

Removal of Black Box Warning Label from Topical Low-Dose Vaginal Estrogen Products

Scope of the problem:

On November 10, 2025, the United States Food & Drug Administration (FDA) announced a request to change the labeling of estrogen-containing products to clarify associated risks.¹ Previously, the FDA had imposed a Boxed Warning for all estrogen products indicating an increased risk of serious adverse events including cardiovascular disease, cancer, and probable dementia. The warning was largely based on data extrapolated from the Women's Health Initiative (WHI) trial, which primarily studied systemic estrogen initiated in a postmenopausal population with a mean age of 63 years.²⁻⁵

Studies investigating topical low-dose vaginal estrogen have not found significantly increased risks of cardiovascular disease, cancer, thromboembolism, or dementia.⁶⁻¹⁰ Furthermore, studies have demonstrated that exposure to topical low-dose vaginal estrogen therapy is typically associated with systemic estrogen levels near or within a postmenopausal range.¹¹⁻¹³ Topical low-dose vaginal estrogen bypasses first-pass hepatic metabolism, resulting in distinct pharmacokinetics from systemic hormone therapy. The Boxed Warning applied to all estrogen products, regardless of route and dose, led many providers and patients to avoid appropriate, evidence-based, therapeutic application of topical low-dose vaginal estrogen in an attempt to mitigate risks that have not been associated with these products.

The American Urogynecologic Society previously submitted public comment to the FDA encouraging review of the evidence related to topical low-dose vaginal estrogen and labelling of estrogen products. The FDA has requested that labeling remove language related to cardiovascular diseases, breast cancer and probable dementia. Specific to local vaginal estrogen products, they have requested to condense safety information and prioritize information relevant to topical vaginal formulations.

Recommendations for clinical practice:

Topical low-dose vaginal estrogen is a safe and effective treatment for genitourinary syndrome of menopause, other gynecologic conditions, and the prevention of recurrent urinary tract infections. Patients and providers should be reassured that topical low-dose vaginal estrogen has not been associated with increased risk of cardiovascular disease, thromboembolism, breast or endometrial cancer, nor dementia.

- The American Urogynecologic Society; North American Menopause Society; American Urological Association; and Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction have issued practice guidelines supporting the use of topical vaginal estrogen for genitourinary syndrome of menopause as indicated.
- The American Urogynecologic Society; American Urological Association; Canadian Urological Association, and the Society of Urodynamics; Female Pelvic Medicine & Urogenital Reconstruction have issued practice guidelines supporting the use of topical vaginal estrogen for prevention of recurrent urinary tract infections in peri- and post-menopausal patients when no contraindications exist.

Clinicians should feel confident offering topical low-dose vaginal estrogen to appropriate patients, including those with genitourinary syndrome of menopause and recurrent urinary tract infections. Shared decision-making should emphasize strong safety data, minimal systemic absorption, and substantial quality-of-life benefits.

Conclusion:

The American Urogynecologic Society supports the FDA's request to remove the Boxed Warning on topical low-dose vaginal estrogen products. While the FDA has not yet finalized its guidance, we applaud the requested labeling changes and continue to stand by clinical guidance documents and national societies supporting topical low-dose vaginal estrogen as a safe treatment for genitourinary syndrome of menopause, other gynecologic conditions, and the prevention of recurrent urinary tract infections.¹⁴⁻¹⁸

Acknowledgement

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