

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FEMTRACE safely and effectively. See full prescribing information for FEMTRACE.

Femtrace® (estradiol acetate tablets), for oral use
Initial U.S. Approval: 1975

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER, AND PROBABLE DEMENTIA

See full prescribing information for complete boxed warning.

Estrogen-Alone Therapy

- There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.2)
- Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia (5.1, 5.3)
- The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) (5.1)
- The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.3)

Estrogen Plus Progestin Therapy

- Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia (5.1, 5.3)
- The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism (PE), and myocardial infarction (MI) (5.1)
- The WHI estrogen plus progestin substudy reported an increased risk of invasive breast cancer (5.2)
- The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.3)

RECENT MAJOR CHANGES

Contraindications (4)	08/2014
Warnings and Precautions, Hereditary Angioedema (5.15)	08/2014

INDICATIONS AND USAGE

Femtrace is an estrogen indicated for the treatment of moderate to severe vasomotor symptoms due to menopause (1.1)

DOSAGE AND ADMINISTRATION

- Start therapy with 0.45 mg/day taken orally once daily. Dosage adjustment should be guided by the clinical response (2.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 0.45 mg, 0.9 mg, and 1.8 mg (3)

CONTRAINDICATIONS

- Undiagnosed abnormal genital bleeding (4)
- Known, suspected, or history of breast cancer (4, 5.2)
- Known or suspected estrogen-dependent neoplasia (4, 5.2)
- Active DVT, PE, or history of these conditions (4, 5.1)
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions (4, 5.1)
- Known anaphylactic reaction or angioedema to Femtrace (4)
- Known liver impairment or disease (4, 5.10)
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders (4)
- Known or suspected pregnancy (4, 8.1)

WARNINGS AND PRECAUTIONS

- Estrogens increase the risk of gallbladder disease (5.4)
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs (5.5, 5.6, 5.9, 5.10)
- Monitor thyroid function in women on thyroid replacement therapy (5.11, 5.18)

ADVERSE REACTIONS

Most common adverse reactions (incidence > 5 percent) are vaginal bleeding and breast tenderness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Warner Chilcott at 1-800-521-8813 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Inducers and/or inhibitors of CYP3A4 may affect estrogen drug metabolism (7.1)

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Estrogen administration to nursing women has been shown to decrease the quantity and quality of breast milk (8.3)
- Geriatric Use: An increased risk of probable dementia in women over 65 years of age was reported in the Women's Health Initiative Memory ancillary studies of the Women's Health Initiative (5.3, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 08/2014

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FULL PRESCRIBING INFORMATION

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, 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 (5.2)*].

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia [*see Warnings and Precautions (5.1 and 5.3), and Clinical Studies (14.2, 14.3)*].

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]-alone, relative to placebo [*see Warnings and Precautions (5.1), and Clinical Studies (14.2)*].

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of the 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 (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.3)*].

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 (5.1, 5.3) and Clinical Studies (14.2, 14.3)*].

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo [*see Warnings and Precautions (5.1), and Clinical Studies (14.2)*].

The WHIMS estrogen plus progestin ancillary study of the WHI reported 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 (5.3), Use in Specific Populations (8.5) and Clinical Studies (14.3)*].

Breast Cancer

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 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.

1 INDICATIONS AND USAGE

1.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause.

2 DOSAGE AND ADMINISTRATION

Generally, when estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be considered to reduce the risk of endometrial cancer.

A woman without a uterus does not need a progestin. In some cases, however, hysterectomized women with a history of endometriosis may need a progestin [see Warnings and Precautions (5.2, 5.14)].

Use of estrogen-alone, or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

2.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

Start therapy with Femtrace 0.45 mg/day taken once daily. Dosage adjustment should be guided by the clinical response.

Therapy should be started at the lowest effective dose and the shortest duration consistent with the treatment goals. Attempts to taper or discontinue the medication should be made at 3 to 6 month intervals.

3 DOSAGE FORMS AND STRENGTHS

Femtrace (estradiol acetate tablets) are available as follows:

- Femtrace 0.45 mg tablets contain 0.45 mg of estradiol acetate and are cream, round tablets debossed with “WC 389” on one side and the tablet logo on the other side.
- Femtrace 0.9 mg tablets contain 0.9 mg of estradiol acetate and are white, round tablets debossed with “WC 390” on one side and the tablet logo on the other side.
- Femtrace 1.8 mg tablets contain 1.8 mg of estradiol acetate and are yellow, round tablets debossed with “WC 391” on one side and the tablet logo on the other side.

4 CONTRAINDICATIONS

Femtrace is contraindicated 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 DVT, PE or history of these conditions
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions
- Known anaphylactic reaction or angioedema to Femtrace

- Known liver impairment or disease
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders
- Known or suspected pregnancy

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Disorders

An increased risk of stroke and DVT has been reported with estrogen-alone therapy. An increased risk of PE, DVT, stroke, and MI has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately.

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

Stroke

In the 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)-alone 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 1 and persisted [see *Clinical Studies (14.2)*]. Should a stroke occur or be suspected, estrogen-alone therapy 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)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years).¹

In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age 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)*]. The increase in risk was demonstrated after the first year and persisted.¹ Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

Coronary Heart Disease

In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo² [see *Clinical Studies (14.2)*].

Subgroup analyses of women 50 to 59 years of age suggest a statistically non-significant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 woman-years).¹

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events reported 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).¹ 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 postmenopausal women with documented heart disease (n = 2,763), average 66.7 years of age, 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 CHD. 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 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 plus MPA group and the placebo group in HERS, HERS II, and overall.

