

femhrt[®]
(norethindrone acetate/ethinyl estradiol tablets)

WARNING

Estrogens and progestins should not be used for the prevention of cardiovascular disease or dementia. (See **WARNINGS, Cardiovascular disorders** and **Dementia**.)

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo. (See **CLINICAL PHARMACOLOGY, Clinical Studies** and **WARNINGS, Cardiovascular disorders** and **Malignant neoplasms, Breast cancer**.)

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies, WARNINGS, Dementia** and **PRECAUTIONS, Geriatric Use**.)

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, 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.

DESCRIPTION

femhrt[®] (norethindrone acetate/ethinyl estradiol tablets) is a continuous dosage regimen of a progestin-estrogen combination for oral administration.

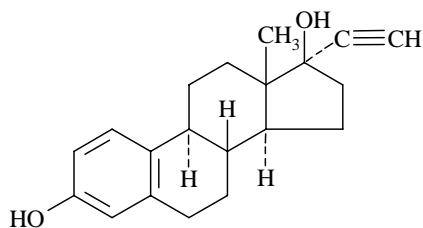
The following two strengths of *femhrt* tablets are available:

femhrt (0.5 mg/2.5 mcg): Each white oval tablet contains 0.5 **mg** norethindrone acetate and 2.5 **mcg** ethinyl estradiol.

femhrt (1 mg/5 mcg): Each white D-shaped tablet contains 1 **mg** norethindrone acetate and 5 **mcg** ethinyl estradiol.

Each tablet also contains the following inactive ingredients: calcium stearate, lactose monohydrate, microcrystalline cellulose, and cornstarch.

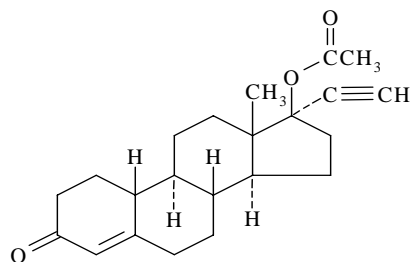
The structural formulas are as follows:



Ethinyl Estradiol [19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-]

Molecular Weight: 296.41

Molecular Formula: C₂₀H₂₄O₂



Norethindrone Acetate [19-Norpregn-4-en-20-yn-3-one, 17-(acetyloxy)-, (17α)-]

Molecular Weight: 340.47

Molecular Formula: C₂₂H₂₈O₃

CLINICAL PHARMACOLOGY

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, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women. The pharmacologic effects of ethinyl estradiol are similar to those of endogenous estrogens.

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 follicle stimulating hormone (FSH) through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

Progestin compounds enhance cellular differentiation and generally oppose the actions of estrogens by decreasing estrogen receptor levels, increasing local metabolism of estrogens to less active metabolites, or inducing gene products that blunt cellular responses to estrogen. Progestins exert their effects in target cells by binding to specific progesterone receptors that interact with progesterone response elements in target genes. Progesterone receptors have been identified in the female reproductive tract, breast, pituitary, hypothalamus, bone, skeletal tissue and central nervous system. Progestins produce similar endometrial changes to those of the naturally occurring hormone progesterone.

Pharmacokinetics

Absorption

Norethindrone acetate (NA) is completely and rapidly deacetylated to norethindrone after oral administration, and the disposition of norethindrone acetate is indistinguishable from that of orally administered norethindrone. Norethindrone acetate and ethinyl estradiol (EE) are rapidly absorbed from *femhrt* tablets, with maximum plasma concentrations of norethindrone and ethinyl estradiol generally occurring 1 to 2 hours postdose. Both are subject to first-pass metabolism after oral dosing, resulting in an absolute bioavailability of approximately 64% for norethindrone and 55% for ethinyl estradiol. Bioavailability of *femhrt* tablets is similar to that from solution for norethindrone and slightly less for ethinyl estradiol. Administration of *femhrt* tablets with a high fat meal decreases rate but not extent of ethinyl estradiol absorption. The extent of norethindrone absorption is increased by 27% following administration of *femhrt* tablets with food.

The full pharmacokinetic profile of *femhrt* tablets was not characterized due to assay sensitivity limitations. However, the multiple-dose pharmacokinetics were studied at a dose of 1 **mg** NA/10 **mcg** EE in 18 post-menopausal women. Mean plasma concentrations are shown below (Figure 1) and pharmacokinetic parameters are found in Table 1. Based on a population pharmacokinetic analysis, mean steady-state concentrations of norethindrone for 1 **mg** NA/5 **mcg** EE and 1/10 are slightly more than proportional to dose when compared to 0.5 **mg** NA/2.5 **mcg** EE tablets. It can be explained by higher sex hormone binding globulin (SHBG) concentrations. Mean steady-state plasma concentrations of ethinyl estradiol for the *femhrt* 0.5/2.5 tablets and *femhrt* 1/5 tablets are proportional to dose, but there is a less than proportional increase in steady-state concentrations for the NA/EE 1/10 tablet.

Figure 1. Mean Steady-State (Day 87) Plasma Norethindrone and Ethinyl Estradiol Concentrations Following Continuous Oral Administration of 1 mg NA/10 mcg EE Tablets

