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

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Product Name:	Phexxi (lactic acid, citric acid, and potassium bitartrate)
Pediatric Labeling Approval Date:	May 22, 2020
Application Type/Number:	NDA 208352
Applicant:	Evofem, Inc.
TTT Record ID:	2023-3638

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Phexxi (lactic acid, citric acid, and potassium bitartrate) 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 United States (U.S.) serious unlabeled adverse events associated with Phexxi in pediatric patients.

The FDA approved Phexxi on May 22, 2020, and it is indicated for the prevention of pregnancy in females of reproductive potential as an on-demand method of contraception. The safety and efficacy of Phexxi have been established in females of reproductive potential and are expected to be the same for post-menarchal females less than 17 years of age as for users 17 years of age and older. Phexxi use before menarche is not indicated.

DPV searched FAERS for all reports with Phexxi in pediatric patients less than 17 years of age from May 22, 2020 - January 31, 2023, and did not identify any reports. Therefore, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths associated with Phexxi in pediatric patients less than 17 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Phexxi (lactic acid, citric acid, and potassium bitartrate) 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 United States (U.S.) serious unlabeled adverse events associated with Phexxi in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Phexxi was FDA approved on May 22, 2022, and is a vaginal gel containing a combination of lactic acid 1.8%, citric acid 1%, and potassium bitartrate 0.4%. It is indicated for the prevention of pregnancy in females of reproductive potential as an on-demand method of contraception. One pre-filled applicator of Phexxi (5 grams[a]) is administered intravaginally immediately before or up to one hour before each act of vaginal sexual intercourse. If more than a single act of vaginal sexual intercourse occurs within the one hour, an additional dose of Phexxi must be administered.[1]

The safety and efficacy of Phexxi have been established in females of reproductive potential and are expected to be the same for post-menarchal females less than 17 years of age as for users 17 years of age and older. Phexxi use before menarche is not indicated.[1]

The efficacy of Phexxi for the prevention of pregnancy was evaluated in a multi-center, open-label, single-arm clinical trial within the U.S. (Study AMP002; NCT03243305). The study enrolled females of reproductive potential from 18 to 35 years of age with regular menstrual cycles (range: 21 to 35 days). Subjects agreed to engage in at least three acts of heterosexual, vaginal intercourse per cycle, and a dose of Phexxi (5 grams) was self-administered intravaginally up to one hour before each episode of intercourse (for a 7-cycle maximum). A total of 101 on-treatment pregnancies occurred in 1,183 subjects contributing 4,769 cycles. The 7-cycle cumulative pregnancy rate was 13.7% (95% Confidence Interval [CI]: 10.0%, 17.5%), excluding cycles < 21 days or > 35 days in length, cycles with back-up contraception, and cycles in which no intercourse was reported. The estimated Pearl Index was 27.5 (95% CI: 22.4%, 33.5%).[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] Additionally, the use of Phexxi was not expected to affect adolescent growth and no other safety concerns specific to the pediatric patient population were identified pre-approval.[3] 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 Phexxi.

[a] Five grams of Phexxi contains 90 mg of lactic acid, 50 mg of citric acid, and 20 mg of potassium bitartrate.[1]

1.2 RELEVANT LABELED SAFETY INFORMATION

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

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

- Cystitis and Pyelonephritis: Avoid use in women with a history of recurrent UTI or urinary tract abnormalities (5.1)

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

Most common adverse reactions (≥ 2%) were vulvovaginal burning sensation, vulvovaginal pruritus, vulvovaginal mycotic infection, urinary tract infection, vulvovaginal discomfort, bacterial vaginosis, vaginal discharge, genital discomfort, dysuria, and vulvovaginal pain. (6.1)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of Phexxi have been established in females of reproductive potential. Efficacy is expected to be the same for post-menarchal females under the age of 17 as for users 17 years and older. The use of Phexxi 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	May 22, 2020† - January 31, 2023
Search types	RxLogix PV Reports Profile Report and RxLogix PV Reports Quick Query
Product term	PAI: Citric acid monohydrate\lactic acid, l-\potassium bitartrate
MedDRA search terms (Version 25.1)	All MedDRA PTs
* See **Appendix A** for a description of the FAERS database † U.S. approval date for Phexxi **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 May 22, 2020 - January 31, 2023, with Phexxi.

Table 2. Total Adult and Pediatric FAERS Reports*† Received by FDA From May 22, 2020 - January 31, 2023, With Phexxi			
	All reports (U.S.)	**Serious‡ (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	19 (19)	12 (12)	0 (0)
Pediatrics (0 - < 17 years)	0 (0)	0 (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 event			

3.1.2 Summary of Fatal Pediatric Cases (n=0)

We did not identify any fatal pediatric adverse event cases.

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

We did not identify any non-fatal pediatric adverse event cases.

4 DISCUSSION

DPV searched FAERS for all reports with Phexxi in pediatric patients less than 17 years of age from May 22, 2020 - January 31, 2023, and did not identify any reports.

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

5 CONCLUSION

DPV did not identify any new or unexpected pediatric safety concerns for Phexxi 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 Phexxi.

7 REFERENCES

[1] Phexxi (lactic acid, citric acid, and potassium bitartrate) vaginal gel [package insert]. San Diego, CA: Evofem, Inc.; February 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208352s002lbl.pdf
[2] U.S. Food and Drug Administration. NDA Approval Letter for NDA 208352, Phexxi (lactic acid, citric acid, and potassium bitartrate) vaginal gel. May 22, 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/208352Orig1s000ltr.pdf
[3] U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Multi-Discipline Review and Evaluation of NDA 208352, Phexxi (lactic acid, citric acid, and potassium bitartrate) vaginal gel. May 21, 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/208352Orig1s000MultidisciplineR.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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