Venous Thromboembolism

In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE), was increased for women receiving daily CE (0.625 mg)-alone 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 years³ [see *Clinical Studies (14.2)*]. Should a VTE occur or be suspected, estrogen-alone therapy 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 demonstrated during the first year and persisted⁴ [see *Clinical Studies (14.2)*]. Should a VTE occur or be suspected, estrogen plus progestin therapy 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.

5.2 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 times 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 increased risks of 15- to 24-fold for 5 to 10 years or more. 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 WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer (relative risk [RR] 0.80)⁵ [see *Clinical Studies (14.2)*].

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 invasive 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 CE plus MPA compared with placebo [see *Clinical Studies (14.2)*]. 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 CE plus MPA 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 CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were 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 groups⁶ [see *Clinical Studies (14.2)*].

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 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 CI, 0.77-3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.⁷ In some epidemiologic studies, the use of estrogen plus progestin and 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.

5.3 Probable Dementia

In the WHIMS estrogen-alone 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)-alone or placebo.

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 CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years⁸ [see *Use in Specific Populations (8.5), and Clinical Studies (14.3)*].

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.

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 CI, 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-years⁸ [see *Use in Specific Populations (8.5), and Clinical Studies (14.3)*].

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both ancillary substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women⁸ [see *Use in Specific Populations (8.5) and Clinical Studies (14.3)*].

5.4 Gallbladder Disease

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

5.5 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.

5.6 Visual Abnormalities

Retinal vascular thrombosis has been reported in women receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

5.7 Addition of a Progestin When a Woman Has Not Had a Hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer.

5.8 Elevated Blood Pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen.

5.9 Hypertriglyceridemia

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs.

5.10 Hepatic Impairment and/or a Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in women with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

5.11 Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T₄ and T₃ serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

5.12 Fluid Retention

Estrogens may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as cardiac or renal impairment, warrant careful observation when estrogen-alone is prescribed.

5.13 Hypocalcemia

Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

5.14 Exacerbation of Endometriosis

A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

5.15 Hereditary Angioedema

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema.

5.16 Exacerbation of Other Conditions

Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus and hepatic hemangiomas, and should be used with caution in women with these conditions.

5.17 Laboratory Tests

Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of moderate to severe vasomotor symptoms.

5.18 Drug-Laboratory Test Interactions

Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Increased TBG levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T₄ levels (by column or by radioimmunoassay) or T₃ levels by radioimmunoassay. T₃ resin uptake is decreased, reflecting the elevated TBG. Free T₄ and free T₃ concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone.

Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

Increased plasma high-density lipoprotein (HDL) and HDL₂ cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentration, increased triglycerides levels.

Impaired glucose tolerance.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Cardiovascular Disorders [*see Boxed Warning, Warnings and Precautions (5.1)*].
- Malignant Neoplasms [*see Boxed Warning, Warnings and Precautions (5.2)*].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In two 12-week clinical trials that included 327 postmenopausal women treated with Femtrace and 221 women treated with placebo tablets, adverse reactions that occurred in any treatment group at a rate of ≥ 2 percent associated with the use of Femtrace are summarized in Table 1.

Table 1. Associated Adverse Reactions Reported by ≥ 2 Percent of Subjects in Any Treatment Group by Body System^a

BODY SYSTEM/ Adverse Reaction	Number (percent) of Subjects			
	Placebo (n = 221)	Femtrace 0.45 mg/day (n = 132)	Femtrace 0.9 mg/day (n = 100)	Femtrace 1.8 mg/day (n = 95)
	n (%)	n (%)	n (%)	n (%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	6 (2.7)	2 (1.5)	9 (9.0)	16 (16.8)
Vaginal Hemorrhage	2 (0.9)	1 (0.8)	3 (3.0)	7 (7.4)
Breast Tenderness	3 (1.4)	0 (0.0)	0 (0.0)	5 (5.3)
Vaginal Discharge	0 (0.0)	1 (0.8)	4 (4.0)	3 (3.2)
Intermenstrual Bleeding	2 (0.9)	0 (0.0)	2 (2.0)	3 (3.2)
Genital Pruritus – Female	0 (0.0)	0 (0.0)	1 (1.0)	2 (2.1)
GASTROINTESTINAL DISORDERS	3 (1.4)	2 (1.5)	3 (3.0)	4 (4.2)
Abdominal Pain – NOS	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.1)
NERVOUS SYSTEM DISORDERS	7 (3.2)	1 (0.8)	4 (4.0)	3 (3.2)
Headache – NOS	5(2.3)	1 (0.8)	4 (4.0)	3 (3.2)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.5)	0 (0.0)	4 (4.0)	0 (0.0)
Acne – NOS	0 (0.0)	0 (0.0)	2 (2.0)	0 (0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.5)	0 (0.0)	3 (3.0)	1 (1.1)
Fatigue	0 (0.0)	0 (0.0)	2 (2.0)	0 (0.0)

AE = adverse event; NOS = not otherwise specified

^a Each subject is counted only once in the body system's total using the most related adverse event. Only the most related for a subject is counted in each adverse event's total. Subjects may be counted more than once in the total number of subject's with AEs.

6.2 Postmarketing Experience

The following additional adverse reactions have been identified during post-approval use of Femtrace. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Genitourinary System

Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; increase in size of uterine leiomyomata, vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer; ovarian cyst.

Breasts

Tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer; breast disorder.

