https://www.regulations.gov/commenton/FDA-2025-N-2589-0001

Whom It May Concern,

On behalf of the American Urogynecologic Society we respectfully submit this public comment in support of revising the Black Box warning on low-dose topical vaginal estrogen products.

Low-dose topical vaginal estrogen therapies are safe and effective treatments for genitourinary syndrome of menopause, recurrent urinary tract infections, and other gynecologic conditions. The current Black Box warning misrepresents the risk profile of these products by attributing adverse effects to these medications when such risks have not been substantiated in formulations with minimal systemic absorption. Specifically, the warning that the low-dose topical use of vaginal estrogen can cause endometrial cancer, cardiovascular disorders, breast cancer and probable dementia is not evidence-based.

The current warning is largely based on data extrapolated from the Women's Health Initiative (WHI) trial, which primarily studied systemic hormone therapies initiated in a high-risk population already in their 60s. This extrapolation is inappropriate and misleading, as it fails to account for the pharmacokinetic distinctions between systemic and local estrogen therapies. Clinical and pharmacologic evidence consistently demonstrates that low-dose topical vaginal estrogen is associated with serum estradiol levels within a postmenopausal range. Specifically, WHI analyses of low-dose topical vaginal estrogen actually refute the claims on the Black Box warning label. The labelling of low-dose topical vaginal estrogen should emphasize information from studies of low-dose topical vaginal estrogen, and not data from systemic estrogen. This suggestion is based on the precedent set by other drugs, including lidocaine, where a Black Box warning may be on one formulation but not another, and the risks emphasized in the labeling are specific to that formulation.

This current inaccurate labeling of low-dose topical vaginal estrogen has harmful real-world consequences. Many postmenopausal patients experience avoidable morbidity due to fear and confusion generated by the current warning. These fears prevent appropriate use of a highly effective treatment, ultimately compromising the well-being of millions of affected women. For example, vaginal estrogen is an incredibly effective non-antibiotic option to prevent recurrent urinary tract infections in postmenopausal patients. However, many patients decline this therapy when they read that vaginal estrogen can give them cancer, heart disease, and dementia. This leads to unnecessary urinary tract infections and the overuse of antibiotics, with widespread implications on antimicrobial resistance in our communities.

In light of the substantial evidence supporting the safety and efficacy of low-dose vaginal estrogen products—and the clear distinction from systemic estrogen therapies—we urge the FDA to reconsider the Black Box warning on low-dose topical vaginal estrogen formulations. It would be appropriate to maintain that genital bleeding should be reported to a provider. Furthermore, amongst women with a history of breast cancer on aromatase inhibitors, the evidence surrounding the risks and benefits of various formulations of vaginal estrogen (ring, tabled, cream) should be reviewed with the patient and their Oncologist prior to use.

Respectfully submitted,

The American Urogynecologic Society
www.augs.org

Supportive readings for consideration:

1. Crandall CJ, Hovey KM, Andrews CA, Chlebowski RT, Stefanick ML, Lane DS, Shifren J, Chen C, Kaunitz AM, Cauley JA, Manson JE. Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women's Health Initiative Observational Study.

Menopause. 2018 Jan;25(1):11-20. doi: 10.1097/GME.0000000000000956. PMID: 28816933; PMCID: PMC5734988

2. Streff A, Chu-Pilli M, Stopeck A, Chalasani P. Changes in serum estradiol levels with Estring in postmenopausal women with breast cancer treated with aromatase inhibitors. Support Care Cancer. 2021 Jan;29(1):187-191. doi: 10.1007/s00520-020-05466-1. Epub 2020 Apr 23. PMID: 32328775.
3. McVicker L, Labeit AM, Coupland CAC, Hicks B, Hughes C, McMenamin Ú, McIntosh SA, Murchie P, Cardwell CR. Vaginal Estrogen Therapy Use and Survival in Females With Breast Cancer. JAMA Oncol. 2024 Jan 1;10(1):103-108. doi: 10.1001/jamaoncol.2023.4508. PMID: 37917089; PMCID: PMC10623297.
4. Bhupathiraju SN, Grodstein F, Stampfer MJ, Willett WC, Crandall CJ, Shifren JL, Manson JE. Vaginal estrogen use and chronic disease risk in the Nurses' Health Study. Menopause. 2018 Dec 17;26(6):603-610. doi: 10.1097/GME.0000000000001284. PMID: 30562320; PMCID: PMC6538478.
5. Constantine GD, Graham S, Lapane K, Ohleth K, Bernick B, Liu J, Mirkin S. Endometrial safety of low-dose vaginal estrogens in menopausal women: a systematic evidence review. Menopause. 2019 Jul;26(7):800-807. doi: 10.1097/GME.0000000000001315. PMID: 30889085; PMCID: PMC6636806.