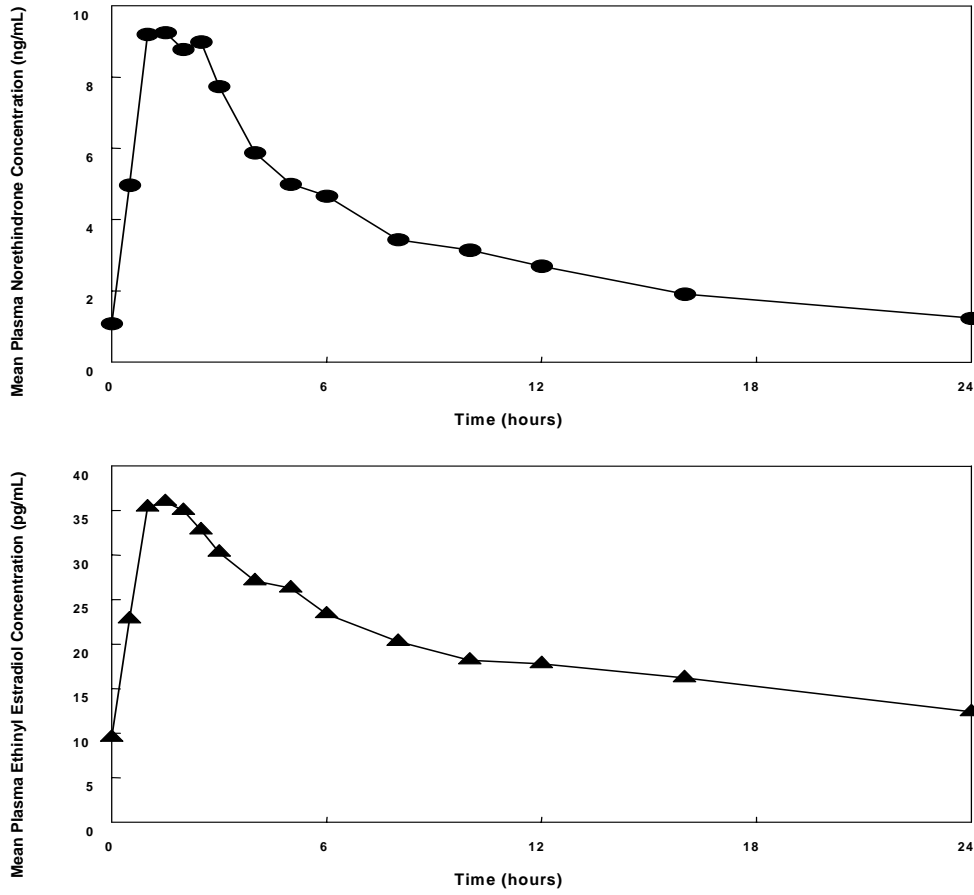


Table 1. Mean (SD) Single-Dose (Day 1) and Steady-State (Day 87) Pharmacokinetic Parameters^a Following Administration of 1 mg NA/10 mcg EE Tablets

| | C _{max} | t _{max} | AUC(0-24) | CL/F | t _{1/2} |
|--------------------------|------------------|------------------|-------------|-----------------|------------------|
| Norethindrone | ng/mL | hr | ng·hr/mL | mL/min | hr |
| Day 1 | 6.0 (3.3) | 1.8 (0.8) | 29.7 (16.5) | 588 (416) | 10.3 (3.7) |
| Day 87 | 10.7 (3.6) | 1.8 (0.8) | 81.8 (36.7) | 226 (139) | 13.3 (4.5) |
| Ethinyl Estradiol | pg/mL | hr | pg·hr/mL | mL/min | hr |
| Day 1 | 33.5 (13.7) | 2.2 (1.0) | 339 (113) | ND ^b | ND ^b |
| Day 87 | 38.3 (11.9) | 1.8 (0.7) | 471 (132) | 383 (119) | 23.9 (7.1) |

^aC_{max} = Maximum plasma concentration; t_{max} = time of C_{max}; AUC(0-24) = Area under the plasma concentration-time curve over the dosing interval; and CL/F = Apparent oral clearance; t_{1/2} = Elimination half-life

^bND = Not determined

Based on a population pharmacokinetic analysis, average steady-state concentrations (C_{ss}) of norethindrone and ethinyl estradiol for *femhrt* 1/5 tablets are estimated to be 2.6 ng/mL and 11.4 pg/mL, respectively. C_{ss} values of norethindrone and ethinyl estradiol for *femhrt* 0.5/2.5 tablets are estimated to be 1.1 ng/mL and 5.4 ng/mL, respectively.

The pharmacokinetics of ethinyl estradiol and norethindrone acetate were not affected by age, (age range 40-62 years), in the postmenopausal population studied.

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 sex hormone binding globulin (SHBG) and albumin.

Volume of distribution of norethindrone and ethinyl estradiol ranges from 2 to 4 L/kg. Plasma protein binding of both steroids is extensive (>95%); norethindrone binds to both albumin and sex hormone binding globulin (SHBG), whereas ethinyl estradiol binds only to albumin. Although ethinyl estradiol does not bind to SHBG, it induces SHBG synthesis.

Metabolism

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 the 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 gut 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.

Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites. A small amount of norethindrone acetate is metabolically converted to ethinyl estradiol, such that exposure to ethinyl estradiol following administration of 1 **mg** of norethindrone acetate is equivalent to oral administration of 2.8 **mcg** ethinyl estradiol. Ethinyl estradiol is also extensively metabolized, both by oxidation and by conjugation with sulfate and glucuronide. Sulfates are the major circulating conjugates of ethinyl estradiol and glucuronides predominate in urine. The primary oxidative metabolite is 2-hydroxy ethinyl estradiol, formed by the CYP3A4 isoform of cytochrome P450. Part of the first-pass metabolism of ethinyl estradiol is believed to occur in gastrointestinal mucosa. Ethinyl estradiol may undergo enterohepatic circulation.

Excretion

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

Norethindrone and ethinyl estradiol are excreted in both urine and feces, primarily as metabolites. Plasma clearance values for norethindrone and ethinyl estradiol are similar (approximately 0.4 L/hr/kg). Steady-state elimination half-lives of norethindrone and ethinyl estradiol following administration of 1 **mg** NA/10 **mcg** EE tablets are approximately 13 hours and 24 hours, respectively.

Special Populations

Pediatric

femhrt is not indicated in children.

Geriatrics

The pharmacokinetics of *femhrt* have not been studied in a geriatric population.

Race

The effect of race on the pharmacokinetics of *femhrt* has not been studied.

Patients with Renal Insufficiency

The effect of renal disease on the disposition of *femhrt* has not been evaluated. In premenopausal women with chronic renal failure undergoing peritoneal dialysis who received multiple doses of an oral contraceptive containing ethinyl estradiol and norethindrone, plasma ethinyl estradiol concentrations were higher and norethindrone concentrations were unchanged compared to concentrations in premenopausal women with normal renal function (see **PRECAUTIONS, Fluid Retention**).