Cardiovascular

Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; cerebrovascular accident (stroke); chest pain; increase in blood pressure; dyspnea; transient ischemic attack.

Gastrointestinal

Nausea, vomiting; cholestatic jaundice; pancreatitis, enlargement of hepatic hemangiomas; bloating, abdominal cramps; abdominal pain; increased incidence of gallbladder disease.

Skin

Chloasma or melasma that may persist when drug is discontinued; generalized erythema; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; rash, pruritus.

Eyes

Retinal vascular thrombosis; visual impairment; intolerance to contact lenses.

Central Nervous System (CNS)

Headache; migraine; dizziness; depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy, dementia.

Miscellaneous

Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthralgias; leg cramps; back pain; changes in libido; urticaria, angioedema, anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides; hypersensitivity.

7 DRUG INTERACTIONS

No drug interaction studies have been conducted for Femtrace.

7.1 Metabolic Interactions

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's wort (*Hypericum perforatum*) preparations, phenobarbital, carbamazepine and rifampin may decrease the plasma concentration of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase the plasma concentration of estrogens and may result in side effects.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Femtrace should not be used during pregnancy [see *Contraindications (4)*]. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy.

8.3 Nursing Mothers

Femtrace should not be used during lactation. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogens have been identified in the breast milk of women receiving estrogen-alone therapy. Caution should be exercised when Femtrace is administered to a nursing woman.

8.4 Pediatric Use

Femtrace is not indicated in children. Clinical studies have not been conducted in the pediatric population.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric women involved in clinical studies utilizing Femtrace to determine whether those over 65 years of age differ from younger subjects in their response to Femtrace.

The Women's Health Initiative Studies

In the WHI estrogen-alone substudy (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age [see *Clinical Studies (14.2)*].

In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age [see *Clinical Studies* (14.2)].

The Women's Health Initiative Memory Study

In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen-alone or estrogen plus progestin when compared to placebo [see *Warnings and Precautions* (5.3), and *Clinical Studies* (14.3)].

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women⁸ [see *Warnings and Precautions* (5.3), and *Clinical Studies* (14.3)].

8.6 Renal Impairment

The effect of renal impairment on the pharmacokinetics of Femtrace has not been studied.

8.7 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of Femtrace has not been studied.

10 OVERDOSAGE

Overdosage of estrogen may cause nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of Femtrace with institution of appropriate symptomatic care.

11 DESCRIPTION

Femtrace (estradiol acetate tablets) for oral administration are available in the following three strengths:

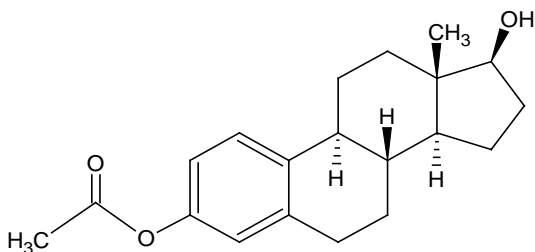
Femtrace (0.45 mg): Each cream, round tablet contains 0.45 mg estradiol acetate

Femtrace (0.9 mg): Each white, round tablet contains 0.9 mg estradiol acetate

Femtrace (1.8 mg): Each yellow, round tablet contains 1.8 mg estradiol acetate

Femtrace contains the following inactive ingredients: ferric oxide, povidone, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, silicon dioxide, magnesium stearate and acetic acid; ferric oxide, a coloring agent, is not an ingredient in the 0.9 mg tablets.

The structural formula is as follows.



Estradiol acetate is chemically described as *estra-1,3,5(10)-triene-3,17 β -diol-3-acetate*. The molecular formula of estradiol acetate is $C_{20}H_{26}O_3$ and the molecular weight of estradiol acetate is 314.42.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, which is secreted by the adrenal cortex, to estrone in the peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and FSH through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

12.2 Pharmacodynamics

There are no pharmacodynamic data for Femtrace.

12.3 Pharmacokinetics

In vitro studies suggest that within 5 minutes of administration, all estradiol acetate will be hydrolyzed to estradiol *in vivo*.

Absorption

Estradiol was rapidly absorbed following oral administration of estradiol acetate. Mean serum estradiol concentrations following multiple dosing are shown in Figure 1. Estradiol and estrone serum concentrations increased proportionally with increasing dose; the corresponding estradiol C_{avg} values were 23.5, 44.4 and 92.1 pg/mL for the 0.45, 0.9 and 1.8 mg doses, respectively (see Table 2).

Figure 1. Mean (\pm SD) Serum Estradiol Concentration Following Multiple-Dose Administration of Femtrace to Healthy Postmenopausal Women

