DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Catherine Maher, PhD, VP, Regulatory Affairs
Evofem Biosciences
12400 High Bluff Drive, Suite 600
San Diego, CA 92130

RE: NDA 208352
PHEXXI (lactic acid, citric acid, and potassium bitartrate) vaginal gel
MA 176

Dear Dr. Maher:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the promotional communication, a direct-to-consumer brochure, "Digital Patient Brochure - April 2022" (EVFM-US-001962) (brochure) for PHEXXI (lactic acid, citric acid, and potassium bitartrate) vaginal gel (Phexxi) submitted by Evofem Biosciences (Evofem) under cover of Form FDA 2253. The FDA Bad Ad Program also received a complaint regarding other promotional communications with claims and presentations similar to those discussed in this letter. This brochure makes false or misleading claims and representations about the benefits of Phexxi. Thus, the brochure misbrands Phexxi within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and makes its distribution violative. 21 U.S.C. 352(a), (n); 321(n), 331(a). See 21 CFR 202.1 (e)(5). This violation is concerning from a public health perspective because it overstates the expected benefits associated with the use of Phexxi.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Phexxi.[1] According to the INDICATIONS and USAGE section of the FDA-approved prescribing information (PI):

> PHEXXI is indicated for the prevention of pregnancy in females of reproductive potential for use as an on-demand method of contraception.
>
> Limitations of Use: PHEXXI is not effective for the prevention of pregnancy when administered after intercourse.

The PI for Phexxi includes warnings and precautions regarding cystitis and pyelonephritis. The most common adverse reactions reported with Phexxi were vulvovaginal burning sensation, vulvovaginal pruritus, vulvovaginal mycotic infection, urinary tract infection,

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional communication(s) cited in this letter.

vulvovaginal discomfort, bacterial vaginosis, vaginal discharge, genital discomfort, dysuria, and vulvovaginal pain.

False or Misleading Benefit Presentation

Prescription drug advertisements and labeling (promotional communications) misbrand a drug if they are false or misleading with respect to benefits. The determination of whether a promotional communication is misleading includes, among other things, not only representations made or suggested in the promotional communication, but also the extent to which the promotional communication fails to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the promotional communication.

Page three of the brochure includes the following claims regarding the efficacy of Phexxi (bolded emphasis original; underlined emphasis added):

> And in a separate analysis **99%** of pregnancies were prevented per act of sex (101 pregnancies over 24,289 acts of sex).
>
> Since Phexxi is an on-demand birth control, during the clinical trial, the effectiveness of Phexxi was also looked at each time Phexxi was used (per act of sex). This means Phexxi prevented pregnancy **99%** of the time."

These claims create a misleading impression by overstating the efficacy of Phexxi. The 99% pregnancy prevention rate claimed in the brochure is based on efficacy "per act of sex" which is not a validated measure to demonstrate the efficacy of contraceptive products. Specifically, this methodology incorrectly assumes that the likelihood of becoming pregnant is the same with each act of sex throughout the menstrual cycle. However, conception depends on the timing of intercourse in relation to ovulation, which is referred to as the fertile window.[2] Calculating the overall likelihood of pregnancy per act of intercourse does not take into account the fact that the likelihood of pregnancy is not the same throughout the menstrual cycle and is significantly lower during time points outside the fertile window. Therefore, calculating the pregnancy prevention rate based on "per act of sex" misleadingly overestimates the effect of Phexxi on pregnancy prevention.

In contrast the endpoints used to evaluate the efficacy of Phexxi in preventing pregnancy, as described in the PI (a Kaplan-Meier life-table analysis and the Pearl Index), analyze cumulative failure rates over specific lengths of exposure, rather than a failure rate based on individual acts of intercourse. The 7-cycle typical use cumulative pregnancy rate as derived by Kaplan-Meier life-table analysis was 13.7% (95% CI: 10.0%, 17.5%), excluding cycles with back-up contraception, cycles <21 days or >35 days in length and cycles in which no intercourse was reported. This corresponds with an 86% cumulative pregnancy prevention rate. The PI also reports the estimated Pearl Index[3], calculated based on data from the 7-

[2] Wilcox et al (1995) demonstrated that conception only occurred when intercourse took place during a six-day period that ended on the estimated day of ovulation. *See* Wilcox AJ, Weinberg CR, Baird DD. Timing of sexual intercourse in relation to ovulation. Effects on the probability of conception, survival of the pregnancy, and sex of the baby. *N Engl J Med*. 1995;333(23):1517-1521.

[3] The Pearl Index is defined as the number pregnancies per 100 women-with their first year of typical method use. A low Pearl Index is associated with fewer pregnancies. *See* https://www.fda.gov/media/150299/download.

cycle study, as 27.5 (95% CI: 22.4%, 33.5%). This Pearl Index value corresponds with a 72.5% cumulative pregnancy prevention rate. The suggestion that Phexxi prevented pregnancy 99% of the time, in contrast to the pregnancy prevention rates noted in the PI, overstates the efficacy of the product.

We acknowledge the inclusion of the following statement with these claims, “These data are not found in the Product Information and have not undergone the same rigorous evaluation as other data from the study.” However, this does not mitigate the misleading overstatement of efficacy created by these claims.

Conclusion and Requested Action

For the reasons discussed above, the brochure misbrands Phexxi within the meaning of the FD&C Act and makes its distribution violative. 21 U.S.C. 352(a), (n); 321(n); 331(a). See 21 CFR 202.1(e)(5).

This letter notifies you of our concerns and provides you with an opportunity to address them. OPDP requests that Evofem cease any violations of the FD&C Act. Please submit a written response to this letter within 15 working days from the date of receipt, addressing the concerns described in this letter, listing all promotional communications (with the 2253 submission date) for Evofem that contain representations like those described above, and explaining any plan for discontinuing use of such communications, or for ceasing distribution of Phexxi.

If you believe that your products are not in violation of the FD&C Act, please include in your submission to us your reasoning and any supporting information for our consideration within 15 working days from the date of receipt of this letter.

The concerns discussed in this letter do not necessarily constitute an exhaustive list of potential violations. It is your responsibility to ensure compliance with each applicable requirement of the FD&C Act and FDA implementing regulations.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. A courtesy copy can be sent by facsimile to (301) 847-8444. Please refer to MA 176 in addition to the NDA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter. You are encouraged, but not required, to submit your response in eCTD format. All correspondence submitted in response to this letter should be placed under eCTD Heading 1.15.1.6. Additionally, the response submission should be coded as an Amendment to eCTD Sequence 1169 under NDA 208352. Questions related to the submission of your response letter should be emailed to the OPDP RPM at CDER-OPDP-RPM@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Elvy Varghese, PharmD.
Regulatory Review Officer
Division of Advertising & Promotion Review 2
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{See appended electronic signature page}

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/s/

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