

Submitted by: Brandon Howard, PhD
Name: Brandon Howard, PhD
Title: Head of Medical Affairs
Company/Organization: Evofem Biosciences, Inc.
Address: 12400 High Bluff Drive, Suite 600, San Diego, CA 92130
Phone: (201) 783-6749
Email: bhoward@evofem.com
Date of request: July XX, 2021
NCCN Guidelines Panel: Breast Cancer

Dear NCCN Breast Cancer Guidelines Panel:

On behalf of Evofem Biosciences, I would like to respectfully request that the NCCN Breast Cancer Guidelines Panel review the enclosed data to support the inclusion of Phexxi® vaginal gel, a novel vaginal pH modulator (VPM), as an alternative non-hormonal contraceptive option for women receiving treatment for breast cancer in the next iteration of the Clinical Practice Guidelines in Oncology Breast Cancer.

Specific Changes:

Request to add “use of non-hormonal, pH-modulating vaginal gel” as an alternative method of birth control under BINV-C (Fertility and Birth Control) as supported by published data from a large, multi-site phase 3 clinical study.

FDA Status:

VPM is approved by the FDA for use as a non-hormonal, on-demand method of contraception for the prevention of pregnancy in women of reproductive potential. Please refer to the product prescribing information for the full FDA-approved indications and safety information of Phexxi®, available at: <https://phexxi.com/themes/custom/phexxiDTC/dist/pdf/PhexxiUSPI.pdf>

Rationale:

Due to the increased risk of venous thromboembolism or possible recurrence of disease, hormonal contraception is not recommended for women of childbearing age who have a history of hormonally mediated cancer or are receiving treatment for cancer.¹ While copper-containing intrauterine devices (IUDs) are recommended as non-hormonal options, they are associated with increased incidence of menstrual cramping and vaginal bleeding, which some women may find unacceptable.² Some physicians may encounter difficult insertions due to uterine structure and missing IUD threads or deeply embedded IUDs may complicate removal, potentially requiring hysteroscopy.^{3,4} Furthermore, these IUDs may not meet the needs of some women who may desire a contraceptive option that can be used only when they need it.

Data Summary:

VPM is a non-hormonal, woman-controlled, water-based contraceptive vaginal gel designed to maintain the acidic vaginal environment even in the presence of alkaline semen.⁵ The gel has a pH of approximately 3.55 and contains three active ingredients (L-lactic acid, citric acid, and potassium bitartrate) to provide acidic pH buffering, thereby maintaining the acidic vaginal environment.⁶ Additionally, the bioadhesive and viscosity-retaining properties of VPM allow it to form a long-lasting, protective layer over the vaginal and cervical epithelia.⁵⁻⁷ Compared with five other commercially available vaginal gels, VPM demonstrated significantly greater bioadhesive strength and retained its viscosity on dilution 21–271 times better than the other gels.⁵

Results from several phase 1 clinical studies have demonstrated the safety of VPM.⁶ Use of VPM was not associated with any intravaginal toxicities, although mild to moderate burning/itching/irritation were reported.^{8,9} When VPM was used consecutively for 6 days, visual or colposcopic inspection revealed no vaginal or cervical irritation and no patient complaints were recorded.⁷ No negative effects on vaginal microbiological and inflammatory markers (eg, vaginal pH, Nugent scores, H₂O₂-producing lactobacillus or leukocytes, and IL-6) were found on vaginal swabs collected 72 hours post-coitus from women who used VPM prior to intercourse.⁹

The contraceptive effectiveness, safety, and acceptability of VPM was evaluated in AMPOWER, a large, multi-site, phase 3 clinical study that enrolled 1,384 sexually active 18–35 year old women at risk of pregnancy (NCT03243305).¹⁰ The seven-cycle cumulative pregnancy percentage was 13.7% (95% CI, 10.0–17.5%) with typical use and ranged from 6.7% to 9.99% with perfect-use.^{10,11} Consistent with the findings from the phase 1 study, the most commonly reported AEs in AMPOWER were vaginal burning sensation (20%), vaginal pruritus (11%), urinary tract infection (6%), and vaginal pain (4%).¹⁰ Overall satisfaction levels with VPM was high, with 82%–90% of women reporting feeling “very satisfied” or “satisfied” with VPM use on-study.¹⁰ In addition, VPM has unique viscosity-retaining properties that may also offer women the benefit of lubrication. Results from AMPOWER showed that after one cycle of use, over twice as many women reported a positive impact on their sexual satisfaction and that their sex life was “a lot” or “a little” better compared with their sexual satisfaction with their previous contraceptive method reported at baseline.¹² Most women also reported improvements in many sexual function measures (eg, no difficulty maintaining lubrication, no vaginal dryness), which were maintained throughout the study.¹²

Please do not hesitate to contact me should you have further questions. Thank you for your time and consideration.