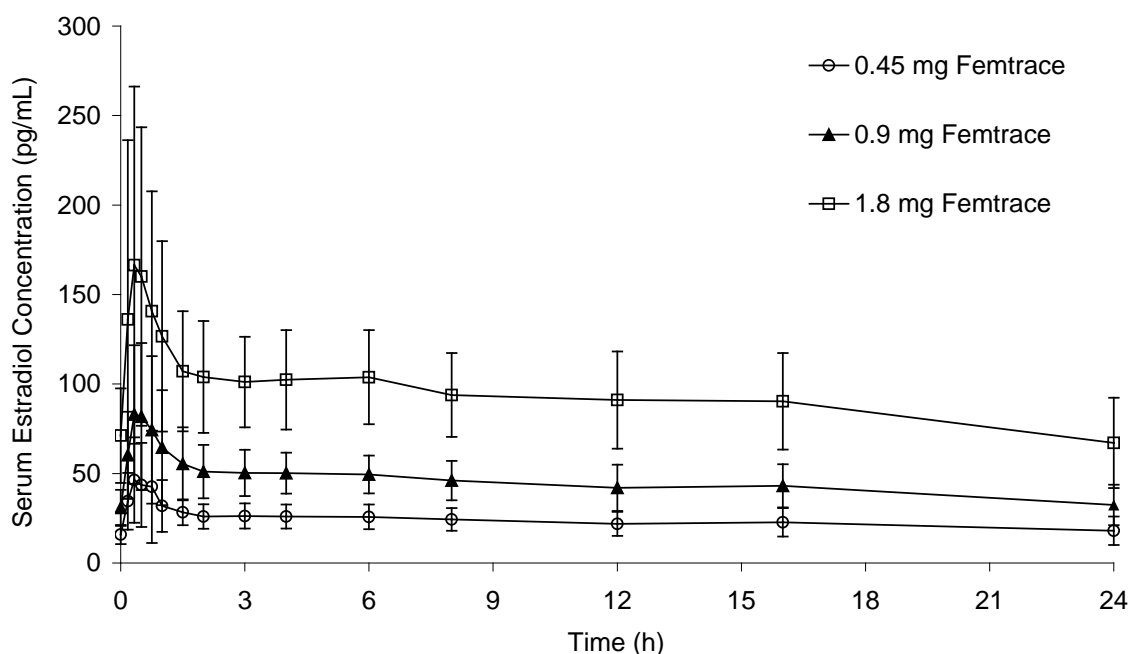


Table 2. Summary of Mean (%CV)* Pharmacokinetic Parameters Following Multiple-Dose Administration of Femtrace to Healthy Postmenopausal Women (n = 18)

Estradiol Acetate Dose	Analyte	C _{max} (pg/mL)	t _{max} ** (hour)	AUC(0-τ) (pg·h/mL)	t _{1/2} **** (hour)
0.45 mg	Estradiol	56.7 (57)	0.50	565.0 (26)	25.9
	Estrone***	155.0 (40)	6.0	2363.8 (34)	15.9
0.9 mg	Estradiol	90.1 (51)	0.43	1066.5 (25)	22.2
	Estrone***	313.9 (25)	5.0	4980.9 (32)	16.1
1.8 mg	Estradiol	177.3 (55)	0.75	2211.3 (26)	21.4
	Estrone***	680.6 (25)	6.0	11510.8 (32)	17.6

* Coefficient of Variation
** Median value reported for T_{max}
*** Baseline-adjusted values
**** Harmonic mean value reported for t_{1/2}

C_{max}: Maximum serum concentration
t_{max}: Time of C_{max}
AUC(0-τ): Area under the serum concentration-time curve over the dosing interval
t_{1/2}: Half-life

Effect of Food

The maximum serum concentration (C_{max}) of estradiol following administration of 1.8 mg estradiol acetate was 36 percent lower in the fed state compared to the fasted state. However, the area under the serum concentration versus time curve (AUC) was comparable among the fed and fasted states.

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to SHBG and albumin.

Metabolism

Estradiol acetate is hydrolyzed *in vivo* to estradiol. Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is a major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the intestine followed by reabsorption. In postmenopausal women, a significant proportion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

The estradiol apparent elimination half-life value is 21 to 26 hours.

Use in Specific Populations

No pharmacokinetic studies were conducted with Femtrace in specific populations, including women with renal or hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

Estradiol acetate was assayed for mutation in four histidine-requiring strains of *Salmonella typhimurium* and in one tryptophan-requiring strain of *Escherichia coli*. Estradiol acetate did not induce mutations in any of the bacterial strains tested under the conditions employed.

14 CLINICAL STUDIES

14.1 Effects on Vasomotor Symptoms

Two 12-week double-blind, placebo-controlled clinical trials were conducted to evaluate the efficacy of Femtrace in the treatment of moderate to severe vasomotor symptoms in postmenopausal women who had at least 7 moderate to severe hot flushes daily or at least 60 moderate to severe hot flushes per week before randomization. In one study, 289 postmenopausal women (mean age 53.4 years [range 41 to 68 years], 78 percent Caucasian) were randomized to receive either placebo, Femtrace 0.9 mg/day or Femtrace 1.8 mg/day. In the second study, 221 postmenopausal women (mean age 52.2 years [range 36 to 80 years], 80 percent Caucasian) were randomized to receive either placebo or Femtrace 0.45 mg/day. The results in Tables 3a and 4a indicate that compared with placebo, Femtrace 0.9 mg/day and Femtrace 1.8 mg/day produced a reduction in both the frequency and severity of moderate to severe vasomotor symptoms at weeks 4 and 12. The results in Tables 3b and 4b indicate that compared with placebo, Femtrace 0.45 mg/day produced a reduction in the frequency of moderate to severe vasomotor symptoms at weeks 4 and 12, and a reduction in the severity of moderate to severe vasomotor symptoms at weeks 7 and 12.