Patients with Hepatic Impairment

The effect of hepatic disease on the disposition of *femhrt* has not been evaluated. However, ethinyl estradiol and norethindrone may be poorly metabolized in patients with impaired liver function (see **PRECAUTIONS**).

Drug Interactions

See **PRECAUTIONS, Drug 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 preparations (*Hypericum perforatum*), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations 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 plasma concentrations of estrogens and may result in side effects.

Clinical Studies

Effects on Vasomotor Symptoms

A 12-week placebo-controlled, multicenter, randomized clinical trial was conducted in 266 symptomatic women who had at least 56 moderate to severe hot flushes during the week prior to randomization. On average, patients had 12 hot flushes per day upon study entry.

A total of 66 women were randomized to receive *femhrt* 1/5, 67 women were randomized to receive *femhrt* 0.5/2.5 and 66 women were randomized to the placebo group. *femhrt* 1/5 and *femhrt* 0.5/2.5 were shown to be statistically better than placebo at weeks 4 and 12 for relief of the frequency of moderate to severe vasomotor symptoms. See Table 2. In Table 3, *femhrt* 1/5 was shown to be statistically better than placebo at weeks 4 and 12 for relief of the severity of moderate to severe vasomotor symptoms; *femhrt* 0.5/2.5 was shown to be statistically better than placebo at weeks 5 and 12 for relief of the severity of moderate to severe vasomotor symptoms.

Table 2. Mean Change from Baseline in the Number of Moderate to Severe Vasomotor Symptoms per Week - ITT Population, LOCF

| Visit | Placebo (N = 66) | <i>femhrt</i> 0.5/2.5 (N = 67) | <i>femhrt</i> 1/5 (N = 66) |
|----------------------------------|-----------------------------|---|---|
| Baseline [1] | | | |
| Mean (SD) | 76.5 (21.4) | 77.6 (26.5) | 70.0 (16.6) |
| Week 4 | | | |
| Mean (SD) | 39.4 (27.6) | 30.2 (26.1) | 20.4 (22.7) |
| Mean Change from Baseline (SD) | -37.0 (26.6) | -47.4* (26.1) | -49.6* (22.1) |
| p-Value vs. Placebo (95% CI) [2] | | 0.041 (-20.0, -1.0) | <0.001 (-22.0,-6.0) |
| Week 12 | | | |
| Mean (SD) | 31.1 (27.0) | 13.8 (20.4) | 11.3 (18.9) |
| Mean Change from Baseline (SD) | -45.3 (30.2) | -63.8* (27.5) | -58.7* (23.1) |
| p-Value vs. Placebo (95% CI) [2] | | <0.001 (-27.0, -7.0) | <0.001 (-25.0, -5.0) |

* Denotes statistical significance at the 0.05 level

[1] The baseline number of moderate to severe vasomotor symptoms (MSVS) is the weekly average number of MSVS during the two week prerandomization observation period.

[2] ANCOVA - Analysis of Covariance model where the observation variable is change from baseline; independent variables include treatment, center and baseline as covariate. The 95% CI - Mann-Whitney confidence interval for the difference between means (not stratified by center).

ITT = intent to treat; LOCF = last observation carried forward; CI = confidence interval
2 randomized subjects (1 in Placebo and 1 in *femhrt*) did not return diaries.

Table 3. Mean Change from Baseline in the Daily Severity Score of Moderate to Severe Vasomotor Symptoms per Week - ITT Population, LOCF

| Visit | Placebo (N = 66) | <i>femhrt</i> 0.5/2.5 (N = 67) | <i>femhrt</i> 1/5 (N = 66) |
|----------------------------------|---------------------|--------------------------------------|----------------------------------|
| Baseline [1] | | | |
| Mean (SD) | 2.49 (0.26) | 2.48 (0.22) | 2.47 (0.23) |
| Week 4 | | | |
| Mean (SD) | 2.13 (0.74) | 1.88 (0.89) | 1.45 (1.03) |
| Mean Change from Baseline (SD) | -0.36 (0.68) | -0.59 (0.83) | -1.02* (1.06) |
| p-Value vs. Placebo (95% CI) [2] | - | 0.130 (-0.3, 0.0) | <0.001 (-0.9, -0.2) |
| Week 5 | | | |
| Mean (SD) | 2.06 (0.79) | 1.68 (0.99) | 1.23 (1.03) |
| Mean Change from Baseline (SD) | -0.44 (0.74) | -0.80* (0.94) | -1.24* (1.07) |
| p-Value vs. Placebo (95% CI) [2] | - | 0.041 (-0.4, -0.0) | <0.001 (-1.2, -0.3) |
| Week 12 | | | |
| Mean (SD) | 1.82 (1.03) | 1.22 (1.11) | 1.02 (1.16) |
| Mean Change from Baseline (SD) | -0.67 (1.02) | -1.26* (1.08) | -1.45* (1.19) |
| p-Value vs. Placebo (95% CI) [2] | - | 0.002 (-0.9, -0.2) | <0.001 (-1.4, -0.3) |

* Denotes statistical significance at the 0.05 level

[1] The baseline severity of moderate to severe vasomotor symptoms (MSVS) is the daily severity score of MSVS during the two week prandomization observation period.

[2] ANCOVA - Analysis of Covariance model where the observation variable is change from baseline; independent variables include treatment, center and baseline as covariate. The 95% CI - Mann-Whitney confidence interval for the difference between means (not stratified by center).

ITT = intent to treat; LOCF = last observation carried forward; CI = confidence interval
2 randomized subjects (1 in Placebo and 1 in *femhrt*) did not return diaries.

Endometrial Hyperplasia

A 2-year, placebo-controlled, multicenter, randomized clinical trial was conducted to determine the safety and efficacy of *femhrt* on maintaining bone mineral density, protecting the endometrium, and to determine effects on lipids. A total of 1265 women were enrolled and randomized to either placebo, 0.2 mg NA/1 mcg EE, *femhrt* 0.5/2.5, *femhrt* 1/5 and 1 mg NA/10 mcg EE or matching unopposed EE doses (1, 2.5, 5, or 10 mcg) for a total of 9 treatment groups. All participants received 1000 mg of calcium supplementation daily. Of the 1265 women randomized to the various treatment arms of this study, 137 were randomized to placebo, 146 to *femhrt* 1/5, 136 to *femhrt* 0.5/2.5 and 141 to EE 5 mcg and 137 to EE 2.5 mcg. Of these, 134 placebo, 143 *femhrt* 1/5, 136 *femhrt* 0.5/2.5, 139 EE 5 mcg and 137 EE 2.5 mcg had a baseline endometrial result. Baseline biopsies were classified as normal (in approximately 95% of subjects), or

insufficient tissue (in approximately 5% of subjects). Follow-up biopsies were obtained in approximately 70-80% of patients in each arm after 12 and 24 months of therapy. Results are shown in Table 4.