Sincerely,

Brandon Howard, PhD
Head of Medical Affairs
Evofem Biosciences, Inc.

References:

1. Patel A, Schwarz EB. Cancer and contraception. Release date may 2012. SFP guideline #20121. *Contraception*. 2012;86(3):191-198.
2. Schwarz EB, Hess R, Trussell J. Contraception for cancer survivors. *J Gen Intern Med*. 2009;24(suppl 2):S401-S406.
3. Johnson BA. Insertion and removal of intrauterine devices. *Am Fam Physician*. 2005;71(1):95-102.
4. Prine L, Shah M. Long-acting reversible contraception: Difficult insertions and removals. *Am Fam Physician*. 2018;98(5):304-309.
5. Garg S, Anderson RA, Chany CJ 2nd, et al. Properties of a new acid-buffering bioadhesive vaginal formulation (Acidform). *Contraception*. 2001;64(1):67-75.
6. Bayer LL, Jensen JT. Acidform: A review of the evidence. *Contraception*. 2014;90(1):11-18.
7. Amaral E, Faundes A, Zaneveld L, Waller D, Garg S. Study of the vaginal tolerance to Acidform, an acid-buffering, bioadhesive gel. *Contraception*. 1999;60(6):361-366.

8. Keller MJ, Carpenter CA, Lo Y, et al. Phase I randomized safety study of twice daily dosing of Acidform vaginal gel: Candidate antimicrobial contraceptive. *PLoS One*. 2012;7(10):e46901.
9. Amaral E, Perdigao A, Souza MH, et al. Vaginal safety after use of a bioadhesive, acid-buffering, microbicidal contraceptive gel (Acidform) and a 2% nonoxynol-9 product. *Contraception*. 2006;73(5):542-547.
10. Thomas MA, Chappell BT, Maximos B, Culwell KR, Dart C, Howard B. A novel vaginal pH regulator: Results from the phase 3 AMPOWER contraception clinical trial. *Contracept X*. 2020;2:100031.
11. Chappell BT, Culwell K, Dart C, Howard B. Perfect-use pregnancy rates with the vaginal pH regulator: Efficacy results from AMPOWER [abstract]. *Obstet Gynecol*. 2020;135(suppl):995.
12. Thomas MA, Culwell KR, Dart C, Howard B. Characterization of women according to their sexual satisfaction after treatment with the novel vaginal pH regulator (VPR™) during the ampower study. *Fertil Steril*. 2020;114(3):e172-e173.

The following articles are submitted within the supplement in support of this proposal.

1. Garg S, Anderson RA, Chany CJ 2nd, et al. Properties of a new acid-buffering bioadhesive vaginal formulation (Acidform). *Contraception*. 2001;64(1):67-75.
2. Bayer LL, Jensen JT. Acidform: a review of the evidence. *Contraception*. 2014;90(1):11-18.
3. Amaral E, Faundes A, Zaneveld L, Waller D, Garg S. Study of the vaginal tolerance to Acidform, an acid-buffering, bioadhesive gel. *Contraception*. 1999;60(6):361-366.
4. Amaral E, Perdigao A, Souza MH, et al. Vaginal safety after use of a bioadhesive, acid-buffering, microbicidal contraceptive gel (Acidform) and a 2% nonoxynol-9 product. *Contraception*. 2006;73(5):542-547.
5. Thomas MA, Chappell BT, Maximos B, Culwell KR, Dart C, Howard B. A novel vaginal pH regulator: results from the phase 3 AMPOWER contraception clinical trial. *Contracept X*. 2020;2:100031.
6. Chappell BT, Culwell K, Dart C, Howard B. Perfect-use pregnancy rates with the vaginal pH regulator: efficacy results from AMPOWER [abstract]. *Obstet Gynecol*. 2020;135(suppl):995.
7. Thomas MA, Culwell KR, Dart C, Howard B. Characterization of women according to their sexual satisfaction after treatment with the novel vaginal pH regulator (VPR™) during the AMPOWER study. *Fertil Steril*. 2020;114(3):e172-e173.