Table 3a. Mean Change from Baseline in the Number of Moderate to Severe Vasomotor Symptoms per Week – ITT Population, LOCF

Visit	Placebo (n = 94)	Femtrace 0.9 mg/day (n = 100)	Femtrace 1.8 mg/day (n = 95)
Baseline¹			
Mean (SD)	86.1 (40.2)	78.5 (24.9)	82.4 (39.1)
Week 4*			
Mean (SD)	51.5 (47.2)	24.3 (28.4)	21.9 (25.9)
Mean (SE) Change from Baseline	-30.1 (3.3)	-56.5 (3.2)	-59.3 (3.4)
p value vs. Placebo ²	-	<0.001	<0.001
Week 12*			
Mean (SD)	46.8 (54.6)	17.5 (28.9)	7.3 (15.2)
Mean (SE) Change from Baseline	-36.3 (3.5)	-63.9 (3.4)	-74.8 (3.6)
p value vs. Placebo ²	-	<0.001	<0.001

*Primary endpoints

¹ The baseline number of moderate to severe vasomotor symptoms (MSVS) is the weekly average number of MSVS during the two weeks between screening and randomization

² p values were based on Wilcoxon rank sum test (van Elteren test)

ITT = intent to treat; LOCF = last observation carried forward; SD = standard deviation; SE = standard error

Table 3b. Mean Change from Baseline in the Number of Moderate to Severe Vasomotor Symptoms per Week – ITT (modified)¹ Population, LOCF

Visit	Placebo (n = 108)	Femtrace 0.45 mg/day (n = 113)
Baseline²		
Mean (SD)	85.8 (37.8)	86.2 (34.8)
Week 4*		
Mean (SD)	51.5 (37.1)	44.1 (39.5)
Mean (SE) Change from Baseline	-33.8 (3.5)	-41.5 (3.5)
p value vs. Placebo ³	-	0.014
Week 12*		
Mean (SD)	43.1 (38.1)	34.1 (40.9)
Mean (SE) Change from Baseline	-41.5 (3.5)	-51.2 (3.5)
p value vs. Placebo ³	-	0.005

*Primary endpoints

¹ITT (modified): intent to treat modified by excluding 24 unblinded subjects

²The baseline number of moderate to severe vasomotor symptoms (MSVS) is the weekly average number of MSVS during the two weeks between screening and randomization

³p values were based on Wilcoxon rank sum test (van Elteren test)

ITT = intent to treat; LOCF = last observation carried forward; SD = standard deviation; SE = standard error

Table 4a. Mean Change from Baseline in the Severity of Moderate to Severe Vasomotor Symptoms per Week – ITT Population, LOCF

Visit	Placebo (n = 94)	Femtrace 0.9 mg/day (n = 100)	Femtrace 1.8 mg/day (n = 95)
Baseline¹			
Mean (SD)	2.5 (0.2)	2.5 (0.2)	2.5 (0.2)
Week 4*			
Mean (SD)	2.3 (0.6)	1.8 (1.0)	1.9 (1.0)
Mean (SE) Change from Baseline	-0.2 (1.0)	-0.7 (0.1)	-0.7 (0.1)
p value vs. Placebo ²	-	0.001	0.002
Week 12*			
Mean (SD)	2.2 (0.8)	1.4 (1.2)	1.0 (1.2)
Mean (SE) Change from Baseline	-0.3 (0.1)	-1.1 (0.1)	-1.5 (0.1)
p value vs. Placebo ²	-	<0.001	<0.001

*Primary endpoints

¹The baseline severity of moderate to severe vasomotor symptoms (MSVS) is the average severity of MSVS during the two weeks between screening and randomization

²p values were based on Wilcoxon rank sum test (van Elteren test)

Note: Hot flush severity was scored using the following scale: 1 = Mild, 2 = Moderate, 3 = Severe

ITT = intent to treat; LOCF = last observation carried forward; SD = standard deviation; SE = standard error

Table 4b. Mean Change from Baseline in the Severity of Moderate to Severe Vasomotor Symptoms per Week – ITT (modified)¹ Population, LOCF

Visit	Placebo (n = 108)	Femtrace 0.45 mg/day (n = 113)
Baseline²		
Mean (SD)	2.6 (0.2)	2.5 (0.2)
Week 4*		
Mean (SD)	2.4 (0.5)	2.3 (0.7)
Mean (SE) Change from Baseline	-0.2 (0.1)	-0.3 (0.06)
p value vs. Placebo ³	-	0.787
Week 12*		
Mean (SD)	2.3 (0.8)	1.9 (1.1)
Mean (SE) Change from Baseline	-0.3 (0.1)	-0.7 (0.1)
p value vs. Placebo ³	-	0.016

*Primary endpoints

¹ITT (modified): intent to treat modified by excluding 24 unblinded subjects

²The baseline severity of moderate to severe vasomotor symptoms (MSVS) is the average severity of MSVS during the two weeks between screening and randomization

³p values were based on Wilcoxon rank sum test (van Elteren test)

Note: Hot flush severity was scored using the following scale: 1 = Mild, 2 = Moderate, 3 = Severe

ITT = intent to treat; LOCF = last observation carried forward; SD = standard deviation; SE = standard error

14.2 Women’s Health Initiative Studies

The WHI enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of daily oral CE (0.625 mg)-alone or in combination with MPA (2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of CHD (defined as nonfatal MI, silent MI and CHD death], with invasive breast cancer as the primary adverse outcome. A “global index” included the earliest occurrence of CHD, invasive breast cancer, stroke, PE, endometrial cancer (only in the CE plus MPA substudy), colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE-alone or CE plus MPA on menopausal symptoms.

WHI Estrogen-Alone Substudy

The WHI estrogen-alone substudy was stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen-alone in predetermined primary endpoints.

Results of the estrogen-alone substudy, which included 10,739 women (average 63 years of age, range 50 to 79; 75.3 percent White, 15.1 percent Black, 6.1 percent Hispanic, 3.6 percent Other), after an average follow-up of 7.1 years, are presented in Table 5.

