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September 24, 2025

Martin A. Makary, MD, MPH
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: FDA Expert Panel on Menopause and Hormone Replacement Therapy for Women; Docket No. FDA-2025-N-2589

Dear Dr. Makary:

The American Urological Association (AUA) appreciates the opportunity to provide input on the Food and Drug Administration (FDA) request for comments following the FDA Expert Panel on Menopause and Hormone Replacement Therapy for Women. We thank you for your leadership in considering various perspectives on the risks and benefits related to menopause hormone therapy.

The AUA is a leading advocate for the specialty of urology and has more than 24,000 members throughout the world. Our members represent the world's largest collection of expertise and insight into the treatment of urologic disease. Of the total AUA membership, more than 17,000 are based in the United States and provide invaluable support to the urologic community by fostering the highest standards of urologic care through education, research, and the formulation of health policy.
As detailed further below, AUA maintains that low-dose vaginal estrogen is a safe and effective treatment for certain menopause-related conditions. Furthermore, AUA recommends that the FDA remove or revise the required warning labels for these products.

Menopause Can Cause Significant Genitourinary Symptoms
Genitourinary syndrome of menopause (GSM) describes the spectrum of symptoms and physical changes resulting from declining estrogen and androgen concentrations in the genitourinary tract during perimenopause and after menopause.[i] GSM prevalence estimates in postmenopausal patients vary widely from 13 to 87 percent.[ii]

Symptoms of GSM can take many forms (vulvovaginal, urinary, or sexual). Vulvovaginal symptoms associated with menopause include dryness, burning, and irritation.[iii] Urinary symptoms include urgency, frequency, dysuria, and recurrent urinary tract infections (UTI).[iv] UTIs are of particular concern because they are characterized by a range of symptoms, including irritative voiding, bacteremia, sepsis, and death.[v]

The vulvovaginal and urinary effects of menopause are often considered the cause of sexual symptoms of GSM, including pain and bleeding during intercourse, as well as broader impacts on sexual function, such as reduced libido, arousal, and orgasm.[vi,vii,viii] Unlike vasomotor symptoms of menopause (i.e., hot flashes and/or night sweats), the prevalence and intensity of some genitourinary symptoms, such as vulvovaginal dryness, increase with advancing age.[ix,x]

AUA Guidelines Recommend Local Low-dose Vaginal Estrogen to Patients with GSM to Improve Vulvovaginal Discomfort, Dryness, and/or Dyspareunia

The AUA produces clinical practice guidelines based on rigorous, systematic reviews of published clinical evidence. In April 2025, AUA released *Genitourinary Syndrome of Menopause: AUA/SUFU/AUGS Guideline* (2025).[xi] This guideline was produced in partnership with Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) and American Urogynecologic Society (AUGS) and was endorsed by The International Society for the Study of Women's Sexual Health (ISSWSH) and The Menopause Society (TMS) - all organizations dedicated to improving women's health.

AUA's guideline provides that local low-dose vaginal estrogen may be administered in the form of a cream, tablet, insert, or ring to improve symptoms of GSM.[xii] The evidence particularly supports the use of local low-dose vaginal estrogen to treat vaginal dryness. Seven studies show mixed effects of vaginal estrogen on dryness when compared to placebo.[xiii] In an RCT without placebo, Eriksen et al. showed significantly more patients experienced resolution of dryness in the vaginal estrogen group (81%) as compared to no treatment.[xiv] Seven RCTs found mixed effects of vaginal estrogen compared to placebo on dyspareunia (painful intercourse).[xv] Finally, local estrogen therapy has been shown to reduce UTI incidence and time to recurrence in post-menopausal women.[xvi]

Low-Dose Vaginal Estrogen Does Not Cause Cancer or Blood Clots

The safety of low-dose vaginal estrogen is supported by Mitchell et al. and Constantine et al., both of whom found significant improvement in GSM symptoms with no increase in serum estradiol levels.[xvii,xviii,xix] Likewise, a 2019 systematic review of 20 RCTs, 10 interventional trials, and 8 observational studies found no increased endometrial hyperplasia or cancer risk in patients on low-dose estrogen (without progestogen).[xx] There has been evidence of safety in breast cancer survivors using low-dose vaginal estrogen as well.[xxi,xxii,xxiii] Finally, an 18-year follow-up of women enrolled in the Nurse's Health Study found no increased risk for chronic disease for low-dose vaginal estrogen when compared to systemic estrogen.[xxiv]