Table 4. Endometrial Biopsy Results After 12 and 24 Months of Treatment (CHART Study, 376-359)

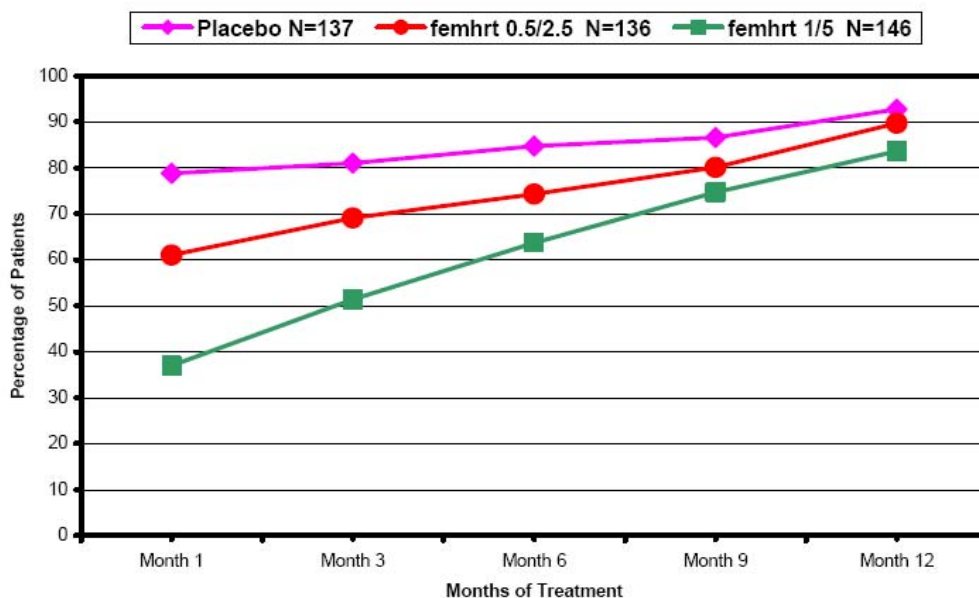
| Endometrial Status | Placebo | <i>femhrt</i> | | EE Alone | |
|--|----------|---------------|----------|----------|----------|
| | | 0.5/2.5 | 1/5 | 2.5 µg | 5 µg |
| Number of Patients Biopsied at Baseline | N = 134 | N = 136 | N = 143 | N = 137 | N = 139 |
| MONTH 12 (% Patients) | | | | | |
| Patients Biopsied (%) | 113 (84) | 103 (74) | 110 (77) | 100 (73) | 114 (82) |
| Insufficient Tissue | 30 | 34 | 45 | 20 | 20 |
| Atrophic Tissue | 60 | 41 | 41 | 15 | 2 |
| Proliferative Tissue | 23 | 28 | 24 | 65 | 91 |
| Endometrial Hyperplasia ^a | 0 | 0 | 0 | 0 | 1 |
| MONTH 24 (% Patients) | | | | | |
| Patients Biopsied (%) | 94 (70) | 99 (73) | 102 (71) | 89 (65) | 107 (77) |
| Insufficient Tissue | 35 | 42 | 37 | 23 | 17 |
| Atrophic Tissue | 38 | 30 | 33 | 6 | 2 |
| Proliferative Tissue | 20 | 27 | 32 | 60 | 86 |
| Endometrial Hyperplasia ^a | 1 | 0 | 0 | 0 | 2 |

^aAll patients with endometrial hyperplasia were carried forward for all time points

Irregular Bleeding/Spotting

The cumulative incidence of amenorrhea, defined as no bleeding or spotting obtained from subject recall, was evaluated over 12 months for *femhrt* 0.5/2.5, *femhrt* 1/5 and placebo arms. Results are shown in Figure 2.

Figure 2. Patients With Cumulative Amenorrhea Over Time:
Intent-to-Treat Population, Last Observation Carried Forward