Table 5. Relative and Absolute Risk Seen in the Estrogen-Alone Substudy of WHI^a

Event	Relative Risk CE vs. Placebo (95 percent nCI ^b)	CE	Placebo
		n = 5,310	n = 5,429
		Absolute Risk per 10,000 Women- Years	
CHD events ^c	0.95 (0.78-1.16)	54	57
<i>Non-fatal MI^c</i>	<i>0.91 (0.73-1.14)</i>	<i>40</i>	<i>43</i>
<i>CHD death^c</i>	<i>1.01 (0.71-1.43)</i>	<i>16</i>	<i>16</i>
All strokes ^c	1.33 (1.05-1.68)	45	33
<i>Ischemic stroke^c</i>	<i>1.55 (1.19-2.01)</i>	<i>38</i>	<i>25</i>
Deep vein thrombosis ^{c,d}	1.47 (1.06-2.06)	23	15
Pulmonary embolism ^c	1.37 (0.90-2.07)	14	10
Invasive breast cancer ^c	0.80 (0.62-1.04)	28	34
Colorectal cancer ^c	1.08 (0.75-1.55)	17	16
Hip fracture ^c	0.65 (0.45-0.94)	12	19
Vertebral fractures ^{c,d}	0.64 (0.44-0.93)	11	18
Lower arm/wrist fractures ^{c,d}	0.58 (0.47-0.72)	35	59
Total fractures ^{c,d}	0.71 (0.64-0.80)	144	197
Deaths due to other causes ^{e,f}	1.08 (0.88-1.32)	53	50
Overall Mortality ^{c,d}	1.04 (0.88-1.22)	79	75
Global Index ^g	1.02 (0.92-1.13)	206	201

^aAdapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.

^bNominal confidence intervals unadjusted for multiple looks and multiple comparisons.

^cResults are based on centrally adjudicated data for an average follow-up of 7.1 years.

^dNot included in “global index”.

^eResults are based on an average follow-up of 6.8 years.

^fAll deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

^gA subset of the events was combined in a “global index” defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

For those outcomes included in the WHI “global index” that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE-alone were 12 more strokes, while the absolute risk reduction per 10,000 women-years was 7 fewer hip fractures.⁹ The absolute excess risk of events included in the “global index” was a non-significant 5 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality.

No overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE-alone compared with placebo was reported in final centrally adjudicated results from the estrogen-alone substudy, after an average follow-up of 7.1 years. See Table 5.

Centrally adjudicated results for stroke events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no significant difference in distribution of stroke subtype or severity, including fatal strokes, in women receiving CE-alone compared to placebo. Estrogen-alone therapy increased the risk of ischemic stroke, and this excess was present in all subgroups of women examined.¹⁰ See Table 5.

Timing of the initiation of estrogen-alone therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen-alone substudy stratified by age, showed in women 50 to 59 years of age, a non-significant trend toward reduced risk for CHD [*hazard ratio (HR) 0.63 (95 percent CI, 0.36-1.09)*] and overall mortality [*HR 0.71 (95 percent CI, 0.46-1.11)*].

WHI Estrogen Plus Progestin Substudy

The WHI estrogen plus progestin substudy was also stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the “global index”. The absolute excess risk of events included in the “global index” was 19 per 10,000 women-years.

For those outcomes included in the WHI “global index” that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women-years in the group treated with CE plus MPA were 7 more CHD events, 8 more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures.

Results of the CE plus MPA substudy, which included 16,608 women (average 63 years of age, range 50 to 79; 83.9 percent White, 6.8 percent Black, 5.4 percent Hispanic, 3.9 percent Other) are presented in Table 6. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

Table 6. Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years^{a,b}

Event	Relative Risk CE/MPA vs. Placebo (95% nCI ^c)	CE/MPA	Placebo
		n = 8,506	n = 8,102
Absolute Risk per 10,000 Women-Years			
CHD events	1.23 (0.99-1.53)	41	34
<i>Non-fatal MI</i>	<i>1.28 (1.00-1.63)</i>	<i>31</i>	<i>25</i>
<i>CHD death</i>	<i>1.10 (0.70-1.75)</i>	<i>8</i>	<i>8</i>
All strokes	1.31 (1.03-1.68)	33	25
<i>Ischemic stroke</i>	<i>1.44 (1.09-1.90)</i>	<i>26</i>	<i>18</i>
Deep vein thrombosis ^d	1.95 (1.43-2.67)	26	13
Pulmonary embolism	2.13 (1.45-3.11)	18	8
Invasive breast cancer ^e	1.24 (1.01-1.54)	41	33
Colorectal cancer	0.61 (0.42-0.87)	10	16
Endometrial cancer ^d	0.81 (0.48-1.36)	6	7
Cervical cancer ^d	1.44 (0.47-4.42)	2	1
Hip fracture	0.67 (0.47-0.96)	11	16
Vertebral fractures ^d	0.65 (0.46-0.92)	11	17
Lower arm/wrist fractures ^d	0.71 (0.59-0.85)	44	62
Total fractures ^d	0.76 (0.69-0.83)	152	199
Overall Mortality ^{c,f}	1.00 (0.83-1.19)	52	52
Global Index ^g	1.13 (1.02-1.25)	184	165

^aAdapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.

^bResults are based on centrally adjudicated data.

^cNominal confidence intervals unadjusted for multiple looks and multiple comparisons.

^dNot included in “global index”.

^eIncludes metastatic and non-metastatic breast cancer with the exception of *in situ* cancer.

