May 23, 2022

Dear West Virginia Drug Utilization Review Board,

Thank you for your request and considering our submission on Phexxi® (lactic acid, citric acid, and potassium bitartrate), a non-hormonal, on-demand, prescription indicated for the prevention of pregnancy.

Mechanism of Action

Phexxi's combination of three active ingredients, lactic acid, citric acid, and potassium bitartrate results in a unique mechanism of action, as the first in class Vaginal pH Modulator (as defined by First Data Bank and Medispan).[1,2] In *in vitro* studies, Phexxi produced a normal vaginal pH range (pH 3.5 - 4.5) in the presence of semen; the vaginal pH buffering effect of Phexxi causes a reduction in sperm motility and contributes to Phexxi's intravaginal contraceptive activity.[1] The introduction of semen (pH 7.2 - 8.0) into the vagina causes a rise in pH above 6.0 due to the alkalinity of the ejaculate, which neutralizes the normally acidic vaginal environment allowing the survival of spermatozoa.[3] Without the acid-neutralizing effect of semen, spermatozoa cannot survive the acidic environment of the vagina; spermatozoa are inactivated at pH ≤ 5.0.[3,4] Therefore, the administration of Phexxi, as a vaginal pH modulator, maintains the normal acidic pH of the vagina (pH 3.5 - 4.5) even in the presence of alkaline semen (pH 7.2 - 8), thus creating an inhospitable environment for sperm.

Clinical Efficacy and Safety

The approval of Phexxi was based on a single pivotal trial, AMPOWER, which enrolled 1349 women in the United States, as well as the combined safety database from AMPOWER and a previous Phase 3 trial, AMP-001, which together provided over 19,000 cycles of exposure in 2804 women from the US.[1,2] The primary endpoint for the AMPOWER trial recommended by the U.S. Food and Drug Administration (FDA) was the 7-cycle cumulative pregnancy rate, as measured by the Kaplan-Meier life table method. The secondary endpoints included efficacy measured by Pearl Index (PI, *estimated* based on the 7-cycle trial results), incidence of safety events, and overall satisfaction assessed using survey questionnaires. Phexxi demonstrated contraceptive efficacy with a 7-cycle cumulative pregnancy rate of 13.7% (95%: 10.0%, 17.5%) with typical use, and 6.67% with perfect use (95% CI: 4.61%, 8.73%), corresponding to an efficacy rate of 86% and 93%, respectively.[1,2,6]

The estimated PI based on data from the 7-cycle trial was 27.5% (95% CI: 22.4%, 33.5%).[1,2]
Notably, although the FDA required inclusion of the PI in the Phexxi Prescribing Information as part of class-labeling, contraceptive experts agree that comparing PI from an efficacy trial with a duration of less than one year with those of trials with duration greater than one year is misleading because the inclusion of fewer menstrual cycles results in higher calculated failure rates.[5] Additionally, it is well-established that the likelihood of pregnancy declines over time because those most likely to become pregnant do so at earlier durations of new contraceptive use. All methods that require user intervention, including combined oral contraceptives, demonstrate higher failure rates in the early months of the trial as women who are less compliant (and, perhaps, more fertile) will become pregnant sooner with lower rates as the study gets closer to a full 13-cycles of use. Thus, there is no appropriate statistical calculation to configure a PI for trials shorter than one year in length. Despite these methodologic hurdles which make efficacy comparisons with older studies of other contraceptive

methods difficult, AMPOWER met its pre-specified efficacy threshold for the primary endpoint as agreed with FDA with the upper limit of the 95% confidence interval for the 7-cycle cumulative pregnancy rate of <21% (13.7%, 95% CI: 10.0, 17.5%).[1,2] The most common adverse reactions reported during the clinical trials (>5%) were: vulvovaginal burning sensation (18.0%), vulvovaginal pruritus (14.5%), vulvovaginal mycotic infection (9.1%), urinary tract infection (9.0%), vulvovaginal discomfort (9.0%), bacterial vaginosis (8.4% and vaginal discharge (5.5%).

Phexxi is not a spermicide and does not contain any surfactant ingredients

Unlike other contraceptives including spermicides, Phexxi's unique mechanism of action through vaginal pH modulation results in immobilization of spermatozoa by maintaining the normally low vaginal pH, even in the presence of semen. The only similarity that Phexxi has to a spermicide is the delivery system (vaginal gel). In contrast, spermicides contain surfactants such as nonoxynol-9, with a mechanism of action that causes irreversible membrane alterations of the sperm cells thereby damaging the sperm cell membranes and killing the sperm cells.[6,7]

The reported efficacy of a contraceptive based on clinical trials designed to support a New Drug Application is driven by the statistical analysis rules required by the FDA.

Under the U.S. Health Resources and Services Administration (HRSA) Women's Preventive Services Guidelines, the full range of FDA- approved, -granted, or -cleared contraceptives, effective family planning practices, and sterilization procedures should be available as part of contraceptive care; and, the full range of contraceptives includes those currently listed in the FDA's Birth Control Guide and any additional contraceptives approved, granted, or cleared by the FDA. Under the U.S. Department of Labor FAQ update, plans are required to cover an FDA- approved, cleared, or granted contraceptive, if a provider deems it medically necessary, at $0 cost share, whether or not it is specifically identified in the current FDA Birth Control Guide. We hope that you reconsider Phexxi as a "must add" for addition to West Virginia Medicaid, as it is important that women in West Virginia have access to affordable contraceptive options.

References:

1. Evofem, Inc. February 2022. PHEXXI: US Package insert - Full prescribing information. San Diego, CA.
2. Thomas MA et al. A novel vaginal pH regulator: results from the phase 3 AMPWER contraception clinical trial. Contraception. 2020; doi: 10.1016/j.conx.2020.100031.
3. Garg S et al. Properties of a new acid- buffering bioadhesive vaginal formulation (ACIDFORM). Contraception. 2001;64(1):67-75.
4. Zhou J et al. The Semen pH Affects Sperm Motility and Capacitation. PLOS One. 2015; 10: e0132974.
5. Portman D et al. Variability in contraceptive clinical trial design and the challenges in making comparisons across trials. Adv Thera. 2021;(38):5425-5430.
6. Schill WB et al. Ultrastructure of human spermatozoa in the presence of the spermicide nonoxynol-9 and a vaginal contraceptive containing nonoxynol-9. Andrologia 1981; 13:42–9.
7. Grimes et al. Spermicide Used Alone for Contraception. Cochrane Database of Systematic Reviews 2013, Issue 9. Art. No.: CD005218.