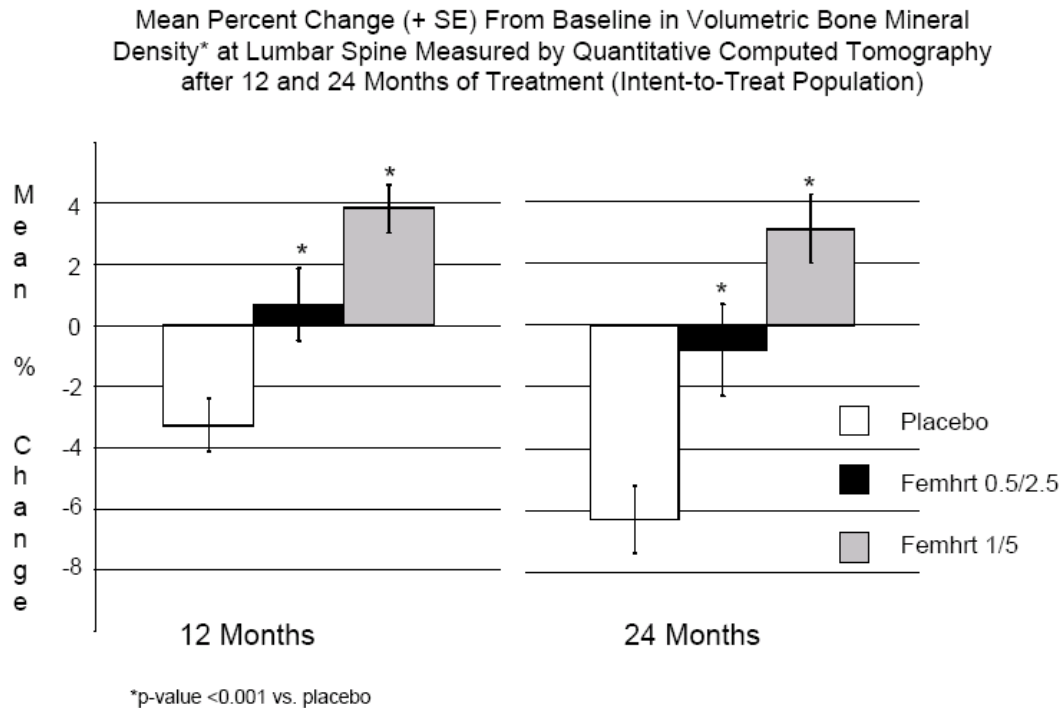


Effect on Bone Mineral Density

In the 2 year study, trabecular bone mineral density (BMD) was assessed at lumbar spine using quantitative computed tomography. A total of 419 postmenopausal primarily Caucasian women, aged 40 to 64 years, with intact uteri and non-osteoporotic bone mineral densities were randomized (1:1:1) to *femhrt* 1/5, *femhrt* 0.5/2.5 or placebo. Approximately 75% of the subjects in each group completed the two-year study. All patients received 1000 mg calcium in divided doses. Vitamin D was not supplemented.

As shown in Figure 3, women treated with *femhrt* 1/5 had an average increase of 3.1% in lumbar spine BMD from baseline to Month 24. Women treated with *femhrt* 0.5/2.5 and placebo had average decreases of -0.8% and -6.3%, respectively, in spinal BMD from baseline to Month 24. The differences in the changes from baseline to Month 24 in the two *femhrt* groups compared with the placebo group were statistically significant.

Figure 3.



*It should be noted that when measured by QCT, BMD gains and losses are greater than when measured by dual X-ray absorptiometry (DXA). Therefore, the differences in the changes in BMD between the placebo and active drug treated groups will be larger when measured by QCT compared with DXA. Changes in BMD measured by DXA should not be compared with changes in BMD measured by QCT.

Women's Health Initiative Studies

The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either the use of oral 0.625 mg conjugated estrogens (CE) per day alone or the use of oral 0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate (MPA) per day compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE or CE/MPA on menopausal symptoms.

The CE/MPA substudy was stopped early because, according to the predefined stopping

rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the “global index”. Results of the CE/MPA substudy, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years are presented in Table 5 below:

| Table 5. RELATIVE AND ABSOLUTE RISK SEEN IN THE CE/MPA SUBSTUDY OF WHI^a | | | |
|---|---|--------------------------------------|--------------------|
| Event ^c | Relative Risk CE/MPA vs placebo at 5.2 Years (95% CI*) | Placebo n = 8102 | CE/MPA n = 8506 |
| | | Absolute Risk per 10,000 Women-years | |
| CHD events | 1.29 (1.02-1.63) | 30 | 37 |
| <i>Non-fatal MI</i> | <i>1.32 (1.02-1.72)</i> | 23 | 30 |
| <i>CHD death</i> | <i>1.18 (0.70-1.97)</i> | 6 | 7 |
| Invasive breast cancer ^b | 1.26 (1.00-1.59) | 30 | 38 |
| Stroke | 1.41 (1.07-1.85) | 21 | 29 |
| Pulmonary embolism | 2.13 (1.39-3.25) | 8 | 16 |
| Colorectal cancer | 0.63 (0.43-0.92) | 16 | 10 |
| Endometrial cancer | 0.83 (0.47-1.47) | 6 | 5 |
| Hip fracture | 0.66 (0.45-0.98) | 15 | 10 |
| Death due to causes other than the events above | 0.92 (0.74-1.14) | 40 | 37 |
| Global Index ^c | 1.15 (1.03-1.28) | 151 | 170 |
| Deep vein thrombosis ^d | 2.07 (1.49-2.87) | 13 | 26 |
| Vertebral fractures ^d | 0.66 (0.44-0.98) | 15 | 9 |
| Other osteoporotic fractures ^d | 0.77 (0.69-0.86) | 170 | 131 |

^a adapted from JAMA, 2002; 288:321-333

^b includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer

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

^d not included in Global Index

* nominal confidence intervals unadjusted for multiple looks and multiple comparisons

For those outcomes included in the "global index", the absolute excess risks per 10,000 women-years in the group treated with CE/MPA were 7 more CHD events, 8 more strokes, 8 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. The absolute excess risk of events included in the “global index” was 19 per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See **BOXED WARNING, WARNINGS, and PRECAUTIONS.**)

Women’s Health Initiative Memory Study

The Women’s Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were age 65 to 69 years, 35% were 70 to 74 years, and 18% were 75 years of age and

older) to evaluate the effects of CE/MPA (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate) on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 4 years, 40 women in the estrogen/progestin group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI, 1.21 to 3.48) compared to placebo. Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNING** and **WARNINGS, Dementia.**)

INDICATIONS AND USAGE

femhrt is indicated in women with an intact uterus for the:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis. Non-estrogen medications should be carefully considered.

The mainstays for decreasing the risk of postmenopausal osteoporosis are weight-bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy. Postmenopausal women require an average of 1500 mg/day of elemental calcium. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake. Vitamin D supplementation of 400-800 IU/day may also be required to ensure adequate daily intake in postmenopausal women.

Risk factors for osteoporosis include low bone mineral density, low estrogen levels, family history of osteoporosis, previous fracture, small frame (low BMI), light skin color, smoking, and alcohol intake. Response to therapy can be predicted by pre-treatment serum estradiol, and can be assessed during treatment by measuring biochemical markers of bone formation/resorption, and/or bone mineral density.

Estrogen therapy reduces bone resorption and retards or halts postmenopausal bone loss. Studies have shown a risk ratio of about 0.4 for hip and wrist fractures in women whose estrogen therapy was begun within a few years of menopause, compared to women taking calcium and vitamin D alone. Studies also suggest that estrogen reduces the rate of vertebral fractures. Even when started as late as 6 years after menopause, estrogen reduces further loss of bone mass for as long as treatment is continued. When estrogen therapy is discontinued, bone mass declines at a rate comparable to the immediate postmenopausal period.