^fAll deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

^gA subset of the events was combined in a “global index” defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

Timing of initiation of estrogen plus progestin therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen plus progestin substudy stratified by age showed in women 50 to 59 years of age a non-significant trend toward reduced risk for overall mortality [*HR 0.69 (95 percent CI, 0.44-1.07)*].

14.3 Women’s Health Initiative Memory Study

The WHIMS estrogen-alone ancillary study of WHI enrolled 2,947 predominantly healthy hysterectomized postmenopausal women 65 to 79 years of age and older (45 percent were 65 to 69 years of age; 36 percent were 70 to 74 years of age; 19 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg)-alone on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 5.2 years, the relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 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. Probable dementia as defined in this study included Alzheimer’s disease (AD), vascular dementia (VaD) and mixed types (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [*see Warnings and Precautions (5.3), and Use in Specific Populations (8.5)*].

The WHIMS estrogen plus progestin ancillary study of WHI enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent were 65 to 69 years of age, 35 percent were 70 to

74 years of age, and 18 percent were 75 years of age and older) to evaluate the effects of CE (0.625 mg) plus MPA (2.5 mg) on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 4 years, the relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 per 10,000 women-years. Probable dementia as defined in this study included AD, VaD and mixed types (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the substudy was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [see *Warnings and Precautions* (5.3), and *Use in Specific Populations* (8.5)].

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 CI, 1.19-2.60). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women [see *Warnings and Precautions* (5.3), and *Use in Specific Populations* (8.5)].

15 REFERENCES

1. Rossouw JE, et al. Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause. *JAMA*. 2007;297:1465-1477.
2. Hsia J, et al. Conjugated Equine Estrogens and Coronary Heart Disease. *Arch Int Med*. 2006;166:357-365.
3. Curb JD, et al. Venous Thrombosis and Conjugated Equine Estrogen in Women Without a Uterus. *Arch Int Med*. 2006;166:772-780.
4. Cushman M, et al. Estrogen Plus Progestin and Risk of Venous Thrombosis. *JAMA*. 2004;292:1573-1580.
5. Stefanick ML, et al. Effects of Conjugated Equine Estrogens on Breast Cancer and Mammography Screening in Postmenopausal Women With Hysterectomy. *JAMA*. 2006;295:1647-1657.
6. Chlebowski RT, et al. Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women. *JAMA*. 2003;289:3234-3253.
7. Anderson GL, et al. Effects of Estrogen Plus Progestin on Gynecologic Cancers and Associated Diagnostic Procedures. *JAMA*. 2003;290:1739-1748.
8. Shumaker SA, et al. Conjugated Equine Estrogens and Incidence of Probable Dementia and Mild Cognitive Impairment in Postmenopausal Women. *JAMA*. 2004;291:2947-2958.
9. Jackson RD, et al. Effects of Conjugated Equine Estrogen on Risk of Fractures and BMD in Postmenopausal Women With Hysterectomy: Results From the Women's Health Initiative Randomized Trial. *J Bone Miner Res*. 2006;21:817-828.
10. Hendrix SL, et al. Effects of Conjugated Equine Estrogen on Stroke in the Women's Health Initiative. *Circulation*. 2006;113:2425-2434.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Femtrace (estradiol acetate tablets) is available in bottles of 100 tablets.

N 0430-0389-24 Femtrace 0.45 mg (estradiol acetate tablets) are cream, round tablet debossed with "WC 389" on one side and the tablet logo on the other side.

N 0430-0390-24 Femtrace 0.9 mg (estradiol acetate tablets) are white, round tablet debossed with "WC 390" on one side and the tablet logo on the other side.

N 0430-0391-24 Femtrace 1.8 mg (estradiol acetate tablets) are yellow, round tablet debossed with "WC 391" on one side and the tablet logo on the other side.

16.2 Storage and Handling

Store at 20°C to 25°C (66°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

17.1 Vaginal Bleeding

Inform postmenopausal women of the importance of reporting abnormal vaginal bleeding to their healthcare provider as soon as possible [*see Warnings and Precautions (5.2)*].

17.2 Possible Serious Adverse Reactions with Estrogen-Alone Therapy

Inform postmenopausal women of possible serious adverse reactions of estrogen-alone therapy including Cardiovascular Disorders, Malignant Neoplasms, and Probable Dementia [*see Warnings and Precautions (5.1, 5.2, 5.3)*].

17.3 Possible Less Serious but Common Adverse Reactions with Estrogen-Alone Therapy

Inform postmenopausal women of possible less serious but common adverse reactions of estrogen-alone therapy such as headache, breast pain and tenderness, nausea and vomiting.

Manufactured by:

Pharmaceutics International, Inc.

Hunt Valley, MD 21031

for Warner Chilcott Company, LLC

Fajardo, PR 00738

Marketed by:

Warner Chilcott (US), LLC

Rockaway, NJ 07866

1-800-521-8813



Revised 08/2014

Patient Information

FEMTRACE (fem-trace)

(estradiol acetate)

Tablets

Read this Patient Information before you start taking FEMTRACE and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms or your treatment.

What is the most important information I should know about FEMTRACE (an estrogen hormone)?

