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NAMS Responds to European Medicines Agency Statement on Vaginal Estradiol Creams

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The regulatory body for medications in the European Union, the European Medicines Agency, issued a statement on October 4, 2019, indicating that the use of "high-strength" vaginal estradiol creams be limited to a single treatment period of up to 4 weeks in order to minimize the risk of adverse effects. This advice is not evidence based. In addition, it fails to recognize that genitourinary syndrome of menopause (GSM) is a chronic, progressive condition; symptoms do not resolve with time or short-term treatment. This warning from the European Medicines Agency is likely to result in women avoiding a safe, effective, and much-needed treatment for this common condition. Untreated GSM can have a devastating effect on vulvovaginal health and women's self-image, quality of life, and intimate relationships.

The North American Menopause Society (NAMS) has been working with FDA for several years to remove the black-box warning from local vaginal estrogen therapies. Here are some key issues NAMS has emphasized to support the removal of the black-box warning on low-dose vaginal estrogens and that should provide reassurance to clinicians and women regarding the safety of low-dose vaginal estrogen products:

- The dramatic differences in blood hormone levels achieved by low-dose vaginal estrogen (eg, Vagifem tablets [estradiol 10 µg], Estring [releasing estradiol 7.5 µg/d], Imvexxy [estradiol 4 µg and 10 µg], or comparable low-dose vaginal estrogen cream formulations) versus standard systemic estrogen therapy (whether oral, transdermal, or vaginal ring).
- Differences in metabolism of oral and local low-dose vaginal products.
- Absence of randomized trial evidence or consistent observational evidence linking low-dose vaginal estrogen to cancer, cardiovascular disease, dementia, or other conditions highlighted in the boxed warning. In fact, observational data supports the absence of long-term adverse effects of low-dose vaginal estrogens.
- Absence of evidence that changes in blood hormone levels of the small magnitude achieved with these products increased the risk of any of these conditions.
- As a result of the boxed warning, a large number of older women with symptomatic VVA and genitourinary symptoms are being undertreated or turn to unapproved, unlabeled compounded products and do not receive the substantial health and quality-of-life benefits that the low-dose vaginal estrogen products approved for VVA could provide.
- The boxed warning on the package label for low-dose vaginal estrogen discourages clinicians from prescribing the product and women from taking it even after purchase.
- This labeling is confusing to healthcare providers, indicating that perhaps they should be prescribing a progestin. One of the benefits of low-dose vaginal products is the lack of a need for concomitant progestins.

NAMS continues to endorse the use of low-dose vaginal estrogens as safe and effective therapies for treatment of GSM, a long-term, progressive condition.