Data from the Women's Health Initiative study showed that use of estrogen-plus-progestin (dose equivalent to 0.625 mg CE and 2.5 mg MPA) resulted in about 5 less hip fractures per 10,000 women-years, compared to use of placebo (risk ratio about 0.66).

CONTRAINDICATIONS

femhrt should not be used in women with any of the following conditions:

1. Undiagnosed abnormal genital bleeding.
2. Known, suspected, or history of cancer of the breast.
3. Known or suspected estrogen-dependent neoplasia.
4. Active deep vein thrombosis, pulmonary embolism or history of these conditions.
5. Active or recent (e.g., within past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
6. Liver dysfunction or disease.
7. *femhrt* should not be used in patients with known hypersensitivity to its ingredients.
8. Known or suspected pregnancy. There is no indication for *femhrt* in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy. (See **PRECAUTIONS.**)

WARNINGS

See **BOXED WARNING**

1. Cardiovascular disorders

Estrogen and estrogen/progestin therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogen/progestin therapy should be discontinued immediately.

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

a. Coronary heart disease and stroke

In the Women's Health Initiative (WHI) study, an increase in the number of strokes was observed in women receiving CE compared to placebo.

In the CE/MPA substudy of WHI, an increased risk of coronary heart disease (CHD) events (defined as non-fatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 vs 30 per 10,000

women-years). The increase in risk was observed in year one and persisted. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

In the same substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 vs 21 per 10,000 women-years). The increase in risk was observed after the first year and persisted. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with CE/MPA - 0.625 mg/2.5 mg per day demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/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/MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty one 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/MPA group and the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

b. Venous thromboembolism (VTE)

In the Women's Health Initiative (WHI) study, an increase in VTE was observed in women receiving CE compared to placebo.

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the CE/MPA group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

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

2. Malignant Neoplasms

a. Breast cancer

The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) substudy of CE/MPA (See **CLINICAL PHARMACOLOGY, Clinical Studies**). The results from observational studies are generally consistent with those of the WHI clinical trial and report no significant variation in the risk of breast cancer among different estrogens or progestins, doses, or routes of administration.

The CE/MPA substudy of WHI reported an increased risk of breast cancer in women who took CE/MPA for a mean follow-up of 5.6 years. Observational studies have also reported an increased risk for estrogen/progestin combination therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. In the WHI trial and from observational studies, the excess risk increased with duration of use. From observational studies, the risk appeared to return to baseline in about five years after stopping treatment. In addition, observational studies suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen/progestin combination therapy as compared to estrogen-alone therapy.

In the CE/MPA substudy, 26% of the women reported prior use of estrogen-alone and/or estrogen/progestin combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 vs 33 cases per 10,000 women-years, for CE/MPA 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 vs 25 cases per 10,000 women-years, for CE/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 vs 36 cases per 10,000 women-years for CE/MPA compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA 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.

The use of 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.

b. Endometrial cancer

The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. 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 one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten 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 taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal 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 has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

3. Dementia

In the Women's Health Initiative Memory Study (WHIMS), 4,532 generally healthy postmenopausal women 65 years of age and older were studied, of whom 35% were 70 to 74 years of age and 18% were 75 or older. After an average follow-up of 4 years, 40 women being treated with CE/MPA (1.8%, n = 2,229) and 21 women in the placebo group (0.9%, n = 2,303) received diagnoses of probable dementia. The relative risk for CE/MPA versus placebo was 2.05 (95% confidence interval 1.21 – 3.48), and was similar for women with and without histories of menopausal hormone use before WHIMS. The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years, and the absolute excess risk for CE/MPA was 23 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies** and **PRECAUTIONS, Geriatric Use**.)

4. Gallbladder Disease

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

5. Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in patients 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.

6. Visual Abnormalities

Retinal vascular thrombosis has been reported in patients 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.

PRECAUTIONS

A. General

1. Addition of a progestin when a woman has not had a hysterectomy

A daily dose of *femhrt* contains a progestin.

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 treatment. These include a possible increased risk of breast cancer.

2. 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 estrogens on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

3. Hypertriglyceridemia

In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

4. Impaired liver function and past history of cholestatic jaundice

Estrogens may be poorly metabolized in patients with impaired liver function. For patients 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. Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients 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. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

6. Fluid retention

Because estrogens may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

7. Hypocalcemia

Estrogens should be used with caution in individuals with severe hypocalcemia.

8. Ovarian cancer

The CE/MPA substudy of WHI reported that estrogen-plus-progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA versus placebo was 1.58 (95% confidence interval 0.77 – 3.24) but was not statistically significant. The absolute risk for CE/MPA versus placebo was 4.2 versus 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen-alone, in particular for ten or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

9. Exacerbation of endometriosis

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

10. Exacerbation of other conditions

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

B. PATIENT INFORMATION

Physicians are advised to discuss the PATIENT INFORMATION leaflet with patients for whom they prescribe *femhrt*.

See text of Patient Information which appears after the **HOW SUPPLIED** section.

C. LABORATORY TESTS

Estrogen administration should be initiated at the lowest dose approved for the indication and then guided by clinical response rather than by serum hormone levels (e.g., estradiol, FSH).

D. DRUG/LABORATORY TEST INTERACTIONS

The following drug/laboratory interactions have been observed with estrogen therapy, and/or *femhrt*:

1. In a 12-week study, *femhrt* 0.5/2.5 and *femhrt* 1/5 decreased Factor VII, and *femhrt* 1/5 decreased plasminogen activator inhibitor-1 from baseline in a dose-related manner but remained within the laboratory reference range for postmenopausal women. Mean levels of fibrinogen and partial thromboplastin time changed minimally from baseline for *femhrt* 0.5/2.5 and *femhrt* 1/5.
2. Estrogen therapy may increase thyroxine-binding globulin (TBG), leading to increased circulating total thyroid hormone (T₄) as measured by protein-bound iodine

(PBI), T₄ levels (by column or radioimmunoassay), or T₃ levels by radioimmunoassay. T₃ resin uptake is decreased, reflecting the elevated TBG. Free T₄ and free T₃ concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.

