from JoAnn V. Pinkerton, MD, NCMP, Executive Director

NAMS
THE NORTH AMERICAN MENOPAUSE SOCIETY

NAMS Citizen's Petition and FDA Response
June 7, 2018

The North American Menopause Society (NAMS) has received a disappointing response to the citizen's petition submitted by the Working Group on Women's Health and Well-Being in Menopause and NAMS asking FDA to "modify the label for low-dose vaginal estrogen products approved for treating symptoms of vulvovaginal atrophy (VVA)."

Our requests were

1. To remove the black box warning in the Warnings and Precautions section of the labeling but retain the text (in regular font) about the risks identified in the Women's Health Initiative (WHI) trials of oral systemic (higher dose) hormone therapy.
2. To highlight in the Warnings and Precautions section of the labeling as it relates to the use of low-dose vaginal estrogen products for the treatment of VVA symptoms that
   a. Genital bleeding is a concern because bleeding may be a sign of endometrial cancer. Report any bleeding or spotting without delay.
   b. Women with estrogen-sensitive breast cancer should consult with their oncologists before use of the product.

In their denial of our petition, FDA sent a 22-page letter in which they reconfirmed that all estrogen products will have the black box warning ("class labeling") and that "the prescribing information should state that the lowest effective doses of estrogens (with or without progestins) should be prescribed for the shortest duration consistent with the treatment goals and risks for the individual patient."

NAMS continues to believe that the black box warning for low-dose vaginal estrogen, defined as dosed appropriately such that blood levels remain within the normal postmenopause range, unnecessarily frightens women and keeps them from much-needed treatment.[1] The genitourinary syndrome of menopause (GSM) is chronic and progressive and can have many medical consequences including increased urinary tract infections and risk for vaginal infection and may affect relationships, quality of life, daily activities, and enjoyment of sex. The recent report from the WHI observational study by Crandall and associates[2] did not find a significantly increased risk of breast or endometrial neoplasia for women using low-dose vaginal estrogen therapy nor any increased risk of cardiovascular disease, total cancer, or all-cause mortality. This supports our understanding that low-dose vaginal estrogens have primarily local vaginal estrogen effects without significant endometrial or systemic effect because minimal absorption occurs.[3]

There are low-dose vaginal estrogen options available, including vaginal 10-µg estradiol tablets, estradiol 7.5-mg ring, the new 4- and 10-mg vaginal soft gel inserts, and both vaginal creams (conjugated estrogen and estradiol) that can be dosed at 0.5 g. Postmenopausal bleeding, if it occurs, should be evaluated to rule out endometrial neoplasia. Use in women with prior breast cancer needs to be individualized and involve the woman's oncologist. There is more concern for women on aromatase

inhibitors, in which serum estrogen levels are markedly suppressed, and even small amounts of systemic absorption could offset aromatase effects. Newer nonestrogen therapies for women with dyspareunia but not tested or approved for women with breast cancer include oral ospemifene and intravaginal dehydroepiandrosterone. Vaginal laser therapy appears effective, although larger sham-controlled studies are needed.

NAMS recommends that clinicians discuss the evidence-based risks and benefits for individual women for the products and dosages that are being recommended. Women should be informed that the black box warning on all estrogen products remains because of class labeling but that we continue to believe, based on our interpretation of the current literature, that the risks from systemic estrogen and progestin seen in the WHI do not apply to low-dose vaginal estrogen products—those that are dosed to keep blood levels within the postmenopause range. NAMS will be preparing a draft handout for patients on this topic, which should be available within several weeks, for clinicians to use in their practices and is considering next steps to continue our advocacy to modify this class label policy in order to improve the health and well-being of postmenopausal women with GSM.

Sincerely yours,

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References

1. Manson JE, Goldstein SR, Kagan R, et al; Working Group on Women's Health and Well-Being in Menopause. Why the product labeling for low-dose vaginal estrogen should be changed. *Menopause*. 2014;21(9):911-916.
2. Crandall CJ, Hovey KM, Andrews CA, et al. Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women's Health Initiative Observational Study. *Menopause*. 2018;25(1):11-20.
3. Pinkerton JV, Kaunitz AM, Manson JE. Vaginal estrogen in the treatment of genitourinary syndrome of menopause and risk of endometrial cancer: an assessment of recent studies provides reassurance. *Menopause*. 2017;24(12):1329-1332.