Three recently published, large volume population-based case cohort trials demonstrate that low-dose estrogen does not pose a risk of cancer. The largest, McVicker (2023) reviewed 49,237 newly diagnosed breast cancer survivors in Scotland and Wales who participated in national registry databases followed from 4-20 years.[xxv] Five percent were noted to have received vaginal estrogen and of those, there was no evidence of a higher risk of breast cancer–specific mortality (HR, 0.77; 95%CI, 0.63-0.94). A slightly smaller retrospective case-cohort study by Agrawal (2023) explored recurrence instead of mortality.[xxvi] They utilized a USA based claims database to identify 42,113 breast cancer survivors with a concurrent diagnosis of GSM and appreciated that 5% received vaginal estrogen as well. This included women with estrogen-receptor positive disease. When compared with the cohort that did not receive vaginal estrogen, no difference in breast cancer recurrence was appreciated (risk ratio 1.03, 95% CI 0.91–1.18). When estrogen-receptor positive women were examined specifically, recurrence rates still failed to be significantly elevated in the group that received vaginal estrogen (risk ratio 0.94, 95% CI 0.77–1.15). Both studies are further supported by a large population-based trial in Denmark. Meaidi (2024) compared vaginal estradiol tablet exposure in 18,997 women newly diagnosed with breast cancer during a 9 year follow up period and compared vaginal estradiol exposure to an age matched cohort of 94,985 women without breast cancer diagnoses and found no difference in exposure with an adjusted hazard ratio of 0.87 (95% confidence interval 0.69 to 1.11).[xxvii]

Finally, vaginal estrogen does not pose increased risk of venous thromboembolism (VTE). Archer (2018) followed 573 women for 12 weeks and no venous thrombotic events (VTEs) were reported in very low dose estradiol cream nor placebo.[xxviii] Similarly, Constantine (2017) followed 765 patients over 12 weeks and appreciated no difference in VTE over placebo.[xxix] Mitchell (2018) also found no increased risk of VTE in 200 women followed over 12 weeks.[xxx]

The "Black Box" Warning for Vaginal Low-dose Estrogen Should be Removed

Since 2003, the FDA has required that *all* menopause hormone therapy medications, regardless of their composition or application, display a "black box" warning of potential side effects. The warning states that the medication might increase the risk of strokes, blood clots, dementia and cancer. The warning is based on findings from the 2002 Women's Health Initiative (WHI) study, which involved high-dose, *systemic* estrogen.[xxxi] It fails to distinguish between systemic and local absorption.

By contrast, low-dose estrogen is usually applied *locally* to the vagina and is not absorbed systemically. Therefore, the WHI study's conclusions remain overbroad

and irrelevant to the well-established safety record of low-dose vaginal estrogen. As a result of the warning, however, take-up of low-dose estrogen remains impeded by several barriers:

- Widespread clinician hesitancy and lack of knowledge to prescribe low-dose vaginal estrogen - even when medically appropriate
- Pharmacist refusal to dispense these medications or substitution with inappropriate systemic products
- ICU physician denial of life-saving local estrogen therapies for patients most at risk of urosepsis
- Patient fear and confusion, leading many to forgo effective and quality-of-life treatment for GSM symptoms including recurrent urinary tract infections, burning, irritation, dyspareunia, vaginal dryness, and substantial alterations to the vaginal microbiome

To reduce these barriers, AUA strongly recommends that the FDA remove the box warning for vaginal estrogen products with demonstrably low systemic absorption or revise the boxed warning language to distinguish between systemic and local hormone therapy and clarify that vaginal estrogen is safe for long-term use in appropriately selected patients, including survivors of hormone-sensitive cancers.

Conclusion

GSM is a serious condition that profoundly affects urinary and sexual health, often driving the use of unnecessary and often overuse of systemic antibiotics or surgeries—complications that are preventable with simple, localized estrogen therapy.

Left untreated, GSM can cause:

- Cause chronic genitourinary infections with risk of urosepsis
- Overactive bladder and urgency
- Vaginal atrophy with bleeding and fragility
- Painful intercourse and intimacy avoidance
- Significant psychological and relationship distress

These consequences lead to avoidable suffering and functional decline for millions of women, especially older adults and cancer survivors, who could safely benefit from localized estrogen therapy.

Overwhelming evidence demonstrates minimal systemic absorption, an excellent safety profile, and significant clinical benefit when low-dose estrogen is used appropriately to treat GSM. Therefore, AUA joins numerous stakeholders and experts in strongly urging the FDA to remove or revise the boxed warning currently required on all local low-dose estrogen-containing products.

American Urological Association

The AUA welcomes the opportunity to work with FDA throughout this process to ensure access to treatment that has been proven effective and safe for women in menopause.

Sincerely,

Mark Edney, MD, MBA, FACS
FACS
Chair, Public Policy Council
American Urological Association

Matthew Nielsen, MD, MS,

Chair, Science & Quality Council
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American Urological Association

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