

# Drug Combo Approved for Advanced Breast Ca

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The Food and Drug Administration has approved lapatinib in combination with letrozole for the treatment of postmenopausal women with advanced breast cancer that is hormone receptor and HER2 positive and for whom hormonal therapy is indicated.

A kinase inhibitor, lapatinib (Tykerb) targets the HER2 protein that is overex-

pressed in HER2-positive breast cancer. Letrozole (Femara), an aromatase inhibitor, is used in patients with hormone-dependent breast cancer.

In a study sponsored by lapatinib manufacturer GlaxoSmithKline, progression-free survival was more than twofold higher among the women treated with the all-oral combination of these two agents, compared with those who received letrozole alone. "It is too early to determine

whether an improvement in overall survival will be observed in the clinical trial," the FDA statement said.

In the trial, median progression-free survival was 35.4 weeks among the 111 women who received lapatinib (1,500 mg/day) plus letrozole (2.5 mg/day), vs. a median of 13 weeks among the 108 women who received letrozole alone, according to the revised label for lapatinib.

The safety profile of lapatinib was

similar to that observed in previous studies of women with advanced breast cancer. Diarrhea, rash, nausea, and fatigue were the most common side effects, according to the FDA. Treatment with lapatinib has been associated with decreased left ventricular ejection fraction and hepatotoxicity, as well as interstitial lung disease and pneumonitis, and it can harm the fetus, the statement added.

Letrozole is marketed by Novartis. ■

## Vagifem® (estradiol vaginal tablets)

### Rx only

**BRIEF SUMMARY.** Please consult package insert for full prescribing information.

**WARNING: CARDIOVASCULAR DISORDERS, ENDOMETRIAL CANCER, BREAST CANCER and PROBABLE DEMENTIA: 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]. Cardiovascular Disorders and Probable Dementia: Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia [see Warnings and Precautions]. 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]. The WHI 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]. 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. **Estrogen Plus Progestin Therapy: Cardiovascular Disorders and Probable Dementia: Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia [see Warnings and Precautions].** 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]. 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]. **Breast Cancer:** The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer [see Warnings and Precautions]. 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 due to Menopause

**CONTRAINDICATIONS:** Vagifem® 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 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:** Vagifem® is intended only for vaginal administration. Systemic absorption occurs with the use of Vagifem®. The warnings, precautions, and adverse reactions associated with the use of systemic estrogen therapy 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 or family 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. 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). 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 non-fatal myocardial infarction [MI], silent MI, or CHD death) was reported in women receiving estrogen alone compared to placebo. Subgroup analysis of women 50 to 59 years of age suggests 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. 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 the 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 the original 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. 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. 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 women 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 associated with prolonged use, with an increased risk 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 estrogen therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. **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]. 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. 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 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