to 8 years and 2) treatment of heavy menstrual bleeding for up to 5 years in patients who choose intrauterine contraception as their method of contraception.

This pediatric postmarketing safety review was prompted by labeling on October 25, 2019, that expanded the indication for Liletta for prevention of pregnancy for up to 6 years.

On September 6, 2018, DPV completed a review of postmarketing adverse event reports with a serious outcome for Liletta in pediatric patients. DPV's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with Liletta. On March 28, 2019, DPV's evaluation was presented to the Pediatric Advisory Committee via webposting.

DPV reviewed all U.S. serious FAERS reports with Liletta in pediatric patients less than 18 years of age from July 19, 2018, to December 22, 2024, and identified two reports; however, all reports were 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 Liletta in pediatric patients less than 18 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Liletta (levonorgestrel-releasing intrauterine system) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with Liletta in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Liletta (levonorgestrel-releasing intrauterine system) is a progestin-containing intrauterine system initially approved in the U.S. on February 26, 2015, for the prevention of pregnancy in women of reproductive age.[1] **Table 1** describes the subsequent labeling changes associated with new indications for Liletta.

Table 1. Liletta Labeling Changes Associated with New Indications

Labeling Date	Indication	Indicated population
2/26/2015[1]	• Prevention of pregnancy for up to 3 years	Females of reproductive age
8/3/2017[2]	• Prevention of pregnancy for up to 4 years	Females of reproductive age
10/15/2018[3]	• Prevention of pregnancy for up to 5 years	Females of reproductive age
10/25/2019[4]	• Prevention of pregnancy for up to 6 years	Females of reproductive age
11/10/2022[5]	• Prevention of pregnancy for up to 8 years	Females of reproductive age
6/29/2023[6]	• Prevention of pregnancy for up to 8 years • Treatment of heavy menstrual bleeding for up to 5 years in patients who choose intrauterine contraception as their method of contraception	Females of reproductive age

This pediatric postmarketing safety review was prompted by pediatric labeling on October 25, 2019, that expanded the indication for Liletta for prevention of pregnancy for up to 6 years.

On September 6, 2018, DPV completed a review of postmarketing adverse event reports with a serious outcome for Liletta in pediatric patients.[7] DPV's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with Liletta. On March 28, 2019, DPV's evaluation was presented to the Pediatric Advisory Committee via webposting.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Liletta labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Liletta labeling information, please refer to the full prescribing information.[6]

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

- Pregnancy (4)
- Use for post-coital contraception (emergency contraception) (4)
- Congenital or acquired uterine anomaly that distorts the uterine cavity and would be incompatible with correct IUS placement (4)
- Acute pelvic inflammatory disease (PID) (4)
- Postpartum endometritis or infected abortion in the past 3 months (4)
- Known or suspected uterine or cervical malignancy (4)
- Known or suspected breast cancer or other hormone-sensitive cancer (4)
- Uterine bleeding of unknown etiology (4)
- Untreated acute cervicitis or vaginitis or other lower genital tract infections (4)
- Acute liver disease or liver tumor (benign or malignant) (4)
- Increased susceptibility to pelvic infections (4)
- A previously inserted IUS that has not been removed (4)
- Hypersensitivity to any component of LILETTA (4)

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

- Remove LILETTA if pregnancy occurs with LILETTA in place and Contraindications (4). If pregnancy occurs, there is increased risk of ectopic pregnancy (including loss of fertility), pregnancy loss, septic abortion (including septicemia, shock, and death), and premature labor and delivery. (5.1, 5.2)
- Severe infection or sepsis, including Group A streptococcal sepsis (GAS) have been reported following insertion of LNG-releasing IUSs; strict aseptic technique is essential during insertion. (5.3)
- Before using LILETTA, consider the risks of pelvic infection. (5.4)
- Perforation may occur and reduce contraceptive effectiveness or require surgery. Risk is increased if inserted in patients who have fixed retroverted
- Partial or complete expulsion may occur. (5.6)
- Evaluate persistent enlarged ovarian follicles or ovarian cysts. (5.7)
- Bleeding patterns can become altered, may remain irregular, and amenorrhea may ensue. (5.8)

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

The most common adverse reactions reported in clinical studies (> 10% participants) are vulvovaginal mycotic infections, vaginal bacterial infections, acne, and nausea or vomiting. (6.1)

8.4 Pediatric Use

Safety and effectiveness of LILETTA have been established in females of reproductive potential. The safety and effectiveness are expected to be the same for postpubertal females under the age of 16 as for users 16 years and older. The LILETTA clinical study on contraception included 11 participants who were 16 to 17 years of age; no differences in safety or effectiveness were identified in these participants through 8 years of use of LILETTA. Use of this product is not indicated before menarche.

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	December 23, 2024
Time period of search	July 19, 2018† - December 22, 2024
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product name: Liletta Case application number: NDA206229
MedDRA search terms (Version 27.1)	All Preferred Terms
Other search terms‡	Case Seriousness: Serious Country Derived: USA

* See Appendix A for a description of the FAERS database.
† The FAERS search period for the most recently completed DPV pediatric postmarketing pharmacovigilance review for Liletta ended on July 18, 2018.
‡ 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.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; USA=United States of America

3 RESULTS

3.1 FAERS

3.1.1 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved two U.S. serious pediatric reports for patients less than 18 years old from July 19, 2018, to December 22, 2024. Neither report described a fatal outcome. We reviewed the two U.S. FAERS pediatric reports with a serious outcome and excluded both reports from the case series as they described labeled adverse events. The cases did not indicate increased severity of the labeled adverse events.

3.1.2 Summary of U.S. Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.3 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 Liletta in pediatric patients less than 18 years of age from July 19, 2018, to December 22, 2024, and identified two reports; however, all reports were 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 Liletta in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Liletta (levonorgestrel-releasing intrauterine system). [Prescribing information]. Parsippany, NJ; Actavis Pharma, Inc.: February 2015.
2. Liletta (levonorgestrel-releasing intrauterine system). [Prescribing information]. Irvine, CA; Allergan USA: August 2017.
3. Liletta (levonorgestrel-releasing intrauterine system). [Prescribing information]. Irvine, CA; Allergan USA: October 2018.
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6. Liletta (levonorgestrel-releasing intrauterine system). [Prescribing information]. North Chicago, IL; AbbVie, Inc.: June 2023.
7. Potter, E. Pediatric Postmarketing Pharmacovigilance Review. NDA 206229. September 6, 2018. Available at: https://www.fda.gov/files/advisory%20committees/published/liletta-pediatric-postmarketing-pharmacovigilance-review.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 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.