3. Estrogen therapy may elevate other binding proteins in serum, i.e., corticosteroid binding globulin (CBG), sex hormone binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

femhrt 0.5/2.5 and *femhrt* 1/5 were associated with an SHBG increase of 15% and 22%, respectively.

4. Estrogen therapy increases plasma HDL and HDL₂ subfraction concentrations, reduces LDL cholesterol concentration and increases triglyceride levels.
5. Estrogen therapy is associated with impaired glucose tolerance.
6. Estrogen therapy reduces response to metyrapone test.

E. Drug/Drug Interactions

No drug-drug interaction studies have been conducted with *femhrt*.

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 preparations (*Hypericum perforatum*), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations 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 plasma concentrations of estrogens and may result in side effects.

The following section contains information on drug interactions with ethinyl estradiol-containing products (specifically, oral contraceptives) that have been reported in the public literature. It is unknown whether such interactions occur with *femhrt* or drug products containing other types of estrogens.

The Effect of Ethinyl Estradiol on Other Drugs

Drug products containing ethinyl estradiol may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporin, prednisolone, and theophylline have been reported with concomitant administration of certain drugs containing ethinyl estradiol (e.g., oral contraceptives containing ethinyl estradiol). In addition, drugs containing ethinyl estradiol may induce the conjugation of other compounds.

Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine, and clofibrac acid have been noted when these drugs were administered with certain ethinyl estradiol-containing drug products (e.g., oral contraceptives containing ethinyl estradiol).

F. CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term continuous administration of estrogen, with and without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. (See **BOXED WARNING, WARNINGS** and **PRECAUTIONS**.)

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.

G. PREGNANCY

femhrt should not be used during pregnancy. (See **CONTRAINDICATIONS**.)

H. NURSING MOTHERS

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of drug have been identified in the milk of mothers receiving these drugs. Caution should be exercised when *femhrt* is administered to nursing mothers.

I. PEDIATRIC USE

femhrt is not indicated in children.

J. GERIATRIC USE

There have not been sufficient numbers of geriatric patients involved in clinical trials utilizing *femhrt* to determine whether those over 65 years of age differ from younger subjects in their response to *femhrt*.

In the Women's Health Initiative Memory Study, including 4,532 women 65 years of age and older, followed for an average of 4 years, 82% (n = 3,729) were 65 to 74 while 18% (n = 803) were 75 and over. Most women (80%) had no prior hormone therapy use. Women treated with conjugated estrogens plus medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. Alzheimer's disease was the most common classification of probable dementia in both the conjugated estrogens plus medroxyprogesterone acetate group and the placebo group. Ninety percent of the cases of probable dementia occurred in the 54% of women that were older than 70. (See **WARNINGS, Dementia**.)

ADVERSE REACTIONS

See **BOXED WARNING, WARNINGS** and **PRECAUTIONS**.

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 practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Adverse events reported in controlled clinical studies of *femhrt* are shown in Table 6 below.

Table 6. All Treatment-Emergent Adverse Events Reported at a Frequency of $\geq 5\%$ of Patients with *femhrt*

| BODY SYSTEM/ Adverse Event | Percent of Patients (%) | | |
|-------------------------------|-------------------------|-------------------------------------|------------------------------|
| | Placebo N = 247 | <i>femhrt</i> 0.5/2.5 N = 244 | <i>femhrt</i> 1/5 N = 258 |
| BODY AS A WHOLE | 40.1 | 38.5 | 39.5 |
| Headache | 14.6 | 15.2 | 18.2 |
| Back Pain | 5.3 | 5.3 | 4.7 |
| Viral Infection | 7.7 | 8.6 | 7.0 |
| DIGESTIVE SYSTEM | 24.4 | 30.5 | 33.0 |
| Nausea and/or Vomiting | 5.3 | 5.3 | 7.4 |
| Abdominal Pain | 4.5 | 10.2 | 8.1 |
| Dyspepsia | 2.0 | 5.3 | 3.1 |
| Diarrhea | 3.6 | 5.7 | 3.9 |
| MUSCULOSKELETAL SYSTEM | 21.7 | 20.3 | 20.4 |
| Arthralgia | 6.9 | 2.9 | 5.8 |
| Myalgia | 8.5 | 8.6 | 7.8 |
| PSYCHOBIOLOGIC FUNCTION | 8.3 | 7.9 | 14.1 |
| Nervousness | 1.6 | 1.6 | 5.4 |
| Depression | 3.6 | 3.7 | 5.8 |
| RESPIRATORY SYSTEM | 37.2 | 33.9 | 35.6 |
| Rhinitis | 15.4 | 12.7 | 15.1 |
| Sinusitis | 9.7 | 9.4 | 8.1 |
| UROGENITAL SYSTEM | 25.0 | 31.6 | 40.8 |
| Breast Pain | 5.3 | 9.0 | 8.1 |
| Urinary Tract Infection | 3.2 | 3.7 | 6.2 |
| Vaginitis | 4.9 | 4.5 | 5.4 |

The following additional adverse reactions have been reported with estrogen and/or progestin therapy.

1. 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.

2. Breasts

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

3. Cardiovascular

Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.

4. Gastrointestinal

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

5. Skin

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

6. Eyes

Retinal vascular thrombosis, intolerance to contact lenses.

7. Central nervous system

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

8. Miscellaneous

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

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of progestin/estrogen-containing oral contraceptives by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur.

DOSAGE AND ADMINISTRATION

Use of estrogen, alone or in combination with a progestin, should be limited to the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (e.g., 3 to 6 month intervals) to determine if treatment is still necessary (see **BOXED WARNING** and **WARNINGS**). For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding. Patients should be evaluated for breast abnormalities in accordance with good clinical practice.

Patients should be started at the lowest dose.

femhrt therapy consists of a single tablet taken once daily.

1. For the Treatment of Moderate to Severe Vasomotor Symptoms associated with the menopause

femhrt should be given once daily for the treatment of moderate to severe vasomotor symptoms associated with the menopause. Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary.

