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IN BRIEF

Label Changes for Menopausal Hormone Therapy Products

The FDA has requested the removal of some boxed warnings from the labels of vaginal and systemic menopausal hormone therapy (MHT) products. The warnings were initially added in 2003 based on the results of two placebo-controlled Women's Health Initiative (WHI) trials evaluating the use of systemic hormones for primary prevention of coronary heart disease (CHD) in postmenopausal women 50-79 years old.[1-3]

THE WHI TRIALS — In the first WHI trial, postmenopausal women 50-79 years old with an intact uterus who took oral conjugated equine estrogens and medroxyprogesterone had an increased risk of invasive breast cancer, CHD, stroke, and pulmonary embolism after a mean follow-up of 5.2 years.[2] In the second WHI trial, postmenopausal women 50-79 years old without a uterus who took conjugated equine estrogens alone (without a progestin) had an increased risk of stroke, but not of breast cancer or CHD, after a mean follow-up of 6.8 years.[3]

In both trials, estrogen therapy was associated with a reduced risk of hip fractures and had no effect on all-cause mortality.

A Secondary Analysis – In a secondary analysis of the WHI trials published in 2025, use of conjugated equine estrogens alone or with medroxyprogesterone in women 50-59 years old with moderate to severe vasomotor symptoms (VMS) was not associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD; a composite of nonfatal myocardial infarction, hospitalization for angina, coronary revascularization, ischemic stroke, peripheral arterial disease, carotid artery disease, or cardiovascular death). Use of conjugated equine estrogens alone in women 60-69 years old was associated with an increase in ASCVD risk that was not statistically significant. In women ≥70 years old, any estrogen use was associated with a significant increase in the risk of ASCVD.[4]

MENOPAUSAL HORMONE THERAPY — Oral conjugated equine estrogens and oral medroxyprogesterone are used infrequently today. Commonly used estrogen products are identical in structure and function to endogenous estrogen and are often administered transdermally or vaginally to bypass the liver and reduce the risk of thromboembolic events. Low-dose vaginal estrogen, which has minimal systemic absorption, is preferred for treatment of genitourinary syndrome of menopause (GSM; e.g., vaginal dryness, recurrent urinary tract infections) in women without significant VMS. Systemic estrogen (oral, transdermal, high-dose vaginal) is the most effective treatment for VMS; it is also effective for treatment of GSM and other menopause-related symptoms, and it can prevent bone loss and osteoporosis.[5] It should not be used solely for prevention of cardiovascular disease or dementia.[6]

Risks – Use of systemic estrogen is associated with an increased risk of thromboembolic events and gallbladder disease. Systemic estrogen use in women ≥70 years old has been associated with an increased risk of ASCVD. It can also increase the risk of endometrial cancer; women with an intact uterus who use a systemic estrogen should also receive a progestin or the selective estrogen receptor modulator bazedoxifene *(Duavee)* for endometrial cancer protection. Use of systemic estrogen with a progestin has been associated with a small increase in the risk of breast cancer.

THE LABEL CHANGES — Based on an FDA advisory committee analysis of the potential benefits and risks, the labels of vaginal and systemic MHT products will no longer include boxed warnings about an increased risk of cardiovascular disease, breast cancer, or possible dementia, and will no longer include a recommendation to use the lowest effective dose for the shortest possible duration of time. Systemic MHT product labels will now include data from the WHI trials in women 50-59 years old along with a recommendation to consider starting MHT for moderate to severe VMS before age 60 or within 10 years after menopause onset.

The updated labels for products containing systemic estrogen alone will still contain a boxed warning about the risk of endometrial cancer (when used without a progestin for endometrial protection) and information about possible increased risks of cardiovascular disease and breast cancer.

CONCLUSION — The label changes for systemic and vaginal menopausal hormone therapy products will lead to an increase in their use among perimenopausal and younger postmenopausal women. Long-term data on the safety of commonly used hormonal products in this population would be welcome. ■

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4. JE Rossouw et al. Menopausal hormone therapy and cardiovascular diseases in women with vasomotor symptoms: a secondary analysis of the Women's Health Initiative randomized clinical trials. JAMA Intern Med 2025; 185:1330.
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