

DNA-Based Test for HPV Types 16, 18 Approved

BY ELIZABETH MEHCATIE

A test that detects the genotypes of human papilloma virus (HPV) 16 and 18, which cause the majority of cervical cancer cases, was recently approved by the Food and Drug Administration.

The test, which will be marketed as the Cervista HPV 16/18 test, is the first DNA-based test for these HPV types, ac-

ording to a written statement issued by the FDA. HPV types 16 and 18 cause of about 70% of cervical cancers.

The FDA also approved the Cervista HPV HR test, another DNA-based test, which detects “essentially all of the high-risk HPV types in cervical cell samples.”

Both tests, which are manufactured by Hologic Inc., can be combined with cytology to assess the risk of cervical disease in women aged 30 years and

older, with borderline cytology results, according to the agency statement.

“Results from these two tests, when considered with a physician’s assessment of the patient’s history, other risk factors, and professional guidelines, can help physicians better determine risk and could lead to better patient management,” Dr. Daniel Schultz, director of the FDA’s Center for Devices and Radiological Health, said in the statement.

The Cervista HPV HR test was approved specifically for screening cervical cytology results with atypical squamous cells of undetermined significance to determine the need for referral to colposcopy, according to a statement issued by Hologic.

The company adds that the results of the Cervista HPV 16/18 test “are not intended to prevent women from proceeding to colposcopy.” ■

PREMARIN (conjugated estrogens) VAGINAL CREAM

BRIEF SUMMARY: See Package Insert for full Prescribing Information. For further product information and current package insert, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS AND PROBABLE DEMENTIA FOR ESTROGEN-ALONE THERAPY

ENDOMETRIAL CANCER
There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding [see Warnings and Precautions (5.3)].

CARDIOVASCULAR DISORDERS AND PROBABLE DEMENTIA
Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia [see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3) in full Prescribing Information].

The Women’s Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) (0.625 mg), relative to placebo [see Warnings and Precautions (5.2), and Clinical Studies (14.2) in full Prescribing Information].

The Women’s Health Initiative Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg) alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3) in full Prescribing Information].

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

WARNING: CARDIOVASCULAR DISORDERS, BREAST CANCER AND PROBABLE DEMENTIA FOR ESTROGEN PLUS PROGESTIN THERAPY

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia [see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3) in full Prescribing Information].

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism, stroke and myocardial infarction in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) (2.5 mg), relative to placebo [see Warnings and Precautions (5.2), and Clinical Studies (14.2) in full Prescribing Information].

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer [see Warnings and Precautions (5.3), and Clinical Studies (14.2) in full Prescribing Information].

The WHIMS estrogen plus progestin ancillary study of the WHI, reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3) in full Prescribing Information].

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

INDICATIONS AND USAGE

Treatment of Atrophic Vaginitis and Kraurosis Vulvae

Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause

CONTRAINDICATIONS

PREMARIN Vaginal Cream therapy should not be used in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of breast cancer
- Known or suspected estrogen-dependent neoplasia
- Active deep vein thrombosis, pulmonary embolism or a history of these conditions
- Active arterial thromboembolic disease (for example, stroke, and myocardial infarction), or a history of these conditions
- Known liver dysfunction or disease
- Known or suspected pregnancy

WARNINGS AND PRECAUTIONS

Risks From Systemic Absorption

Systemic absorption occurs with the use of PREMARIN Vaginal Cream. The warnings, precautions, and adverse reactions associated with oral PREMARIN treatment should be taken into account.

Cardiovascular Disorders

An increased risk of stroke and deep vein thrombosis (DVT) has been reported with estrogen-alone therapy. An increased risk of pulmonary embolism, DVT, stroke and myocardial infarction has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogens with or without progestins should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (for example, personal history of venous thromboembolism [VTE], obesity, and systemic lupus erythematosus) should be managed appropriately.

Stroke

In the Women’s Health Initiative (WHI) estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year one and persisted [see Clinical Studies (14.2) in full Prescribing Information]. Should a stroke occur or be suspected, estrogens should be discontinued immediately.

Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg) versus those receiving placebo (18 versus 21 per 10,000 women-years).

In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in all women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to placebo (33 versus 25 per 10,000 women-years) [see Clinical Studies (14.2) in full Prescribing Information]. The increase in risk was demonstrated after the first year and persisted.

Coronary Heart Disease

In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal myocardial infarction [MI], silent MI, or CHD death) was reported in women receiving estrogen alone compared to placebo [see Clinical Studies (14.2) in full Prescribing Information].

Subgroup analyses of women 50 to 59 years of age suggest a statistically non-significant reduction in CHD events (CE 0.625 mg compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years).

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years). An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 [see Clinical Studies (14.2) in full Prescribing Information].

In postmenopausal women with documented heart disease (n = 2,763), average age 66.7 years, in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce

the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE (0.625 mg) plus MPA (2.5 mg) group and the placebo group in HERS, HERS II, and overall.

Venous Thromboembolism (VTE)

In the WHI estrogen-alone substudy, the risk of VTE (DVT and pulmonary embolism [PE]) was increased for women receiving daily CE (0.625 mg) compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years [see Clinical Studies (14.2) in full Prescribing Information]. Should a VTE occur or be suspected, estrogens should be discontinued immediately.

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was observed during the first year and persisted [see Clinical Studies (14.2) in full Prescribing Information]. Should a VTE occur or be suspected, estrogens should be discontinued immediately.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

Malignant Neoplasms

Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears to be associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

In a 52-week clinical trial using PREMARIN Vaginal Cream alone (0.5 g inserted twice weekly or daily for 21 days, then off for 7 days), there was no evidence of endometrial hyperplasia or endometrial carcinoma.

Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the Women’s Health Initiative (WHI) substudy of daily CE (0.625 mg). In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE (0.625 mg) was not associated with an increased risk of invasive breast cancer (relative risk [RR] 0.80) [see Clinical Studies (14.2) in full Prescribing Information].

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for estrogen plus progestin compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years for estrogen plus progestin compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for estrogen plus progestin compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups [see Clinical Studies (14.2) in full Prescribing Information].

Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms, requiring further evaluation.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo, was 1.58 (95 percent nCI 0.77-3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies, and some report no association.

Probable Dementia

In the estrogen-alone Women’s Health Initiative Memory Study (WHIMS), an ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg) or placebo. In the WHIMS estrogen plus progestin ancillary study, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo.

In the WHIMS estrogen-alone ancillary study, after an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent nCI 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years [see Use in Specific Populations (8.3), and Clinical Studies (14.3) in full Prescribing Information].

In the WHIMS estrogen plus progestin ancillary study, after an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent nCI 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years [see Use in Specific Populations (8.3), and Clinical Studies (14.3) in full Prescribing Information].

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent nCI 1.19-2.60). Since both substudies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [see Use in Specific Populations (8.5), and Clinical Studies (14.3) in full Prescribing Information].

Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

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