2. For Prevention of Postmenopausal Osteoporosis

When prescribing solely of the prevention of postmenopausal osteoporosis, *femhrt* should only be prescribed to postmenopausal women who are at significant risk of osteoporosis. Non-estrogen medications should be carefully considered. Risk factors for osteoporosis include low bone mineral density, low estrogen levels, family history of osteoporosis, previous fracture, small frame (low BMI), light skin color, smoking, and alcohol intake. Patients should be treated with the lowest effective dose. This dose should be periodically reassessed by the healthcare provider. Response to therapy can be assessed during treatment by measuring biochemical markers of bone formation/resorption, and/or bone mineral density.

HOW SUPPLIED

femhrt[®] tablets are available in the following strength and package sizes:

| | |
|----------------|--|
| N 0430-0145-23 | Bottle of 90 oval white tablets with 0.5 mg norethindrone acetate and 2.5 mcg ethinyl estradiol; imprinted with WC on one side and 145 on the other. |
| N 0430-0145-14 | Blister card of 28 oval white tablets with 0.5 mg norethindrone acetate and 2.5 mcg ethinyl estradiol; imprinted with WC on one side and 145 on the other. |

- N 0430-0544-23 Bottle of 90 D-shaped white tablets with 1 **mg** norethindrone acetate and 5 **mcg** ethinyl estradiol; imprinted with WC on one side and 144 on the other.
- N 0430-0544-14 Blister card of 28 D-shaped white tablets with 1 **mg** norethindrone acetate and 5 **mcg** ethinyl estradiol; imprinted with WC on one side and 144 on the other.

Rx only

Keep this drug and all drugs out of the reach of children.

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

**INFORMATION FOR THE PATIENT
(Revised October 2009)**

Please read this PATIENT INFORMATION before you start taking *femhrt*[®] and each time you refill *femhrt*. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about *femhrt* (a combination of estrogen and progestin hormones)?

- Do not use estrogens and progestins to prevent heart disease, heart attacks, strokes or dementia.

Using estrogens and progestins may increase your chances of getting heart attack, strokes, breast cancer, and blood clots. Using estrogens, with or without progestins may increase your risk of dementia, based on a study of women age 65 years or older. It is unknown whether this study applies to women who began estrogen and progestin therapy before age 65. You and your healthcare provider should talk regularly about whether you still need treatment with *femhrt*.

What is *femhrt*?

femhrt is medicine that contains two kinds of hormones, an estrogen and a progestin.

What is *femhrt* used for?

femhrt 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 to 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 develop 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; in others they can be severe. You and your healthcare provider should talk regularly about whether you still need treatment with *femhrt*.

- **help reduce your chances of getting osteoporosis (thin, weak bones)**

Osteoporosis from menopause is a thinning of the bones that makes them weaker and easier to break. If you use *femhrt* only to prevent osteoporosis from menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you. You and your healthcare provider should talk regularly about whether you should continue with *femhrt*.

Weight-bearing exercise, like walking or running, and taking calcium and vitamin D supplements may also lower your chances of getting postmenopausal osteoporosis. It is important to talk about exercise and supplements with your healthcare provider before starting them.

Who should not take *femhrt*?

Do not take *femhrt* if you have had your uterus removed (hysterectomy).

femhrt contains a progestin to decrease the chances of getting cancer of the uterus. If you do not have a uterus, you do not need a progestin and you should not take *femhrt*.

Do not start taking *femhrt* if you:

- **currently have or have had certain cancers.** Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast and uterus. If you have or had cancer, talk with your healthcare provider about whether you should take *femhrt*.
- **had a stroke or heart attack in the past year.**
- **currently have or have had blood clots.**
- **currently have or have had liver problems.**
- **are allergic to *femhrt* or any of its ingredients.** See the end of this leaflet for a list of ingredients in *femhrt*.
- **think you may be pregnant.** If you think you may be pregnant, do not take *femhrt*.

Tell your healthcare provider:

- **if you are breastfeeding.** The hormones in *femhrt* can pass into your milk.
- **about all of your medical problems.** Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), migraine, endometriosis, lupus, problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.
- **about all the medicines you take,** including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how *femhrt* works. *femhrt* may also affect how your other medicines work.
- **if you are going to have surgery or will be on bed rest.** You may need to stop taking estrogens and progestins.

How should I take *femhrt*?

Take your *femhrt* pill once a day at about the same time each day. If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and go back to your normal schedule. Do not take two doses at the same time.

Start at the lowest dose and talk to your healthcare provider about how well that dose is working for you.

Estrogens should only be used as long as needed. You and your healthcare provider should reevaluate every 3 to 6 months whether or not you still need treatment with *femhrt*.

What are the possible risks and side effects of *femhrt*?

Less common but serious side effects include:

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer

These are some of the warning signs of serious side effects:

- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain

- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptom that concerns you.

Common side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss

Other side effects include:

- High blood pressure
- Liver problems
- High blood sugar
- Fluid retention
- Enlargement of benign tumors of the uterus (“fibroids”)
- Vaginal yeast infection

These are not all the possible side effects of *femhrt*. For more information, ask your healthcare provider or pharmacist.

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

- Talk with your healthcare provider regularly (every 3-6 months) about whether you should continue taking *femhrt*.
- See your healthcare provider right away if you develop vaginal bleeding while taking *femhrt*.
- Have a 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 (breast x-ray), 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 higher chances for getting heart disease. Ask your healthcare provider for ways of lowering your chances for getting heart disease.

General information about safe and effective use of *femhrt*

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

Keep all drugs out of the reach of children. In case of overdose, call your doctor, hospital, or poison control center right away. This leaflet provides a summary of the most important information about *femhrt*. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about *femhrt* that is written for health professionals. You can get more information by calling the toll free number 800-521-8813.

What are the ingredients in *femhrt*?

Each white tablet contains norethindrone acetate and ethinyl estradiol. Each tablet also contains calcium stearate, lactose monohydrate, microcrystalline cellulose, and cornstarch.

Manufactured by:
Warner Chilcott Company, LLC
Fajardo, Puerto Rico 00738
Marketed by:
Warner Chilcott (US), LLC
Rockaway, NJ 07866
1-800-521-8813

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.



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