- Using estrogen-alone may increase your chance of getting cancer of the uterus (womb). Report any unusual vaginal bleeding right away while you are taking FEMTRACE. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find the cause.
- Do not use estrogen-alone to prevent heart disease, heart attacks, strokes or dementia (decline in brain function).
- Using estrogen-alone may increase your chances of getting strokes or blood clots.
- Using estrogen-alone may increase your chance of getting dementia, based on a study of women 65 years of age or older.
- Do not use estrogens with progestins to prevent heart disease, heart attacks, strokes or dementia.
- Using estrogens with progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots.
- Using estrogens with progestins may increase your chance of getting dementia, based on a study of women 65 years of age or older.
- You and your healthcare provider should talk regularly about whether you still need treatment with FEMTRACE.

What is FEMTRACE?

FEMTRACE is a prescription medicine that contains estradiol (an estrogen hormone).

What is FEMTRACE used for?

FEMTRACE is used after menopause to:

- **Reduce moderate to severe hot flashes**

Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 and 55 years old. This drop in body estrogen levels causes the "change of life" or menopause, the end of monthly menstrual periods. Sometimes both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "surgical menopause".

When estrogen levels begin dropping, some women get very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes" or "hot flushes"). In some women the symptoms are mild, and they will not need to take estrogens. In other women, symptoms can be more severe. You and your healthcare provider should talk regularly about whether or not you still need treatment with FEMTRACE.

Who should not take FEMTRACE?

Do not take FEMTRACE if you:

- **have unusual vaginal bleeding**

Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.

- **currently have or have had certain cancers.**

Estrogens may increase the chance of getting certain types of cancers, including cancer of the breast and uterus. If you have or have had cancer, talk with your healthcare provider about whether you should take FEMTRACE.

- **had a stroke or heart attack**
- **currently have or have had blood clots**
- **currently have or have had liver problems**
- **have been diagnosed with a bleeding disorder**
- **are allergic to FEMTRACE or any of its ingredients**

See the list of ingredients in FEMTRACE at the end of this leaflet.

- **think you may be pregnant**

FEMTRACE is not for pregnant women. If you think you may be pregnant, you should have a pregnancy test and know the results. Do not take FEMTRACE if the test is positive and talk to your healthcare provider.

What should I tell my healthcare provider before I take FEMTRACE?

Before you take FEMTRACE, tell your healthcare provider if you:

- **have any unusual vaginal bleeding**

Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.

- **have any other medical conditions**

Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis, lupus, angioedema (swelling of face and tongue), or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

- **are going to have surgery or will be on bed rest**

Your healthcare provider will let you know if you need to stop taking FEMTRACE.

- **are breastfeeding**

The hormones in FEMTRACE can pass into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may affect how FEMTRACE works. FEMTRACE may also affect how your other medicines work. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take FEMTRACE?

- Take FEMTRACE exactly as your healthcare provider tells you to take it.
- Take 1 FEMTRACE tablet at the same time each day.
- You and your healthcare provider should talk regularly (every 3 to 6 months) about the dose you are taking and whether you still need treatment with FEMTRACE.

What are the possible side effects of FEMTRACE?

Side effects are grouped by how serious they are and how often they happen when you are treated.

Serious, but less common side effects include:

- heart attack
- stroke
- blood clots
- dementia
- breast cancer
- cancer of the lining of the uterus (womb)
- cancer of the ovary

- high blood pressure
- high blood sugar
- gallbladder disease
- liver problems
- changes in your thyroid hormone levels
- enlargement of benign tumors of the uterus (“fibroids”)

Call your healthcare provider right away if you get any of the following warning signs, or any other unusual symptoms that concern you:

- new breast lumps
- unusual vaginal bleeding
- changes in vision or speech
- sudden new severe headaches
- severe pains in your chest or legs with or without shortness of breath, weakness and fatigue

Less serious, but common side effects include:

- headache
- breast pain
- irregular vaginal bleeding or spotting
- stomach or abdominal cramps, bloating
- nausea and vomiting
- hair loss
- fluid retention
- vaginal yeast infection

These are not all the possible side effects of FEMTRACE. For more information, ask your healthcare provider or pharmacist. Tell your healthcare provider if you have any side effects that bother you or does not go away. You may report side effects to Warner Chilcott at 1-800-521-8813 or to FDA at 1-800-FDA-1088.

What can I do to lower my chances of a serious side effect with FEMTRACE?

- Talk with your healthcare provider regularly about whether you should continue taking FEMTRACE.
- If you have a uterus, talk with your healthcare provider about whether the addition of a progestin is right for you.

- The addition of a progestin is generally recommended for a woman with a uterus to reduce the chance of getting cancer of the uterus (womb).
- See your healthcare provider right away if you get vaginal bleeding while taking FEMTRACE.
- Have a pelvic exam, breast exam and mammogram (breast x-ray) every year unless your healthcare provider tells you something else.
- If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.
- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or use tobacco, you may have a higher chance of getting heart disease.

Ask your healthcare provider for ways of lowering your chances of getting heart disease.

How do I store FEMTRACE?

- Store at room temperature 68°F to 77°F (20°C to 25°C).

KEEP FEMTRACE out of the reach of children.

General information about safe and effective use of FEMTRACE

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take FEMTRACE for conditions for which it was not prescribed. Do not give FEMTRACE to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about FEMTRACE. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about FEMTRACE that is written for health professionals.

For more information call Warner Chilcott at 1-800-521-8813.

What are the ingredients in FEMTRACE?

Active Ingredients: estradiol acetate

Inactive Ingredients: ferric oxide, povidone, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, silicon dioxide, magnesium stearate and acetic acid; ferric oxide, a coloring agent, is not an ingredient in the 0.9 mg tablets.

This Patient Information has been approved by the U.S Food and Drug Administration.

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