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

Pediatric Postmarketing Pharmacovigilance Review

Date:	September 6, 2018
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Product Names:	Liletta (levonorgestrel-releasing intrauterine system)
Pediatric Labeling Approval Date:	February 26, 2015
Application Type/Number:	NDA 206229
Applicant/Sponsor:	Medicines360
OSE RCM #:	2018-1220

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Liletta (levonorgestrel-releasing intrauterine system) in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on unlabeled, serious adverse events associated with Liletta in pediatric patients.

Liletta was first approved on February 26, 2015 for the prevention of pregnancy for up to 3 years. FDA approved the extension of the indication for use of Liletta up to 4 years on August 3, 2017. Use of this product before menarche is not indicated.

Our FAERS search retrieved no U.S. serious pediatric reports, or fatalities, through July 18, 2018. DPV did not identify any pediatric safety concerns for Liletta, and we recommend routine pharmacovigilance monitoring at this time.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Liletta (levonorgestrel-releasing intrauterine system, NDA 206229) in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious, unlabeled adverse events associated with Liletta in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

FDA approved Liletta on February 26, 2015 for prevention of pregnancy for up to 3 years in adult and pediatric patients. On August 3, 2017, the indication was expanded for the prevention of pregnancy for up to 4 years in adult and pediatric patients.[1,2] Liletta received exemption from PREA studies as it does not contain a new active ingredient, new indication, new dosage form, new dosage regimen, or route of administration from other intrauterine systems.[3,4] Liletta has not been presented at the Pediatric Advisory Committee (PAC) and DPV has not previously completed a PAC review for Liletta. This review was triggered by the original product approval.

1.2 HIGHLIGHTS OF LABELED SAFETY INFORMATION

CONTRAINDICATIONS

The use of LILETTA is contraindicated when one or more of the following conditions exist:

- Pregnancy or suspected pregnancy
- For use as post-coital contraception (emergency contraception)
- Congenital or acquired uterine anomaly, including fibroids, that distorts the uterine cavity and would be incompatible with correct IUS placement
- Acute pelvic inflammatory disease (PID) or endometritis or a history of PID unless there has been a subsequent intrauterine pregnancy
- Infected abortion in the past 3 months
- Known or suspected uterine or cervical neoplasia
- Known or suspected breast cancer or other hormone-sensitive cancer, now or in the past
- Uterine bleeding of unknown etiology
- Untreated acute cervicitis or vaginitis, including bacterial vaginosis, known chlamydial or gonococcal cervical infection, or other lower genital tract infections until infection is controlled
- Acute liver disease or liver tumor (benign or malignant)
- Conditions associated with increased susceptibility to pelvic infections
- A previously inserted IUS that has not been removed
- Hypersensitivity to any component of LILETTA

WARNINGS AND PRECAUTIONS

5.1 Ectopic Pregnancy

Evaluate women for ectopic pregnancy if they become pregnant with LILETTA in place because the likelihood of a pregnancy being ectopic is increased with LILETTA. Approximately half of pregnancies that occur with LILETTA in place are likely to be ectopic.

5.2 Intrauterine Pregnancy
If pregnancy occurs while using LILETTA, determine if LILETTA is in the uterus. If LILETTA is in the uterus, attempt to remove LILETTA because leaving it in place may increase the risk of spontaneous abortion and preterm labor.

5.3 Sepsis
Severe infection or sepsis, including Group A streptococcal sepsis (GAS), have been reported following insertion of other LNG-releasing IUSs.

5.4 Pelvic Inflammatory Disease or Endometritis
Insertion of LILETTA is contraindicated in the presence of known or suspected PID or endometritis or a history of PID unless there has been a subsequent intrauterine pregnancy

5.5 Perforation
Perforation (total or partial, including penetration/embedment of LILETTA in the uterine wall or cervix) may occur, most often during insertion, although the perforation may not be detected until sometime later. Perforation may reduce contraceptive efficacy and result in pregnancy. This may be associated with severe pain and continued bleeding.
The incidence of perforation during or following LILETTA insertion in the clinical trial, which excluded breastfeeding women, was 0.1%.

5.6 Expulsion
Partial or complete expulsion of LILETTA may occur, resulting in the loss of contraceptive protection.

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	July 19, 2018
Time Period of Search	All reports through July 18, 2018
Search Type	FBIS Product Manufacturer Reporting Summary
Product-Product Name	Liletta
MedDRA Search Terms (Version 21.0)	All PT terms
* See **Appendix A** for a description of the FAERS database.	

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 through July 18, 2018 with Liletta.

Table 2. Total Adult and Pediatric FAERS Reports[*] Received by FDA through July 18, 2018 with Liletta

	All reports (U.S.)	Serious[†] (U.S.)	Death (U.S.)
Adults (≥ 17 years)	976 (976)	64 (64)	None
Pediatrics (0 - <17 years)	12 (12)[‡]	None	None

* 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, and other serious important medical events.

‡ DPV reviewed these non-serious cases and did not identify any pediatric safety concerns for Liletta.

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

Our FAERS search retrieved no U.S. serious pediatric cases through July 18, 2018.

3.1.3 Summary of Fatal Pediatric Cases

We did not identify any fatal pediatric adverse event cases.

4 CONCLUSION

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

5 RECOMMENDATION

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

6 REFERENCES

1. Liletta [package insert]. Medicines 360, Inc, San Francisco, CA.
2. Nguyen, Christine. Supplemental Approval Letter. August 3, 2018. Link: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/206229Orig1s004ltr.pdf
3. Li, Li. Clinical Pharmacology Review of NDA 206229. January 30, 2015. Link: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM446653.pdf
4. Davis, Daniel. Clinical Review of NDA 206229: Liletta (levonorgestrel-releasing intrauterine system). April 29, 2014. Link: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM446648.pdf

7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

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 the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference 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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